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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GENERAL HOSPITAL AND PERSONAL USE DEVICES PANEL

+ + +

November 6, 2019
8:00 a.m.

DoubleTree by Hilton Grand Ballroom
Washington DC North/Gaithersburg
620 Perry Parkway
Gaithersburg, MD 20877

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M E E T I N G

(8:01 a.m.)

DR. LEWIS: Good morning. I'm Dr. Frank Lewis, and I will be chairing this panel of the next 2 days. It's the General Hospital and Personal Use Devices Panel of the Medical Devices Advisory Committee.

I'm a general surgeon specialized in trauma and critical care and in the latter part of my career was executive director of the American Board of Surgery until I retired about 18 months ago, and I'm currently not affiliated directly with any organization.

I note for the record that the members present constitute a quorum as required by 21 C.F.R. Part 14. And I would like to add that the Panel members participating in today's meeting have received training in FDA device law and regulations.

Over the next 2 days, the Panel will discuss industrial sterilization of medical devices with a focus on industrial ethylene oxide sterilization. In the final half-day of the meeting we'll focus on recommendations for reducing the risk of infection from duodenoscopes, multi-use devices that are very difficult to reprocess but have significant medical benefit. Today we will focus on reduction or elimination of ethylene oxide emissions for medical device sterilization, and we'll hear presentations from U.S. regulatory agencies and United Kingdom's Medicines and Healthcare products Regulatory Agency, as well as stakeholders who support the medical device supply chain in the United States.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and your present affiliation. And I would like to begin with Dr. Krause at the left-hand edge of the table and proceed around the table in sequence.

Dr. Krause.

DR. KRAUSE: Good morning, everyone. Thank you for coming. I'm one of the FDA

representatives at the table. My name is David Krause. I'm the Deputy Director of the Office of Surgical and Infection Control Devices, and again, thank you for being here.

DR. SCHWARTZ: Good morning. My name is Suzanne Schwartz, and I'm the Acting Director of the Office of Strategic Partnerships and Technology Innovation at CDRH.

DR. GARDNER-BONNEAU: I'm Daryle Gardner-Bonneau. My specialty is human factors engineering, and I am the retired owner of Bonneau and Associates, a human factors consulting firm.

DR. LI: Good morning. My name is Steve Li. My areas are biomaterials, biomechanics, and research and development of implant devices, and I currently am a private consultant with Li Consulting.

DR. WILCOX: I'm Steve Wilcox. I'm the principal and founder of Design Science, a human factors consultancy, so of course that's my area, human factors.

DR. ARDUINO: I'm Matt Arduino. I'm the Senior Advisor for Environmental Hygiene and Infection Prevention in the Division of Healthcare Quality Promotion at the Centers for Disease Control, and I am the SME for disinfection and sterilization.

DR. BENOWITZ: I'm Isaac Benowitz. I'm a medical epidemiologist, also with CDC Division of Healthcare Quality Promotion. My focus is outbreak investigations in healthcare settings and device reprocessing.

DR. DOMINITZ: My name is Jason Dominitz. I'm a gastroenterologist. I'm the National Program Director for Gastroenterology in the Department of Veterans Affairs and a professor at the University of Washington in Seattle.

DR. YASZEMSKI: My name is Michael Yaszemski. On the research side, I'm a chemical engineer and work in biomaterials. On the clinical side, I'm an orthopedic surgeon and I do orthopedic oncology and spinal surgery, and I work at Mayo Clinic.

DR. TUNG: I'm Avery Tung. I'm a critical care and cardiac anesthesiologist at the

University of Chicago.

CDR GARCIA: Good morning. My name is Patricio Garcia, and I'm the Designated Federal Officer for this meeting today.

DR. BURR: Good morning. My name is Bob Burr, and I'm here from New Mexico. I'm nominally an endocrinologist, but I think I'm here because I have a degree from the University of Massachusetts in Lowell in work environment, and I'm an occupational environmental epidemiologist and have about 20 years of experience in the chemical demilitarization area, so I know something of the industrial processing of hazardous materials.

DR. GUALTIERI: Good morning, I'm Lisa Gualtieri. I'm on the faculty at Tufts University School of Medicine, and I run the digital health program there.

DR. SAUBOLLE: Hi, I'm Mike Saubolle. I'm a clinical microbiologist recently retired from my clinical job, but now I'm an educator at the University of Arizona College of Medicine in Phoenix.

DR. FAULX: Hi, I'm Ashley Faulx. I am a therapeutic gastroenterologist from Cleveland, and I work at both the Cleveland VA and University Hospital there.

MR. SOCOLA: Good morning. I'm Gary Socola, President of HIGHPOWER Labs. My area of expertise is the validation of the instructions for use of reusable medical devices, not only the devices themselves but the validation of sterilizers for FDA 510(k) clearances.

MS. WELLS: Good morning. Teresa Wells. I'm the National Director for Sterile Processing for the Veterans Health Administration. I'm an SME for sterile processing in all aspects for the VA.

DR. MYERS: Good morning. I'm Sandra Myers. I'm a clinical nurse specialist, perioperative background, and I'm the Sterile Processing and Endoscopy Team Chair for the Baptist Health System in Kentucky.

MR. COLLINS: Good morning. My name is Jim Collins. I work at the Cleveland Clinic, and I am the enterprise endoscopy quality assurance and accreditation nurse. I also handle the education and training of all our reprocessing staff throughout the 23 centers at Cleveland Clinic.

MS. PEKAR: Good morning. I'm Carol Pekar. I'm a regulatory affairs consultant, and I've been in the business for about 20 years working for a number of companies like Anika and Abiomed and Keratin Biosciences, and I am the Industry Rep on the Panel.

DR. SULLY: Good morning. I'm Kate Sully. I'm an interventional physiatrist. I am a contract physician for the VA in Pensacola.

MS. DUNN: Good morning. I'm Debra Dunn, and I am a patient advocate. I'm here on behalf of all patients, and I've been working nationally to represent patients since 2002.

DR. LEWIS: I would note that Dr. Charity Morgan from the University of Alabama is attending the meeting by phone, and that Dr. Lynn Goldman will join us later in the morning. Otherwise, that's the full makeup of the Panel.

The questions being raised in this discussion are probably more diverse than in many of the discussions that take place before these kinds of panels and involves expertises in a number of different areas, many of which most of us do not really have. So the makeup of the Panel is actually quite diverse. The FDA has tried to ensure that there are at least two members of the Panel with expertise in each of the areas described and, in addition, that the presentations we will hear will inform us of many areas that we would otherwise not be knowledgeable about.

The decisions in regard to ethylene oxide are going to be difficult and complex to arrive at because they involve a number of decisions, in particular, in regard to areas about which there are probably inadequate facts to determine all the things we'd like to know. As a result, for topics being discussed at today's meeting there will be a variety of opinions,

some of which will be quite strongly held. Our goal is that the meeting will be a fair and open discussion in an open forum for discussion of these issues so that all individuals can express their views without interruption.

Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the Chairperson. We look forward to a productive meeting and have attempted to include presenters from a variety of all opinions, as well as obviously the public forum which will be presented twice today and once in the morning on the subject.

Members of the audience, if you have not already done so, please sign the attendance sheets outside on the registration table.

And we'll now turn to Commander Patricio Garcia, the Designated Federal Officer for the General Hospital and Personal Use Devices Panel, who will make some introductory remarks.

Commander Garcia.

CDR. GARCIA: Good morning, and thank you, Dr. Lewis.

The Food and Drug Administration is convening today's meeting of the General Hospital and Personal Use Devices Panel of 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 considered special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

For this meeting's agenda, the Panel will discuss the topics of industrial ethylene oxide sterilization of medical devices and its role in maintaining public health, as well as the

risk of infection with reprocessed duodenoscopes.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees have been screened for potential conflict of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

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 in accordance with 18 U.S.C. Section 208.

Dr. Frank Lewis, Jr., is serving as Temporary Chair for this meeting.

Ms. Carol Pekar is serving as the Industry Representative, acting on behalf of all related industry. She is principal for Pekar Consulting.

We would like to remind members and consultants that if a discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude him or herself from such involvement and the exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationship they may have with any firm at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Before I turn this meeting back over to Dr. Lewis, I would like to make a few general announcements.

Transcripts for today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting and handouts for today's presentation are available at the registration table outside the meeting room.

The FDA press contact for today's meeting is Sandy Walsh.

All written comments received were provided to the Panel and FDA review team for their review prior to today's meeting. There's an active docket where members of the public can post written comments. The link can be found on the FDA website and at the registration table just outside this meeting room.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Mr. Artair Mallett at the registration desk.

In order to help the transcriptionist identify who is speaking, please be sure to identify yourself each and every time you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you.

Dr. Lewis.

DR. LEWIS: Thank you, Commander Garcia.

We'll begin today's meeting with introductory remarks from three U.S. regulatory agencies and the United Kingdom. Opening remarks will come from the Food and Drug Administration followed by agency remarks from the Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry, respectively. Lastly, the United Kingdom's Medicines and Healthcare products Regulatory Agency will deliver their perspective on industrial ethylene oxide medical device sterilization.

Dr. Ryan Ortega will deliver FDA's opening remarks. Dr. Ortega, would you please approach the podium and begin when you're ready?

DR. ORTEGA: Good morning, everyone, and welcome to this Advisory Committee meeting. My name is Ryan Ortega. I'm a doctor of biomedical engineering on the Sterility Devices Team of the Office of Surgical and Infection Control Devices in FDA's Center for Devices and Radiological Health. Our office is responsible for the review of healthcare sterilizers, and members of our infection control team provide sterility reviews for devices across the Center.

Before we start, I'd like to thank everyone involved in planning and organizing this meeting, which has involved many people from multiple offices across the Center. The dedicated members of the planning and management teams have put in a great deal of effort to make this meeting possible.

I also want to thank members of the Panel for agreeing to serve in this capacity. Thank you for taking the time out of your lives and professions to serve the public health.

Thanks also to our stakeholders in attendance, both in person or online, and this includes members of the public, clinical and industrial stakeholders, personnel from other agencies, and other public servants. We appreciate you engaging with us on the important topics of this meeting.

A major part of this meeting will be a discussion of industrial sterilization of medical

devices with a focus on industrial ethylene oxide sterilization. In the final half-day of the meeting we will focus on recommendations for reducing the risk of infection from duodenoscopes, which are multi-use devices that are very difficult to reprocess. The agenda and Executive Summary are in the panel pack and are available online.

Industrial sterilization using ethylene oxide, which may also be referred to as EtO or EO, is carried out in separate dedicated facilities at a very large scale to generate a terminally sterilized product that's ready for distribution into the medical device supply chain. This is in contrast to hospital sterilization of medical devices, which is often performed to reprocess multi-use devices and generally occurs on a much smaller scale.

Earlier this year, FDA became aware that the Illinois Environmental Protection Agency issued a state EPA seal order for a contract sterilizer in Willowbrook, Illinois. This was due to concerns about the levels of EtO in the air around the facility. Since then, FDA has been working with multiple stakeholders to help ensure that any medical device shortages due to loss of sterilization capacity at this facility are mitigated. You'll hear more about our efforts to mitigate shortages later today.

The issue of environmental emissions from industrial use of EtO as sterilant for medical devices extends beyond the seal order for one facility. Actions impacting national EtO sterilization capacity for medical devices may have far-reaching implications for public health due to resulting device shortages.

Since the closure of sterilization facilities using EtO, we've heard from stakeholders and from colleagues in other federal, state, and local government organizations about their concerns regarding the potential for shortages of critical sterile medical devices, as well as the risks related to EtO exposure in the air around EtO sterilization facilities.

Access to sterile medical devices is a critical component of the healthcare ecosystem. It's important that these devices are effectively sterilized without exposing the

public to unnecessary risk. The FDA is actively working with sterilization experts, medical device manufacturers, and other government agencies to advance innovative ways to sterilize medical devices with lower levels of currently used agents and employing new agents or alternatives while still maintaining device safety and effectiveness. Examples of these activities are the FDA-sponsored sterilization innovation challenges which were released this summer.

Challenge 1 is to identify new sterilization methods and technologies, and Challenge 2 is to reduce EtO emissions from existing processes while still ensuring that devices can be effectively sterilized. The submission period for these challenges has recently ended, and the review of the submissions by internal subject matter experts is ongoing.

This public meeting is another one of our activities in this area. Even though FDA does not regulate the emissions of commercial sterilization facilities, this function falls under the regulatory authority of the U.S. EPA, from whom you will soon hear. We are convening this Advisory Committee meeting to obtain the Panel's expert advice on how emissions to the environment from EtO sterilization of medical devices may be reduced without compromising the assurance of sterility or effective processing of the device. We recognize the public's concern for unsafe environmental levels of ethylene oxide, and we share the public's objective to reduce an overreliance on ethylene oxide for medical device sterilization.

At the same time, FDA has a responsibility to safeguard the availability of sterilized medical devices for patients throughout the U.S. This means working to mitigate shortages of medical devices that patients depend on for their health and that hospitals require for healthcare.

Following these remarks, you'll hear remarks from representatives from U.S. EPA, CDC, and the UK's Medicines and Healthcare products Regulatory Agency. This morning you

will also hear presentations from FDA subject matter experts about the role FDA plays in reviewing medical device sterility. The important differences between industrial sterilization and healthcare-based sterilization of medical devices will be discussed.

Invited speakers will present potential methods to reduce EtO use and to reduce EtO emissions for medical device sterilization processes.

This afternoon's presentations will focus on other sterilization modalities that are currently used to terminally sterilize medical devices in an industrial setting.

Tomorrow morning we'll wrap up the overview of sterilization technology with presentations on sterilization modalities for which the current industrial infrastructure may be limited or not well known to the FDA.

Tomorrow afternoon, the discussion will turn to the issue of reprocessing a difficult-to-reprocess multi-use device, duodenoscopes, where hospital sterilization is an important part of the conversation.

Throughout the meeting, there will be periods for public comment.

During the Panel sessions, you will be asked to provide your feedback, comments, and expert opinion about the feasibility of potential strategies to reduce EtO emissions. This may be accomplished by modifying existing processes or by leveraging other sterilization modalities as potential viable alternatives to EtO.

You'll also be asked for your feedback on any actions you think FDA may be able to take consistent with our responsibility to ensure that patients have access to safe, high-quality, effective medical devices, recognizing that the regulation of EtO emissions are under U.S. EPA authority.

Thank you again to everyone in attendance. I would like to turn the meeting back over to the Panel Chair to bring up the next speaker.

DR. LEWIS: Thank you, Dr. Ortega.

Our next speaker is Dr. -- is Mr. Mike Koerber, Deputy Director, Office of Air Quality Planning and Standards from the U.S. Environmental Protection Agency.

Mr. Koerber, would you please begin when you're ready?

MR. KOERBER: Good morning. It's an honor to be here to represent EPA and talk to you today about EPA's role in addressing ethylene oxide emissions to the air. Anne Idsal, our Acting Assistant Administrator at EPA, is sorry she couldn't be with you today, but I think I speak for her when I say that we take this issue very seriously at U.S. EPA.

This is an important conversation because EPA shares with FDA a mission to protect public health, and it's important that we work together to address this challenge and not only limit emissions of ethylene oxide to the air but also ensure the safety of medical devices and equipment.

Let me begin by providing an overview of our statutory authority under the Clean Air Act. The Clean Air Act Amendments of 1990 identified a list of 187 hazardous air pollutants or air toxics, including ethylene oxide, and as you know, from its ability to sterilize medical devices, ethylene oxide is a potent chemical and has the potential to cause human health effects such as cancer.

The Act directs EPA to regulate emissions of these air toxics from industrial facilities. EPA does this by setting emission standards that apply to emission source categories such as chemical plants and commercial sterilizers, two main industrial sources of ethylene oxide.

We initially set technology based standards based on emission levels that are already being achieved in practice by the best-controlled and lower-emitting facilities. Then, periodically, EPA must review and, as necessary, revise these standards based on residual risk and advancements in technology. These regulations are national standards and apply uniformly across the country.

Separately, as a non-regulatory exercise at EPA, every few years we conduct a national assessment of air toxics. We call this NATA, National Air Toxics Assessment. NATA is a screening tool. It identifies what areas might have elevated risk and where we need to look closer. Our sixth national assessment was released in August of last year. It identified about 20 areas around the country where ethylene oxide is the main contributor to potential cancer risk. The primary industrial sources of ethylene oxide are chemical plants and commercial sterilizers.

One of the reasons ethylene oxide showed up as such a big driver of potential risk in this assessment compared to previous assessments, I mentioned this is the sixth one we've done, previously we did not identify ethylene oxide as a big risk driver. In this one we did, and that was because we used an updated health value, specifically a new unit risk estimate in EPA's Integrated Risk Information System, or IRIS, was used in this particular assessment. This updated IRIS value showed that ethylene oxide was as much as 50 times more potent than what we previously knew.

In response to these results, EPA announced a two-pronged approach for addressing ethylene oxide emissions to the air. Under the first prong, at the national level, EPA has been reviewing its Clean Air Act regulations for facilities that emit ethylene oxide to ensure that they protect the public from significant risk. This work has included gathering information on industrial emissions of ethylene oxide, including where emissions occur, how those emissions can be controlled, and how current emission controls can be important. This data gathering is important to provide a solid database record to ensure that our rules are defensible and sustainable.

We're starting with two rules, one for miscellaneous organic chemical manufacturing and another for commercial sterilizers. Today we will be announcing a proposal for the chemical manufacturing rule. We will take public comment on the proposal, and we will

also hold public hearings. I'll note that EPA is under court order to take final action on this rule by March of next year. This is a significant action because this is the first EPA air toxics rule in which we are using the updated IRIS value in our risk assessment, and we are taking comment on that in this proposal.

For commercial sterilizers, we're in the process of seeking additional data and information to inform the review of the rule and ensure that we once again have a solid database record for our rulemaking.

As we worked more closely with the industry over the past year, one thing we've learned is that there are more than a hundred potentially affected facilities; about one-third of the hundred potentially affected facilities are small businesses. Given this impact, EPA may need to convene a small business panel before taking any significant regulatory action, and we will soon request nominations to serve as small entity representatives to a possible small business advocacy review panel.

We're also taking more steps to gather further information to inform a proposed rulemaking. Very soon we'll be issuing an Advance Notice of Proposed Rulemaking that will describe potential approaches that we might take in our future proposal, and we will provide the industry with an opportunity to voluntarily provide additional information to inform that proposed rulemaking.

In addition, we are planning to issue a request for information under Section 114 of the Clean Air Act, which will require certain companies to provide specific information, once again, that we will use to inform our upcoming rulemaking.

Under the second prong, EPA has been supporting and working with state and local air agencies to get additional information on ethylene oxide emissions to the air from individual facilities, focusing on those areas that our recent National Air Toxics Assessment identified as having the highest risk. This work is ongoing, and it's being led by state and

local air agencies. EPA regional offices are working closely with these air agencies to gather information on emissions and emission reduction strategies. We've already seen progress in some areas with facilities taking steps or committing to take steps to significantly reduce emissions and risk in a number of areas, including in Illinois, Georgia, and other states.

We also think it is critical to actively engage with affected communities. To this end, several of our regional offices have conducted or participated in meetings with local elected officials and community groups. We are committed to continuing this engagement in the necessary areas.

Finally, I should note that we are fully aware of the connection between the actions taken at some facilities, for example, shutting down temporarily to install pollution controls, and the effect on the availability of medical devices. That's why we've been working very closely with FDA and keeping them informed of our activities and those of state and local air agencies as we learn about them. We're eager to learn more about the results of the innovation challenge conducted recently by FDA, and we want to continue to talk with them as we go forward in our future rulemaking.

Thank you.

DR. LEWIS: Thank you, Mr. Koerber.

At this time we will hear agency remarks from Dr. Chris Reh, Associate Director for the Agency for Toxic Substances and Disease Registry.

Dr. Reh, would you please begin when you're ready?

DR. REH: Good morning. My name is Chris Reh, and I'm the Associate Director for the Agency for Toxic Substances and Disease Registry, or ATSDR. It's truly my honor to be here in front of this esteemed panel to talk about ATSDR and the work we are doing related to the impact of ethylene oxide emissions on communities. So with that, I'll just start with a little bit about who's ATSDR, what our mandate is and our mission, to give some

background on our current involvement in this area, and then talk about future activities.

So a little bit about ATSDR. We were created as part of the Superfund Act or the CERCLA legislation in 1980. We have a legislative mandate through CERCLA, RCRA, and the Superfund Reauthorization Act. It's important to note, we are not a regulatory agency. We are an environmental health/public health agency, and we are part of Health and Human Services, and we are affiliated with the Centers for Disease Control.

So what's important about ATSDR and what makes us unique is the role we play in working with communities, especially as it relates to helping them understand the impact of environmental exposures from either hazardous waste sites and in some cases environmental pollution. We also contribute to the science and the toxicology around these exposures, and we also work closely with the communities to help them better understand the exposures, to educate physicians and other healthcare providers. We work very closely with state, tribal, local, and territorial governments in delivering on this mandate.

In this case, as it relates to ethylene oxide, we first got involved with ethylene oxide. In 2018 we were requested by EPA to perform a health consultation related to ethylene oxide environmental concentrations in the community of Willowbrook, Illinois. This is a common way that we get involved in our space. EPA is the regulatory agency. Our people are embedded on a regional basis with the EPA regional offices, and frequently we get asked by EPA to help them with health consultations.

Without going through a lot of the details on the study, what we found, that if the measured and modeled data that was provided to us by EPA for ethylene oxide concentrations reflected long-term exposure conditions, then ethylene oxide may pose a cancer risk to some people in the community. And that's an important caveat because we were looking at what are generally considered short-term exposures for environmental

emissions. But we felt that if these did represent a long-term exposure scenario, then there would be a cancer risk. We recommended for long-term air monitoring, which has been occurring, and we also recommended that the Illinois Department of Public Health conduct a cancer incident study. And, finally, we conducted, through our Pediatric Environmental Health Specialty Unit program, we conducted healthcare education in the community.

Some additional activities since this initial foray, as you would say. In 2018 we have now received petitions to investigate community ethylene oxide exposures in several communities. We're currently conducting these investigations in Georgia and Illinois. And, again, we're more interested in looking at long-term exposure data rather than short-term exposure data.

We are also assisting some states with their cancer incident studies and, you know, one of the things where we assist the states is on how we define exposure because that's critical for this topic.

We're participating on a routine basis in public meetings, and we also, within the National Center for Environmental Health at CDC, we have a world-class biological monitoring laboratory, especially as it relates to measuring chemicals and developing biomarkers for chemicals, and they have developed an ethylene oxide hemoglobin adduct biological marker that we feel is an exposure metric for the past 3 months of exposure, and we're exploring the use of this biomarker in populations that may have community exposures.

I think it would be remiss of me if we don't talk a little bit about the challenges that we see in this area. The first is that ethylene oxide is commonly detected in ambient air, even when known emission sources are not present, and this is an important confounder to the work that we do, and we need to better understand that. We need to do some work to better identify and quantify all ethylene oxide exposures, including fugitive emissions, and

look at these exposures from a holistic standpoint and how they impact the communities.

The second part is really critical to the work we do and that EPA does, and that is risk communication. You really need to spend some time and some careful thought in how you talk to communities about this issue. They come in to the meetings, there's already a heightened level of sensitivity and concern, and the way we communicate risk, actual risk, to the communities is very important going forward, and this is something we in the agency are taking seriously and looking into ways we can best communicate with communities what the risk is.

And with that, this concludes my comments. Thank you.

DR. LEWIS: Thank you, Dr. Reh.

I now would like to introduce Andrew Bent from the United Kingdom's Devices Division, Medicines and Healthcare products Regulatory Agency. Mr. Bent will provide the Panel with the United Kingdom's perspective on industrial ethylene oxide device sterilization.

Mr. Bent, would you please begin when you're ready?

MR. BENT: Good morning to everyone. It's truly an honor to come here and present, on behalf of the MHRA, a UK perspective on industrial EtO medical device sterilization. So thank you very much. Thanks for the invitation.

So just to give you some background, because I'm not too sure how many people are aware of the MHRA, what do they do? So we'll just take through that part quickly. We're a medicines and healthcare products regulatory agency composed of three main divisions. One is CPRD, which is Clinical Practice Research Data, which looks at a lot of data from around a number of practices in the medical field; NIBSC is well known in terms of microbiological standards; and the MHRA itself.

So what is the role that we actually look at in MHRA? Well, safeguarding patient

safety and public health are key indicators. We recognize there are various communities, and we reach out to all of those. So the device is not the end game; in fact, it's the cement that ties all of those areas together. So engagement with patients, public healthcare professions, promoting reporting incidents, dissemination of safety information alerts, encouraging safe innovation, and regulation, which is key, there's not going to be a kneejerk reaction to many situations, and trying to facilitate better practice with shareholders in an honest brokerage between regulators.

The scope: We deal with a whole range of medical devices, and you're possibly thinking so where does ethylene oxide sterilization fit into all of this? We'll get there, we'll get there.

Our organization in the MHRA composes of about 1,200 people, which consists of doctors, nurses, a whole range of specialists who come from industry, worked in practice, and now are working as civil servants bringing their specialization into this field to give better advice and support and innovation.

What is a medical device? Clearly, as part of the UK, we are part of a European medical device regulatory territory, and that comes with its own slightly different to what you have here in the States, and we'll try to touch on some of the differences and how we go about looking at that as device safety and ensuring the device is intended to be used by the manufacturer and that can be delivered.

Devices come in all shapes and sizes. Is ethylene oxide sterilization a device? Well, not really. It wasn't before. The reason why it's a device is because it was an accessory to a medical device. For a medical device that needs to be sterilized, it needs to go through a sterilization process. Ethylene oxide is that process that enables it to be sterile at the point of use. So just a clarification, the processes that determine sterilization are controlled to enable a sterilized device or a medical device.

Obligations on the manufacturer: These are quite critical. Obligations on the manufacturer to place the C mark, which is the conformity assessment for a medical device to be placed on the market in Europe, has to be acceptability of its safety, fit for the intended purpose, and that's what that C mark means. It doesn't mean that it's going to outperform' it just means that it's gone through a number of conformity assessment processes.

Safe: The risks associated with the use of an acceptable, taking into account all the expected benefits. It's used in accordance with the manufacturer's instructions, and that's just one aspect.

The way how the landscape in Europe consists, you have a competent authority, a regulatory agency such as the MHRA, who appoints a notified body. A notified body is an independent commercial organization that assesses manufacturers of a certain class of device. They have in-house experience and knowledge to look at certain aspects of conformity assessment, and they primarily assess conformity for Class II and Class III medical devices.

There are a number of medical notified bodies in Europe that are consistent, and there's a few of them there. BSI is probably well known to many of the companies here in the states.

We've touched on this point already, so I'll go straight on. Well, there's about 600 [sic] medical devices ranging from Class I all the way to Class III. So the importance of sterilization, how does this fit in? Well, devices that are intended to be sterilized have to go through a sterilization process. Ethylene oxide, in many cases, is the preferred option. In the UK and across Europe, in the region of 50 to 60% of single-use medical devices go through that process. That's a significant number. And that's just an outline of the classes of devices. So, typically, we're going to touch on health facilities as well as manufacturers

who sterilize medical devices.

Class I are typically devices that are reprocessed by healthcare facilities, hospitals who use transient devices. Transient devices are devices that are used in surgery that are in contact with a patient for less than 60 minutes. So in a particular theater operation, that's low contact.

Class II devices could be a device that is in contact with a patient for above 60 minutes up to 24 hours, which is short term.

And then you get long-term devices which are implanted. They typically could go through a sterilization process, single use.

Reprocessing of medical devices typically are Class I devices at low risk because of its transient nature. Class II and above could be implanted forever or for a short term or up to 30 days. And, typically, they would be using one of the methods of EtO sterilization or gamma radiation of that nature.

So coming back to regulations, so in my team in the MHRA, there are essential requirements that we look at, and that may be biocompatibility, safety, clinical data, electrical safety, labeling instructions, so they've been broken down to different levels that mean different things, is it safe, is the device safe, has it met all of those conformance assessments and routes to assessment to determine whether it's safe.

At the bottom we've got sterilization. Sterilization has multiple methods of sterilization. Ethylene oxide is one of them. Probably the largest used in terms of single-use devices, for Class II and above. In the UK, Class I devices are pretty much steam, moist steam method of sterilization.

So when we talk about ethylene oxide, we have across Europe and in the UK, we use standards, we have directives that translate into regulations, and on a level for manufacturers and the public, there are standards that we refer to. The one that is

predominantly used for ethylene oxide is BS EN ISO-11135, which is a known standard for ethylene oxide. The fact that it comes in several different versions across Europe and in the UK as well as internationally as an ISO standard, ISO standards are basically harmonized standards that have agreed consensus across a number of different regulatory regions. So, therefore, part of the context is taken, and parts have been rejected through consensus.

The inclusions: The international standard specifies the requirements for the development, validation, and routine controls of ethylene oxide sterilization processes for medical devices in both industrial and healthcare facility settings and the knowledge and similarities and differences between them.

So there's an acknowledgement that there is a difference between what a manufacturer does in terms of sterilizing using ethylene oxide and what a healthcare facility may do in terms of sterilization, and it's about on picking highly specialist types of organizations and also trying to recognize, I think it's on Note 2, what is the primary aim of a healthcare facility? Well, they're to provide health and services to patients. And the standards try to reflect that and try to basically connect with the different communities to understand their needs, their challenges, and work with them to make sure that what they're doing is fit for purpose and right.

There are several other exclusions that are drawn. In the international standard, which is 11135, attention is drawn to national and regional requirements for designating a medical device is sterile. So, therefore, it reaches out to other documentation that has been harmonized to show that. So one standard doesn't capture everything; it reaches out to other standards and other specialties. So that actually forces different parts of the manufacturing process to sterilize for a medical device, which sterilization is one component of that, are connected. And that is quite intrinsic. You're looking for what is the validation, what is the process that binds this whole process together. When it is

operated in isolation, then there will be misinterpretation of what is required. There's also other aspects which we will possibly talk about later on. Further information on safety examples, in the UK there are national and regional regulations which support these standards and work together.

EtO, ethylene oxide, is toxic, flammable, explosive. Where we are looking, EtO sterilization, it is an aggressive method, but it is used primarily on 50% of medical devices. So we're talking about a controlled environment, and that's also making sure that attention is drawn to possible existence in some countries of regulations giving safety requirements for handling this material in a controlled environment. So it's not just one standard; and we've heard that clearly here with the EPA's presentation.

So there is that reaching out and connecting of, yes, I'm trying to sterilize a device and you're going through a critical path to do that, but there are other agencies that need to be involved as well. And that's really important for all aspects because clearly, at the end of the line, there are patients and we are the gatekeepers to ensure that that safety mechanism has been sustained and maintained, and we'll use our powers to correct that, if need be.

There are several other exclusions that force you to reach out, and it's deliberately making that. You have to be a specialist in the field that you're working but also be able to connect with other specialties and understanding their requirements.

The final one that I'll talk about, international standards does not cover methods to determine residual EtO and their reactive position levels. So we reach out to other standards, which I refer to here as 109983, which looks at the biological biocompatibility aspects, which is also important.

The standards provide some good practice in the way of the normative requirements. So the standards, which is produced by a range of manufacturers, academia,

public health, regulatory notified bodies, get together and decide what is required and how it's going to fit together. So that then comes together by sharing that knowledge and information; therefore, you can have some normative information, which is good practice.

And here are a list of some of the other standards that it points to, to ensure that. So it's not looking at one standard; it's looking across a whole spectra of a number of standards that have been brought together by different parts of our communities.

One of the biggest challenges when we look at medical devices, whether you're a manufacturer or whether you are a healthcare facility, is a manufacturer, in terms of the UK's regulatory landscape, they are responsible for validating their processes before they are able to place that device on the market. And that's quite critical. So the manufacturer's instructions for use need to be validated prior to placing it on the market.

If you're a health facility, you're a hospital, then the differences are you're not placing the device on the market, but you're going to be responsible for ensuring that the processes that you use have been validated. And these documents help.

Our collaborations and cooperations: The MHRA works with a number of different organizations, the administrations throughout the UK, in Scotland, Wales, Northern Ireland, EU regulators, the FDA, healthcare Canada, patients and public. So we open up what we do to various communities to get at some of our understanding of their challenges and their needs to ensure that what we do is for the benefit of the patient. We ensure and we look to ensure that medical devices, the benefits to the patient outweigh the risks. And we look at every aspect and whichever community that involves to ensure that they've done their piece in ensuring that this network of activities is consistent, and where innovation is necessary, we look towards that as well. But substantiation, validation, verification, acceptance criteria are all key components in determining that the direction of travel benefits the patient.

Outcomes with the MHRA: We produce medical device alerts, targeted mail to particular centers, clinicians, patient groups. We work with the press to help that. We help with regulators' communications, work with notified bodies, and we have an enforcement action team.

Outside, UK manufacturers of medical devices have been asking for UK-specific guidance. Well, we help work on that to make sure the standards, the directives can be safely interpreted so there is no confusion of interpretations. Essential requirements of directive or regulation, ergonomic features and principles. MHRA aims to clarify the expectations of the regulatory bodies around compliance with the current and future EU medical devices legislation.

So that's what we've got. We've got a number of communities we need to connect. We need to understand what is best practice. We need to understand better how each community communicates what their specifications are and make sure that these are wrapped up into one coherent strategy. And that's what we do as a UK perspective for medical device sterilization using any method of sterilization, which includes the highest percentage, which is ethylene oxide.

Thank you. I'll hand it back over to the Chair.

DR. LEWIS: Thank you, Mr. Bent.

I would note for the Panel that after the next four presentations from the FDA, we will have a 20-minute period for questioning of all eight presentations preceding that. So for panelists, if you would note your questions down for each of the presenters, we'll have an opportunity to go to some clarifying questions at that time.

I would like to also note that Dr. Eugene Kim, who was not here for the initial round, has joined the Panel, and I would like to ask Dr. Kim if he would briefly state your area of expertise, your position and affiliation in regard to the Panel today.

DR. KIM: Thank you. I'm Eugene Kim. I'm a Professor of Surgery and Pediatrics at the Children's Hospital Los Angeles and USC Keck School of Medicine.

DR. LEWIS: Thanks very much.

We now will hear a series of four presentations from the FDA regarding the oversight of medical devices and their sterility. Dr. Adam Saltman will kick off the series by addressing the FDA's Center for Devices and Radiological Health's role in mitigating shortages of critical medical devices across the country.

Dr. Saltman, would you please begin when you're ready?

DR. SALTMAN: Yes. Good morning, and thank you. My name is Adam Saltman. I'm a cardiothoracic surgeon on the clinical and scientific policies staff in CDRH's Office of Product Evaluation and Quality, or OPEQ. I'm also the clinical shortages lead.

One of the most important things that CDRH does is to ensure that patients have access to high-quality medical devices. When a device shortage occurs for whatever reason, it is of concern to us. It is for that reason that CDRH has set up a process to prevent and mitigate the risk of patient harm due to device shortages, and that is what I will be discussing.

For the next few minutes I'm going to cover the following topics. First, some background on what shortages are and why they appear. Then I'll provide some insight into our internal processes and how we approach shortages and potential shortages. As part of that, I'll cover some definitions we use as well. And, finally, I'll show you some examples of tools we use, as regulators, in helping to address and hopefully mitigate shortages.

First, what is the definition of a medical device shortage? While there is not a formal regulatory definition of a shortage, CDRH has a working definition we use; that is, a medical device shortage is a period of time for which the demand or projected demand for a medical device within the U.S. will exceed the supply or projected supply for that device.

But a definition does not tell us how or why medical device shortages happen.

Although this is a complicated slide, I think it draws an important comparison, that is, between the ideal market behavior we all learned about in high school on the left and the medical device market under the abnormal conditions of a shortage on the right. As we have learned, under ideal conditions as price rises, demand falls, in the green line, and supply rises, in the blue line. The two lines will meet at a point of equilibrium, and the price and quantity are set. Small perturbations in the market are handled by normal adjustments in supply and demand until equilibrium is reestablished. So, generally speaking, shortages in the ideal state are usually temporary.

The medical device market, however, differs from the ideal in two important fundamental aspects. The first is that demand is not responsive to price but rather fixed, fixed closely to the medical demand for the product. In other words, we don't implant fewer pacemakers because they cost more money.

So I've drawn the medical device demand line, here in red, as mostly flat. Medical device supply is also not as responsive to price, but this is mostly because ramping up device production is a complicated, expensive, and time-consuming affair. So the supply line is also pretty flat, and when a natural disaster or a critical supply crisis comes along, such as the loss of sterilization capacity, that affects many devices, and so supply is not only flat but it is severely depressed, as I've shown in the purple line. This means that a medical device shortage, rather than being a small market perturbation, becomes instead a significant gap between supply and demand, that is between the red and purple lines, and it often persists, sometimes becoming permanent.

Now, if you imagine for a moment extrapolating those lines all the way out to the right in an attempt to achieve a point of equilibrium, you'll quickly realize that in a shortage situation, the medical device market may experience very high prices, which brings about

abnormal conditions such as black marketeering, hoarding, counterfeiting, and even smuggling. Considering all of what I've just shown you, it's not hard to imagine how medical device shortages can therefore significantly adversely impact patients and healthcare providers and put patients at serious risk of harm.

But what are some actual situations that can cause medical device shortages; that is, when would demand for a medical device outstrip supply? Demand increases, which I've shown here on the left, appear when the user population grows. Examples of this are when expanded indications for use appear, expanded coverage determinations happen, and practice patterns evolve, for example, when physicians start to use devices over more traditional non-device therapies. Generally, these are fairly unusual in our experience, and they tend to happen fairly slowly, which gives the market some time to react as competitors or alternative devices may appear. Although not necessarily resolving as quickly as in the ideal market situation I showed you in the last slide, shortages for demand increases tend to be fairly temporary.

Far more common, however, are the decreases in supply. We see these almost every day, and they appear quite suddenly. Examples would be device removals from the market because of a recall, a manufacturer leaving the market because of business reasons, supply chain interruptions because of a loss of raw materials or a critical process such as sterilization, and manufacturing disruptions due to external forces such as new rules or regulations or a natural disaster. In our experience, shortages because of supply decreases tend to be fairly long lasting and can sometimes be permanent.

So how does CDRH approach and handle these shortages and potential shortages? I'd like you to envision our process as a cycle, each quadrant of which I'll explain in a little more detail in the next few slides. The trigger or start of the process is when CDRH becomes aware of a situation that either is or might be a shortage. The first thing we do

once we appreciate that signal is to reach out to many stakeholders to gather as much information as we can. We then organize, filter, and analyze the data using our shortage assessment tools so that we can design a plan to mitigate the shortage to the best of our ability. After the mitigation plan is operational, we go into a monitoring and maintenance phase where we keep track of the shortage and modify the plan as necessary. The cycle repeats itself as new information becomes available, and it is hopefully terminated when the shortage resolves.

First, as I said, we gather information. But from where do we get it? At the outset, it's important to bear in mind that CDRH does not always hear first from manufacturers that a device may be in shortage or a shortage is anticipated. In fact, as this somewhat complicated diagram shows, our information comes from many sources. I hope that by grouping them together, I've illustrated to you how very different kinds of information are exchanged in order to get a holistic picture of the device landscape.

Stakeholders such as patients, professionals, and user facilities provide us with the user's perspective. Distributors, manufacturers, and group purchasing organizations tell us about the commercial situation. Our internal data sources such as geographic information systems and our registration and listing database provide us with information about the impacted devices and the firms that make them. And interactions with other regulatory agencies, federal, state, and local, help us to understand the situation from their perspectives. I hope you can see that, regardless of the respective space, every one of these stakeholders touches or is touched by a medical device, and all have an interest in resolving or preventing a shortage of that device.

I'd also like you to notice that I've made the information arrows bidirectional. This is important because we do indeed work both proactively and reactively, sourcing and receiving information to and from many of these stakeholders repeatedly throughout the

life cycle of a shortage.

Once we have gathered enough information to understand the situation, we organize it, filter it, and use our analysis tools. We generally proceed in this order: First, we take a look at the economics and logistics of the problem using a shortage assessment tool. Second, as part of our medical necessity determination, we examine the clinical properties of the device in shortage, whether a lack of availability would affect public health and what alternatives are available. Lastly, we formulate a shortage management plan which often changes throughout the life cycle of the shortage as information changes. This enables us to always seek the most effective mitigation of the shortage as it evolves. In the next few slides I'll explain these tools in more detail.

First, the shortage assessment tool: The purpose of this tool is defined here. Simply stated, we try to determine the likelihood that a device cannot be maintained or obtained in sufficient amounts regardless of the cause. The tool takes into account the individual manufacturer's situation as well as the availability of any alternative drugs, devices, or other mitigations. As such, this is our economic and logistical assessment.

The medical necessity determination, in contrast, is the clinical analysis of the situation, that is, the examination of the device in shortage and the impact of its shortage on public health. The MND, as we call it, is completed by a clinician familiar with the device and the disease space. The MND is where we incorporate thinking about the disease or condition, the role and clinical importance of the device, and the benefits and risks of potential mitigations and substitutes.

Our published guidance document, which is titled "Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Enforcement, and Compliance," asks our reviewers to consider whether a device is medically necessary. This is based on whether it is essential to the survival of patients. In other words, would a shortage of that device harm

the public health, and if so, we try to determine the medical necessity of the device, and we consider certain characteristics. I've listed some examples here.

There are some important observations that come from reading this list. For example, if a device is used to treat a serious condition but there are many acceptable alternatives available, then we would not consider it to be medically necessary. On the other hand, if a device does not necessarily treat a serious disease but it's an orphan, then it may very well be necessary for that patient population.

We have found that a fortunate side effect of establishing whether a device is medically necessary or not is that it helps us conserve our scarce resources. It just isn't possible for CDRH to direct its efforts at keeping every single one of its devices in full supply. By directing our resources chiefly at maintaining the supply of those devices where a shortage would impact the public health, we are best positioned to achieve our mission.

And by the way, we do emphasize that just because clinicians or patients may prefer a particular device, we don't typically use that as a reason alone to determine the device to be medically necessary. We appreciate that everyone has favorites, but in times of scarcity, it's responsible to use whatever is an acceptable alternative.

Taken together, the shortage assessment and the medical necessity determination form the foundation of the shortage management plan or how CDRH and stakeholders plan to mitigate the shortage. This brings us to the mitigation and monitoring stages. Besides briefly summarizing the situation and a relevant background, the meat of the shortage management plan is to explain why the device is essential, why FDA believes access to it should be maintained, under what qualifications that decision would stand or be revised, the roles and responsibilities of all of the affected stakeholders, what FDA and the stakeholders plan to do to mitigate the shortage, how the situation will be monitored, and when the shortage will be considered terminated.

The shortage management plan, as I've said, is a living document, and as the situation develops, the cyclical process I've shown you allows for a continual reevaluation and revision of the plan.

Finally, and I've been alluding to this throughout the talk, what can FDA do about a shortage? To answer that, I'd like to show you some examples of the tools we have to mitigate shortages. I divided them into two broad categories, regulatory tools and communication.

Regulatory tools aim at getting and keeping devices on the market to bridge the gap. For example, we can expedite the review of manufacturing site change requests and marketing applications. Another example would be allowing a product to remain on the market that hasn't undergone a formal FDA premarket review but for which FDA has enough information to establish a reasonable level of confidence that the device being introduced is safe and effective, at least for use to bridge the shortage. An example would be the temporary importation of a device from abroad or allowing a device to be used beyond its labeled expiration date.

Communication is the other category. By communicating frequently and transparently, FDA believes that informed stakeholders become enabled to make the best decisions for them to choose what is in their best interest. For example, we publish webpages about specific shortages; we update them frequently as information becomes available. We reach out to affected stakeholders as early and often as we can. A very short list of such stakeholders would be other government agencies, manufacturers and trade associations, health professional associations, distributors, group purchasing organizations, and of course, patients and hospitals.

So I hope that in these few minutes I've been able to give you a bird's eye view of why and when shortages appear, how CDRH approaches shortages and potential shortages,

and a brief insight into the definitions, processes, and tools that we use to help mitigate shortages. Thank you for your attention.

DR. LEWIS: Thank you, Dr. Saltman.

We'll next hear from Dr. Karoll Cortez, who will present on the clinical impact related to the shortage of industrial ethylene oxide sterilized devices.

Dr. Cortez, would you please begin when you're ready?

DR. CORTEZ: Thank you. Good morning. My name is Karoll Cortez. I am a medical doctor board certified in both internal medicine and infectious diseases. I am going to speak on the clinical ramifications of medical device shortage.

Of all medical devices provided sterile in the United States, over 50% rely completely on industrial ethylene oxide sterilization. This accounts for more than 20 billion devices annually. There are some devices for which only ethylene oxide sterilization has been validated. Some examples of these very important life-saving, life-sustaining, and otherwise clinical medical devices include heart valves, pacemakers, and left ventricular assist devices. There are also other medical devices used in large quantities for the day-to-day care of patients that rely completely on ethylene oxide sterilization, such as surgical kits and sutures used in emergency procedures such as C-sections and treatment of acute trauma patients.

FDA keeps information on each cleared or approved product in an internal database that specifies the particular product, its manufacturer, and the validated sterilization modality. Medical devices made from certain polymers, plastic or resins, metals or glass, or that have multiple layers of packaging or hard-to-reach places -- for example, catheters -- are likely to be sterilized with ethylene oxide. A sterilization with other validated methods can ultimately lead to degradation of the materials in the device and therefore are not compatible.

This slide here lists some of the many different medical devices sterilized using ethylene oxide.

To illustrate the issues related to medical device shortage, I want to walk you through a recent example of tracheostomy tube shortage. With the closure of the Willowbrook EtO sterilization facility, FDA looked to identify and mitigate any potential problems related to medical device supply. We were especially focused on medical device supply problems that could delay or disrupt critical care. Despite our best efforts, there was a shortage of the Bivona tracheostomy tubes made by Smiths Medical. These tubes are used in hospitals and at home to help adult and pediatric patients breathe. Although the Bivona tubes are indicated for use in both adult and pediatric patients, a temporary shortage is more likely to impact the pediatric patient because supply of alternative tracheostomy tubes is limited.

The pediatric patient requiring these tracheostomy tubes are a very vulnerable population. They are often born with congenital abnormalities of the respiratory tract and compromised immune systems of various degrees. Because of these congenital abnormalities, these patients often undergo many surgical procedures, and some of them depend on these tracheotomy tubes for ventilation permanently. This device undergoes EtO sterilization as part of the manufacturing process.

The neonatal tracheostomy tube can be reprocessed up to five times, after which it should be replaced by a new tube. Reprocessing should be done following the manufacturer's FDA-cleared instructions for reprocessing. Reprocessing outside of what is in the instructions for use is not recommended as it is unknown if additional reprocessing would damage the device or otherwise render the device unsafe and/or ineffective.

This slide represents a simplification of our very complex healthcare ecosystem. Here, the centerpiece is safeguarding patients and public health. FDA recognized the

challenges to shortage imposed for these pediatric patients who need access to new tubes now. We worked with all the stakeholders to limit the negative impact to patients as much as possible. We did this by communicating the shortage situation, informing the public on device reprocessing, to increase from shortage management working groups at large healthcare facilities and helping the manufacturer move their sterilization to another facility. FDA worked with the manufacturer to implement a real-time review of the sterilization process validation for Bivona tracheostomy tubes at the new EtO sterilization facility. This real-time review of the data expedited the return of the product to the market, preventing a need for extensive rationing or triaging of use.

Medical device shortages can impact patient care with varying severity depending on the acuity of the shortage, the type of device and its intended use, and the effectiveness of the implemented mitigation measures. Prompt action by FDA and other stakeholders can minimize or prevent adverse consequences due to device shortages. However, if a sterile medical device is essential and irreplaceable or unavailable, physicians are rendered unable to make diagnoses or provide lifesaving therapeutic interventions.

I hope I have provided you with a medical device overview of the shortages and the consequences and how quick instituted planning as well as clear, transparent, and frequent communications are needed to protect patients.

Thank you very much for your attention. Now I'd like to return it to the Panel Chair to introduce our next speaker.

DR. LEWIS: Thank you, Dr. Cortez.

Next, we'll hear from Mr. Steven Elliott, who will provide us with an overview of industrial ethylene oxide sterilization.

Mr. Elliott, would you please begin when you're ready?

MR. ELLIOTT: Okay, good morning. My name is Steve Elliott, and I'm a scientific

reviewer, sterilization subject matter expert, and biochemist in the Office of Surgical and Infection Control Devices. The topic I am presenting is an overview of industrial ethylene oxide sterilization of medical devices. This presentation is limited to discussion of industrial sterilization processes and is not intended to address a small chamber of medical devices in a healthcare setting.

My objectives for this presentation are to briefly describe the status of ethylene oxide for the industrial sterilization of medical devices, explain the characteristics of an ethylene oxide sterilization cycle, and provide a simple description of the elements involved in validation of an ethylene oxide sterilization process.

Approximately 40% of medical devices are terminally sterilized in industrial processes prior to distribution to users. Of these sterile devices, approximately 50% are sterilized using ethylene oxide with 40 to 45% being sterilized with gamma radiation and the balance sterilized with thermal or other radiation or chemical processes.

The reasons for the use of ethylene oxide are broad material and device compatibility. Many materials can be processed with the sterilant without functional alteration or biocompatibility concerns. The processes can be gentle enough to handle delicate devices that are sensitive to moisture or high temperatures.

Process flexibility: The parameters of these processes can be adjusted to address load and device challenges.

Penetration through multiple layers of packaging: High throughput processes allow processing of pallets rather than individual packages.

Large capacity facilities: Many sites have multiple chambers from small to very large and can process large volumes of devices daily.

And understood regulatory expectations: These processes have a long history of use, and the processes are familiar and well understood from a medical device regulatory

perspective.

Any sterilization process, including ethylene oxide, requires validation to ensure that it can produce sterile product. The product being sterilized must be defined. This is not limited to the medical device itself. The dimensions, materials of construction, load density, packaging types and amounts, type and amount of microbial contamination, and load configuration can all impact how easy or difficult it is to sterilize a load of medical devices.

If the product is going to be sterilized, you need to know how to do it and what to use. The equipment needs to be characterized and the process defined. The sterilizer, sterilization conditions or parameters, and load being processed are all defined. The size, composition, organization of the load are all known. So many packages, boxes, pallets will be placed in this chamber and are subjected to these sterilization process parameters to yield sterile product.

But the way to have assurance of sterile product is to validate the process or make sure it can kill microorganisms to the threshold that it is supposed to do. Sterilization processes are supposed to meet a predetermined sterility assurance level that can theoretically be equivalent to killing up to a trillion challenge microorganisms.

Validating a sterilization process involves several qualification activities to ensure that the sterilization site, equipment, and process all are or perform within defined specifications. These activities are intended to demonstrate that a sterilization process can deliver the kill or lethality expected for the process.

This is a simplified representation of an ethylene oxide sterilization process. Ethylene oxide sterilization processes generally begin with preconditioning or conditioning phases. Preconditioning can be performed to ensure that appropriate load humidity and temperature, two critical ethylene oxide sterilization parameters, are reached in the most challenging positions of the load prior either to entry into the sterilizer and/or initiation of

the sterilization cycle. The duration of this phase depends on the size and composition of the load. Humidification and temperature equilibrium may also take place in the sterilization chamber itself. Bigger, denser loads with more porous materials may require much longer preconditioning phases.

The added diagram shows the in-chamber sterilization process. Air removal pulses are used to facilitate movement of the sterilant, gaseous ethylene oxide, into the load. The vacuum pulse conditions depend on the sensitivity of the devices and/or packaging to pressure changes. Steam injections are used to maintain acceptable moisture levels for ethylene oxide sterilization, and ethylene oxide is injected into the chamber, possibly followed by inert gas, like nitrogen, to push sterilant into the load.

The exposure or dwell phase involves allowing sufficient concentration of the sterilant to the most difficult areas to reach for a specified period of time to meet the process lethality requirements. Along with exposure time, temperature, ethylene oxide concentration and relative humidity govern the rate of kill or inactivation of microorganisms in the load. Ethylene oxide is then removed using vacuum with inert gases used to ensure that flammability limits are addressed.

On the right side of the diagram aeration is shown. Following exposure, aeration is used to reduce the sterilant residuals to safe levels, often employing elevated temperatures and multiple air exchanges. This can occur inside the sterilization chamber or in a specified aeration chamber.

Moving back to the validation activities, after the sterilization site and equipment are qualified, performance qualification activities are performed to ensure that the process can kill or deactivate the microorganisms at the intended rate and to the intended thresholds. These are used to extrapolate the sterility assurance level for the process. This is usually 10^{-6} and is generated by extending the sterilization exposure phase well beyond

conditions established to kill all microorganisms on a challenge load up to over 1 million per challenge site. The validated process may have sufficient lethality to kill 1 million times 1 million or one trillion microorganisms from worst-case challenge sites.

In addition to microbial performance qualifications, physical performance qualifications are used to show that the process parameters established to achieve sterilization in routine processing can consistently and reproducibly be met.

In addition to the validation activities used to demonstrate that the process can adequately kill to effectively sterilize devices, systems need to be put in place to control and monitor the process as well, for decision making on the release of sterilized loads. A system also needs to be put in place for ensuring that the process continues to maintain effectiveness over time.

There are additional tests associated with the sterilization process, not directly connected to demonstrating kill or lethality. Ethylene oxide residuals remaining on devices is a biocompatibility concern. Adequate removal of residuals after sterilization has to be demonstrated.

Endotoxin and pyrogen tests are conducted to address pyrogenicity of devices following sterilization and support evidence of absence of fever-inducing materials from devices.

Packaging testing must be conducted to ensure that barriers intended to maintain sterility will function correctly and can prevent contamination right up to the time of use for the device.

In conclusion, I provided a brief summary of the status of ethylene oxide for industrial sterilization of medical devices, explained the characteristics of an ethylene oxide sterilization cycle, and provided a simple description of the elements involved in the validation of an industrial ethylene oxide sterilization process.

At this time I'd like to yield back to the speaker.

DR. LEWIS: Thank you, Mr. Elliott, for the excellent presentation.

We will now hear from Mr. Christopher Dugard, who will present on how the FDA reviews sterilization information in premarket regulatory submissions for medical devices.

Mr. Dugard, will you please begin when you're ready?

MR. DUGARD: Thank you. Good morning. My name is Chris Dugard, and I'm a biologist and a reviewer on the sterility devices team in the Office of Surgical and Infection Control Devices. This morning I'm going to be talking to you about how the FDA reviews sterilization information and premarket regulatory submissions for medical devices.

FDA separates sterilization into two categories: industrial, which my colleague Steven Elliott touched on, and healthcare sterilization.

Industrial sterilization is typically used for terminally sterilized product. This means devices that are sterilized at the end of the manufacturing process prior to being released to the market. Industrial sterilization facilities are large and typically sterilize large numbers of devices on an industrial scale and mixed loads. These facilities are routinely inspected by the FDA to ensure they have validated sterilization processes that meet FDA-recognized standards. FDA does not regulate these facilities. Rather, we regulate the sterilization processes these facilities utilize.

Healthcare sterilization refers to any medical device sterilization that occurs in a hospital or healthcare setting, both the sterilization process and the device itself. This can be either for products that are end-user sterilized or are reusable. Healthcare sterilizers are small, with small chambers that typically have limitations on load materials and the weight. They are cleared with a specific set of accessories, for example, biological indicators, chemical indicators, and wraps that also have their own recommended performance testing.

I will now go more into how we review sterilization information and what FDA typically needs to support a premarket submission.

Manufacturers of terminally sterilized devices are encouraged to use our sterility guidance. This is the full title on the slide. This guidance divides up various sterilization methods, modalities, into three general categories.

Established Category A are methods that are well established with recognized consensus standards and a long history of safe and effective use. This includes moist heat sterilization, ethylene oxide, and radiation and dry heat.

Established Category B modalities are methods with no recognized consensus standards, but FDA has some experience evaluating the modality. This includes, for example, hydrogen peroxide, ozone, and flexible chamber systems.

The third category is for non-traditional or alternative sterilization methods, in other words, methods with little to no published information and limited to no history within the FDA.

The information typically needed for these categories in a premarket submission varies. I will discuss this information in the next slide.

Terminally sterilizing a medical device makes sterilization part of the manufacturing process, which FDA does not review in a 510(k). FDA does not regulate the sterilization facility, as I mentioned earlier. However, FDA does regulate the process, so we review the information needed to ensure a device is sterilized to an adequate assurance of sterility. I'll go over specific information that's needed in the next slide. However, we do review manufacturing controls and applications for Class III devices. So in those situations we review full validation reports even for a terminal process.

Healthcare sterilization utilizes FDA-cleared sterilizers in a healthcare setting, whether it is for end-user sterilized single-use devices or reusable devices for reprocessing.

FDA clears these sterilizers with specific cycle conditions that have been shown to meet an adequate assurance of sterility. These submissions also involve concurrent review of any accessories such as biological indicators, chemical indicators, wraps, and trays.

If a device is indicated for sterilization using an FDA-cleared sterilizer, FDA would like to ensure the end user has access to a cycle that will provide an adequate assurance of sterility. For this reason, FDA recommends submitting full validation test reports for review.

There are also additional requirements outlined in FDA's reprocessing guidance that need to be addressed. For example, there are additional requirements on use life and labeling.

Now I'll discuss the general information needed in a 510(k). For Established Category A or B methods, which I described earlier, we would like to see a description of the method, description of the sterilization chamber if it is not a rigid chamber, the sterilization site, sterilant concentration and residuals for chemical sterilants, the validation method and standards used, the sterility assurance level, pyrogens (if applicable), a description of the sterile barrier, and a summary of the methods used to support package integrity. This information can all be provided in a summary format.

For non-traditional or alternative methods, a more detailed review is needed. We recommend that full validation reports be submitted with as much detail about the method, validation, material compatibility, and residuals, etc., as possible to ensure FDA has enough information to support that the method can achieve an adequate assurance of sterility.

The sterility information typically needed for other premarket submissions other than a 510(k), like an IDE or PMA, are different. For IDE, since the device is not yet being marketed but is being exempted for use in a clinical trial, FDA recommends providing enough information to support device sterility throughout the investigational period. This

may be a single-lot release or a full validation of the final terminal process. However, in many cases full reports are recommended for review.

As mentioned earlier, manufacturing controls are reviewed for Class III devices, so additional information is typically needed for a Class III device submission like a PMA, even for terminal sterilization processes.

So I just provided a high-level overview of how the FDA reviews sterility information in a premarket submission. With that, I will turn the meeting back over to the Panel Chair. Thank you.

DR. LEWIS: Thank you, Mr. Dugard.

We'll now have an opportunity for some questions from the Panel regarding clarifications. Could I ask all eight presenters from the morning to please assemble here beside the table so that the questions can be directed to you? Thank you.

While the Panelists are preparing their questions, perhaps I can begin by directing a question to one of the last four presenters. You have given some general remarks about methods of sterilization and the fact that ethylene oxide is used for a little over 50%, gamma radiation for around 45%, and all other methods for basically less than 5 to 10%. So the first obvious question that comes up is to what extent could ethylene oxide sterilization be replaced by gamma radiation or other radiation, since those are the only two forms which seem to form the majority? And I would actually leave that open to whomever feels most competent to answer it.

MR. ELLIOTT: Okay. Well, that question would really depend on several factors. So, unfortunately, there isn't a clear and easy answer for that. Some devices may be sterilized with ethylene oxide for convenience and known regulatory history but may have compatibility with other processes such as gamma radiation; some devices may not, and the only way to determine that would be essentially take those devices, sterilize them with the

intended processes, whatever they may be, and then perform the full gamut of testing on them. So there is a burden associated with changing from one sterilization modality to another.

DR. LEWIS: Are there obvious types of devices for which radiation sterilization is not satisfactory as a replacement for ethylene oxide?

MR. ELLIOTT: Yes. Yes, there are. Radiation-based sterilization processes are going to generally be deep penetrating and can have an impact on device materials, potentially compromising integrity. You need to establish adequate performance and that the device could meet all specifications after exposure to worst-case sterilization processes with something like gamma or x-ray radiation.

DR. LEWIS: Has any quantitative analysis been done at the FDA to try and evaluate the specific devices for which radiation could replace EO?

MR. ELLIOTT: To my knowledge, no, not in detail.

DR. LEWIS: Okay.

Dr. Saltman, you addressed in some detail about the supply-demand parameters in regard to these. At the present time, given the situation you all are confronting, how severe do you think the problem is with the situation in regard to industrial sterilization?

DR. SALTMAN: Well, as I was pointing out in the supply and demand concept, the issue with industrial sterilization is that there has been limited supply, and because some of the sterilizers have been shutting down, any capacity has now been essentially fully utilized. So that line that I showed you is going to go completely flat. So as we run across different manufacturers trying to find other sites, it's becoming less and less possible for them to do so.

DR. LEWIS: So in your assessment, are there examples that have currently come to FDA's attention in which device shortages are currently occurring?

DR. SALTMAN: Yes, I actually was going through a list earlier this morning. We've had about 10 or 12 or so manufacturers who've approached us looking for potential alternatives, and we've been able to provide them, of course, with a list of all of the registered sterilizers, but particularly the smaller firms are having trouble because of the burden imposed upon changing a site, the time burden, the regulatory burden, the cost, and so they are the ones that are most alarmed and are not able to supply their customers.

DR. LEWIS: Thank you.

Questions from the Panel? Dr. Burr, go ahead.

DR. BURR: Thanks. This is probably for EPA or ATSDR. I know we're going to have some discussions on this a little bit later, but that's from the commercial companies involved, and I think I'd rather get the government perspective.

The obvious issue is that these plants are at risk of closure because of failure to abate EtO emissions, so the obvious question is what systems of abatement are used now, and why aren't they effective? Abatement systems can be extraordinarily effective and simply, if properly implemented, prevent the problem. I agree there are other issues that might affect plants, but the Willowbrook plant clearly was closed for that reason. So I wonder if you guys could provide a little perspective on what abatement is used now and why it's not effective.

MR. KOERBER: So the problem that we're seeing is not necessarily noncompliance with EPA standards. As I mentioned earlier, the standards that were set are somewhat dated by EPA. In fact, the emission standards we have for commercial sterilizers are over 15 years old and definitely need to be reviewed, and we have a mandate under the Clean Air Act to do that. And we do have more recent information. The updated cancer potency value that we have for ethylene oxide that I mentioned is something that in our most recent National Air Toxics Assessment did identify a number of communities around the country

that are at risk for elevated cancer, and that's what we're currently trying to deal with, and that is a reaction we're seeing from many of these communities in that they are surprised about the existence of these sterilizers in their communities. They know if there's a chemical plant down the street, they can see it, they can smell it, they can hear it every day. Commercial sterilizers are not so obvious, and many of these communities have acted very strongly, as you're quite aware, and their actions have driven some of what's happened within the industry.

DR. BURR: So just a quick follow-up. So how much additional abatement -- I realize that's a slippery question -- would be required to get these plants to the point that they would comply with your projected standards?

MR. KOERBER: We will go through a rulemaking and take public comment on that. We're in the process of gathering data. We don't have a safe level. We don't set air standards for ethylene oxide. For some air pollutants we do, ozone, particulate matter, we do under the Clean Air Act have authority to set a safe level and manage to that level. In the case of air toxics like ethylene oxide, we set emission standards, and our goal is to reduce emissions and to manage risk accordingly, but we don't have a safe level in the air that we're shooting for.

DR. LEWIS: It's my understanding, at the Willowbrook facility, that one of the precipitating issues was a higher instance of cancer in the folks that lived in the vicinity compared with averages of the state of Illinois. Correct me if that's not correct; that's what I gathered from the Executive Summary. Have similar studies been done in any of the multiple industrial facilities that exist across the country? There are, I gather, at least two or three dozen other large facilities of that type. Has similar data been collected from them?

MR. KOERBER: So our most recent assessment identified about 20 areas with the

potential for elevated cancer risk. In about half of those cases, we're talking about chemical plants, and the other half we're talking about commercial sterilizers, and in all of those areas, EPA is working with state and local air agencies to gather more information to better understand the risk and in some cases actually put out air monitors.

Dr. Reh hit it right on the nose earlier when he said our concern with ethylene oxide is long-term exposure. The information we have currently suggests that there is no immediate short-term health concern. Longer term, however, there is a concern, and we need to get better information on long-term exposures. Also, as Dr. Reh said, our challenge on risk communication is to deal with community members in an effective and appropriate way in communicating that information to them.

DR. LEWIS: Thank you.

Dr. Kim.

DR. KIM: Thank you. As a follow-up to that, I had a question for Dr. Reh.

You had mentioned a biomarker, the EtO hemoglobin marker. What can you tell us with regard to any preclinical work or any clinical human data with regard to those levels and morbidity and disease and cancer formation?

DR. REH: So currently we do not have that connection to preclinical or morbidity or mortality data. This is a fairly new marker from our lab, and we're looking to validate the connection between exposure and the expression of that marker at this stage. We are looking at the NHANES data to give us a good estimate of what background levels of the marker may be, and then we'll go from there. But right now there's still more to learn than what I can tell you.

DR. LEWIS: Dr. Tung.

DR. TUNG: I have a question for the EPA. Being from Illinois, I'm familiar with the Sterigenics thing, at least what the *Chicago Tribune* writes. All the air quality epidemiology

is online, and you can just get to it right away. Is this a Sterigenics problem, or is this a problem with sterilization facilities everywhere?

MR. KOERBER: We're still learning about the extent of the problem. As I said, our focus is on the higher-risk areas. About 10 of the 20 we've identified are associated with commercial sterilizers, and we know a lot about what's coming out of the stacks that might be a result of what's going through a pollution control device, but we're also learning that there are leaks and fugitive emissions that we just don't have a good handle on, and that will take more aggressive emission reduction measures, some of which the industry is in the process of developing and implemented, and they need to be applauded for that, but there's more progress that definitely needs to be made.

DR. LEWIS: Mr. Socola.

MR. SOCOLA: This question is for the EPA. It appears that there's a focus on long-term exposure. What percentage of U.S. citizens live in the same location for 70 years?

MR. KOERBER: When we do our risk assessments, we make certain assumptions, and they're generally conservative in order to be protective of public health. So when we do risk assessments in our regulatory program, we are assuming long-term 70-year lifetime exposures. We don't track, necessarily, movement of people over that 70-year lifetime, but again, we need to make conservative assumptions to be protective of public health.

MR. SOCOLA: Is it realistic to assume that an individual will breathe contaminated air continuously for 70 years?

MR. KOERBER: Again, we just need to make certain assumptions in doing our analyses. We don't do a 70-year analysis, but we do try to estimate through dispersion models, computer models, longer term concentrations and make some assumptions about exposure over the course of somebody's lifetime. But as far as movement across the country of individuals, we don't necessarily account for that.

MR. SOCOLA: I have one more follow-up question. The National Air Toxics Assessment significantly changed in 2014 from that of the 2011 assessment. The American Chemistry Council, among others, believe this assessment is significantly flawed, and they give a number of reasons why. Can you tell me if the methodology for the 2014 assessment was validated, and if so, who validated it?

MR. KOERBER: We do not go through a formal peer review with respects to these non-regulatory assessments that we do every few years. Again, the purpose is to try to highlight those areas that may be at potential elevated risk and to take a closer look in those areas. The initial results are not necessarily a cause for action, but as a result of further investigation, further refinement of the information, directly working with companies in terms of emissions testing, directly working with states who have additional information, they're the permitting authorities, we definitely try to refine the information as a basis for taking any action.

DR. LEWIS: Dr. Dominitz.

DR. DOMINITZ: Thank you.

We've heard a bit about the public health exposure, and I wonder if anybody could comment on occupational exposure and the health effects.

DR. REH: Within CDC, that would be the role of NIOSH, and they do have a current intelligence bulletin on EtO, and they do have some documents on reducing EtO exposures, occupational exposures, in the sterilization industry. They also have done some occupational epidemiology studies. I do not have the information right off the top of my head, but they would be, at least for CDC's response, they would be the agency to turn to.

DR. LEWIS: Yes, Ms. Pekar.

MS. PEKAR: My question is for the FDA. This is Carol Pekar.

As industry, there's a lot of concern out there for innovative products that are being

developed. Folks cannot get time at sterilizers to do their validation. So is the FDA measuring any impact on the future medical devices, you know, in queue by this issue?

MR. ELLIOTT: I'm not aware of specific metrics that would track that element of development, but I'd say we are aware and are concerned with a requirement to sterilize things a certain way. Our goal is to be neutral on that. From a medical device perspective, it is basically a means to an end. We were trying to make sure that products meet a sterile specification, so that would be our goal to do that, and we have activities to try to support innovation now, with our innovation challenges coming through, which hopefully will facilitate, I'd say, an easier regulation of manufacturers who select other methods to process their devices.

DR. LEWIS: Thank you.

We'll have to end the question and answer session because we're a couple minutes over time. We'll try to maintain strict adherence to the schedule this morning in order to give public members and others a chance to present during their time.

So we will now take a 15-minute break, and we'll return here at 10:10. I would caution Panel members to not discuss, among themselves or with any other attendees, any of the subjects at the present time. Again, we'll resume at 10:10 sharp. Thank you.

(Off the record at 9:58 a.m.)

(On the record at 10:10 a.m.)

DR. LEWIS: We will now resume our session. We have a series of presentations now from organizations which will discuss the impact of contract sterilization on the medical device supply chain. Mr. Mark Leahey is representing the Medical Device Manufacturers Association (MDMA).

Mr. Leahey, are you ready to present?

MR. LEAHEY: Yes, I am.

DR. LEWIS: Please begin when you're ready.

Could I please ask everyone to silence their cell phones and silence themselves here so we can get under way?

MR. LEAHEY: Great. Mr. Chair, thank you very much for the invitation and to FDA for participating today. My name is Mark Leahey. I'm the President and CEO of the Medical Device Manufacturers Association. We represent approximately 300 primarily small to midsized medical technology companies in the U.S., and our mission is to ensure that patients have timely access to safe and effective products, and I'm very pleased that you all have assembled a diverse group of stakeholders to discuss this important issue.

I think, as you've heard from the Chair in the opening comments, as well as from FDA, CDC, and the EPA, that this is probably a more complex issue than maybe the Panel has addressed in the past, and I think we also understood that the factors and the cascading impact of certain decisions are something that we must understand before, you know, additional steps are taken, particularly as it relates to shortages I'll get into in a moment.

You know, we've spoken to our members and surveyed our members and, in fact, had a board meeting a couple weeks ago, and I can tell you the urgency here, and the concern, if additional facilities go down, is real. And I think as was indicated at the previous panel here, if there are specific instances with specific facilities, they should certainly be addressed. But I think the broad and, you know, outlying or elimination of EtO as a sterilization method for medical devices is certainly something that would have grave consequences on patient care and innovation and, I think, on just the healthcare in this country. So let me just move forward here.

Again, as I said, we represent about 300 medical device manufacturers, small to midsize. We did a recent survey of our members over the last 10 days, and I think some interesting data points here. Ninety-four percent of respondents said that if their primary

sterilization facility went offline, they would have shortages. So this is not a theoretical risk. I think, again, when the Willowbrook facility went down, there were certainly some immediate issues that arose. A number of our small companies, the Willowbrook was the only facility that they sterilized their products, and so that was certainly of grave concern. And we'll get into the broader capacity here.

The majority of respondents in the survey also said there were no current alternatives to EtO sterilization that exists for devices. That's not to suggest that they haven't explored other alternatives; I think many have, and there just aren't any. That doesn't mean that we shouldn't be looking at advances in the future, and again, we commend FDA for their innovation initiative to explore alternatives down the road. But, currently, as we've heard from previous speakers, whether it's the chemical composition, the products themselves, EtO is the only validated method right now, and I think that's just the reality of the situation that we have to appreciate, and again, certainly can look at alternatives including what I'll get into in a moment, too, which is more of a sustainable EO process that allows for lower amounts of EO to still sterilize at a valid rate and perhaps address both the emission concerns and allow for a valid method to continue. And, again, the products that were outlined by FDA, that's just a small group, surgical kits, catheters, and feeding tubes.

So from our perspective and our members, again, FDA's collaborative effort over the past 6 to 8 months has been extraordinary. This is something that people have been following last fall in Illinois with the Willowbrook facility, and then all of a sudden, you move forward and it was offline. And as I said, there are a number of our manufacturers who it was the only sterilization facility. But FDA was very collaborative communicating with the public, communicating with companies, really working to try and find alternative sites so that there was as limited disruption as possible in the supply chain, and again, I

think they deserve a lot of credit for the engagement that they had, and I think a lot of these problems have been addressed.

The problem is you look down the horizon, there are a couple of facilities in Georgia and as well in Illinois that if additional steps are taken, there's no more slack to pick up. Even if FDA wants to be as collaborative as possible and work, there just isn't going to be capacity to address that. We work and interact with some of the top sterilizers, and they're at a hundred percent capacity. This is not something in which you're running and maybe you have two cycles, two 8-hour cycles, you're going to add a third shift on to take up capacity, or you're running 6 days a week and you're going to add a Sunday. They are operating 7 days a week, 24 hours a day, and if one or two more facilities go down, there's just nowhere else to go.

And I think this impact is particularly acute for the small manufacturers because, you know, they don't have the same, probably, you know, business relationship and the amount of volume that could warrant kind of a switch. And so Karoll mentioned it earlier, I think the two areas of concern is if you're a small manufacturer and have one facility and that goes down and you're not the size, how do you get additional capacity?

And if you're innovating a new technology right now and, again, you're trying to get it sterilized to run your IDE, the time it takes to shut down and, basically, the facility to then sterilize that product for an IDE, it's hard to kind of shut that down and get capacity.

So these are all things that I think I was very pleased that, I think, a number of folks in this room are weighing the potential long-term exposure to EtO versus the very real and acute impact on patients that would exist if some of these state and local municipalities move forward in the direction that takes some of these offline, not because of specific issues with the facility but just a broad-based kind of dissatisfaction with EtO.

And the other element here, I think, that's important, and the FDA deserves credit, is

some of the companies, I think, when they structure their submissions, haven't been -- and the FDA went into this about, you know, if you change sterilization, how is there flexibility and making sure that the submissions are written in such a way that if a facility goes down there is flexibility to find, in that limited capacity, when to move -- you know, shift the sterilization to. And so education about how you structure submissions here, I think, is what FDA's been communicating with companies; we appreciate that, and that needs to continue as well.

So, briefly here, how do products go through the supply chain? I know it's kind of an eye chart here, and it's a generalization, so it's just kind of a best effort, so typically how things go through. First, you have the components shipped to the manufacturing facility; then they get assembled to medical devices and the final packaging in Stage 2. And I think the key states here is from 3 they go to the medical device sterilized and its final packaging, and then it's Stage 4 here -- pardon me, Stage 3, which is the sterilization facility itself. And, again, as I said, the lack of capacity here is one that's the choke point. So if you're looking at how this goes through here, where the shortage issue comes from, it's really in that third circle.

And, you know, how that gets addressed on a go-forward basis, I know a lot of these sterilizers are exploring alternatives to EtO, but again, the capacity right now in the current EtO market is nonexistent, and if additional new models or new methods are found down the road through the innovation or challenge or other, it's not just that there's a new opportunity that can sterilize products and it can be validated, but then you have to scale that up, you have to build capacity, so realistically, it's probably a decade-plus exercise here that certainly should be undertaken, but it's one in which I think we all have to be realistic about the time in which we can transition to alternatives, and in some instances, as I said, science probably is going to indicate that there aren't any other alternatives other than EtO.

So you go through, and then once it gets to the sterilizer, obviously they ship to the regional distribution centers, from there it goes to the distribution centers to the hospitals and the surgery centers, and then ultimately, it goes to the patient.

And I know I've been asked by FDA and others what's the time between each of these phases, you know; is it 1 day, is it 2 days, is it weeks? How much capacity are there at distribution centers that maybe have been sterilized right now if there are shortages? The reality is right now there's such a variation when we talk to our members about, you know, the types of products they manufacture, the size and scale of the operation, and I think a general rule of thumb is companies want to see these move through the process quickly. It's not efficient for anybody in the supply chain if things are sitting. That kind of carrying cost is not beneficial to the distributor; it's not beneficial to the manufacturer. So, again, these are things that we want to see move though quickly, but you can see, when you look at that supply chain here, I think the key choke point here is that third circle there related to the capacity of the commercial sterilizers.

I'm not going to go into great detail about this because it was covered by a previous FDA speaker, but I think it is important just to briefly summarize that simply changing a sterilization, if there's a new sterilization modality that exists, it's not as if you can snap your fingers and move towards it. Again, there's a change process that has to be followed, that if you change it could affect the product materials, it may instigate a product redesign, which is then a new medical device and it's subject to full validation and regulatory approval. Again, if the material is compatible, the change must be assessed for verification and validation activities identified. So you can see, this is a complex process here that if we're going to find an alternative to EtO, it still goes through and impacts the regulatory process. Again, just to go through, similar in North America and in Europe.

But I'll just close with next steps, because I think, again, this meeting is critically

important to bring all the stakeholders together, not just FDA but EPA, CDC, industry, sterilizers, the clinical community. I was pleased to see the docket, and we'll be hearing from, I think, some hospitals as well. A number of top physician groups raised concerns about their ability to treat patients if there was a continued move forward here and EtO facilities went down.

And, again, I would say, as you look at solutions, because we're all here wanting to find a better way to do things, I think in the short term here the sustainable EtO model, which is leveraging a validated EtO sterilization process at lower levels that can reduce the emissions, still keep the medical devices validly sterile for the patients, that's an immediate -- and again, I know we've had webinars with FDA and sterilizers educating industry saying you need to be more proactive here. Yes, we understand the risk, you know. You can add a factor of 10 and a factor 10 and be sure it's sterilized, but in today's environment we need to do more to make sure that we're using an appropriate amount of EtO at the right levels to sterilize effectively and then move forward. So that's an immediate step that is taking place, and we continue to encourage that.

And then in a parallel track, again, those alternatives. Let's have a longer-term initiative here to see are there alternatives to EtO, as was discussed before, because of the complexity. Radiation and others can, you know, break down the device, and it's not effective, but we should explore those more, and again, that can be a long-term path to additional solutions.

So I appreciate the Panel's time, all your effort. This is a critically important issue, and again, we just have to make sure that the long-term concerns that are raised by some are balanced with the acute issues that would impact patients if certain decisions are made, so thank you very much.

DR. LEWIS: Thank you, Mr. Leahey.

We'll now hear from Mr. David Gillian who is representing Vizient, a healthcare company specializing in clinical, operation, and supply chain performance.

Mr. Gillian, could you please begin when you're ready?

MR. GILLIAN: Thank you, Dr. Lewis and Advisory Committee members, for inviting us to be part of today's briefing. I'm David Gillian, Senior Vice President of Supply Chain Operations for Vizient, a healthcare company focused on helping the nation's providers deliver affordable high-quality care. I'm here today to provide insights on how the healthcare providers we serve are impacted by this sterilization issue and the collective steps we're taking to diminish potential disruptions to the healthcare supply chain. Before we get started today, I'd like to tell you a little bit about Vizient.

First, you'll hear me use the word "member." When we say member, we mean the healthcare providers, the hospitals that participate in our services and choose to work with us every day. Our membership comprises just over 50% of all the acute care healthcare systems in the country and more than 95% of the nation's academic medical centers and approximately 20% of the non-acute providers, such as outpatient clinics. Our diverse membership base includes academic medical centers, pediatric facilities, community hospitals, and integrated health delivery networks from the largest systems to the small rural hospitals that are a trusted part of our communities.

Most people know us for supply chain expertise also known as group purchasing or the term GPO. Naturally, the issue of sterilization of medical supplies has the potential to significantly impact the abilities of our members to deliver quality care. Every day we're seeing increased concern from both providers and suppliers about this issue. Each day brings new information; in fact, just this morning, I spoke with two large vendors who shared their limited access to capacity and the reality that they're being asked to pay two and three times what they were paying just a short time ago. The healthcare supply chain,

what GPOs do and what manufacturers, distributors, and vendors do to level set everyone, and similar to what my colleague Mark Leahey shared a few minutes ago, I'll share how the supply chain model works and help clarify the role of the GPO. While we provide a range of services, the GPO segment of our business helps hospitals and other healthcare providers achieve cost savings. We do that by offering our members supply contracts that focus on price in member-centric terms and conditions; however, we're not involved in hospitals' ordering process, nor do we take possession of any supplies. And, unfortunately, we have very little visibility into a hospital's inventory.

Although most choose to use our contracts, pricing, and terms, hospitals actually place their orders through their distributors or directly with vendors. As it relates to inventory, some may keep 2 weeks' worth on hand and others may only keep 2 days based on protocols that work best for their systems and their communities. All supply chains, no matter what industry they serve, have been moving towards lean processes with low inventory to help them operate more efficiently; healthcare is no exception to that.

But the important thing to recognize about reducing EtO sterilization capacity is that no matter how much product is produced, all applicable products must go through a sterilization process. So if the sterilization capacity is limited, that forms a critical choke point for medical supply products. This creates a different type of shortage than we've experienced before. In other instances, we've been able to look for available alternative products, but in this case, no known alternatives are available.

Provider perspectives highlight the complexity of ethylene oxide, the only method approved for certain products. Our hospitals are telling us that even limited access to the use of EtO would have dramatic consequences. Approximately 50% of the nation's medical supplies are sterilized using ethylene oxide, as you've heard, and we know that for many of those supplies there's no alternative method of sterilization. The custom procedure tray,

for example, which I have with me, as you can see, there's a whole variety of different products -- gauze, for example -- very simple things. When we use the term medical device, everybody thinks implantables, but we're talking about everything. What's critical to understand is that for many products, ethylene oxide is currently the only globally accepted FDA-approved sterilization model. As examples, and some of which you heard in the questions earlier, gamma and e-beam radiation make plastics brittle and cause disintegration. High steam temperatures can melt plastics or damage some products. Sterilants like hydrogen peroxide are only effective at surface sterilization, so the kit I just held, how does it get through the kit? Nitrogen dioxide is incompatible with cotton and paper and also limited to the sterilization of surface areas. Virtually all sterile surgical kits require EtO sterilization because it's the only method that's compatible with the disparate range of materials they contain.

Changing the sterilization process for any of these products would require a major product redesign and involve changes to the sourcing of materials as well as changes to the manufacturing and distribution processes. In short, a redesign process would take several years and require lengthy regulatory approvals.

Provider perspectives highlight the complexity of ethylene oxide sterilization, what our members are doing. Our members are telling us that banning access to EtO sterilization as we are seeing happen today would essentially shut down operating rooms in hospitals across the country because they would not be able to perform simple but necessary procedures like suturing.

Based on existing plant closures, our members are currently seeking workarounds for hundreds of products. In a conversation yesterday with one of the largest health systems in the country, they indicated that they've identified as many as 1,400 products short or potentially short in their facility from the existing closings. We estimate that as of

today, there are roughly 520 million devices that are not being sterilized annually as a result of the current plant closures. Examples include IV pump sets, standalone, needle-free valves and more. Our members are focused on taking steps that will allow them to continue to treat patients. They're taking stock of their inventory and working proactively with distributors. They're considering other vendors but at the same time recognizing that all vendors are seeking access to the same limited supply. They're also looking at what they can use instead of preferred devices and what could potentially be a product they could do without, recognizing that either option would require their care practice to change.

Larger systems have the option to share between their hospitals, but that would only help for a short time. Keep in mind that hospitals must go through these considerations for each of the up to 14 [sic] current items that I mentioned are in short supply.

An example, an item as simple as mesh that's used in different forms of hernia repair, the only clinical equivalent would be biologic mesh, but because that comes from cadaver donors, supply is also limited. Hence, a short supply of a simple thing like mesh could result in a delay or prevention of actually having that surgery.

So what is Vizient doing to help? We recognize that this is a complex and sensitive issue. It has serious implications for both public health as well as the care and safety of the nation's patient population. There are no easy answers. For now, Vizient is proactively soliciting vendors for transparency regarding potential supply disruptions, and we communicate any and all of our updates to hospital members as soon as possible. Currently, we're remaining alert to the situation and communicating updates from vendors, including potential threats of disruption and mitigation efforts. At the same time we're cognizant of the fact that over-communicating shortages could essentially cause a run on the bank, so to speak, so we are trying to be as careful as possible with that balance. We also communicate the status of EtO sterilization sites, including all vendors impacted by

plant shutdowns.

Lastly, we're looking at remaining in close contact with the FDA about any key actions, identifying potential substitutions, and recommending conservation strategies and practice changes and encouraging providers to remain vigilant in monitoring and reporting any supply shortages to the FDA. No quick or easy path forward. Stakeholders are doing what they can. With limited alternative sterilants available, we recognize many stakeholders are doing what they can to mitigate the potential supply disruption, and we applaud any and all efforts to that end. But even with our collected heightened focus and willingness to collaborate, there's simply no easy or quick fix, as you've heard me say.

EtO sterilization capacity constraints could compromise providers' ability to deliver care. There's no doubt that this is a major concern for our industry as we evaluate potential solutions on behalf of the hospitals we serve. We echo their call for a thoughtful, measured, and transparent approach with a sufficient runway that allows our care providers to realign their care delivery processes.

Several of our members we spoke to call for a 3-year window to address any changes around EtO sterilization. Without this window, one member cautioned I hope you don't get sick.

We're committed to working together to find the best way forward for the health and safety of the general public and the nation's patient population. We encourage collaboration among all industry leaders to better understand the sterilization process, existing safety protocols, material limitations, and the delicate balance of the healthcare supply chain. We look forward to working with all parties to arrive at a thoughtful and deliberate solution.

Thank you again for the opportunity to participate in today's briefing. That concludes my comments.

DR. LEWIS: Thank you, Dr. Gillian. Or Mr. Gillian.

We'll now hear from Dr. Kara Mascitti from St. Luke's University Health Network. Dr. Mascitti will discuss her organization's perspective of the potential impact on patients due to loss of medical device sterilization capacity.

Dr. Mascitti, would you please begin when you're ready?

DR. MASCITTI: Thank you to the FDA and Advisory Committee members for the opportunity to provide comments today regarding the sterilization of medical devices and its role in protecting public health.

My name is Kara Mascitti, and I am an infectious disease physician at St. Luke's University Health Network. In addition to my clinical role caring for patients with infections, I also serve as the Medical Director for Healthcare Epidemiology and Infection Prevention for my network. St. Luke's University Health Network is a nonprofit regional fully integrated and nationally recognized network providing services at 10 hospitals and more than 300 sites throughout Pennsylvania and New Jersey. St. Luke's averages more than 72,000 admissions and 279,000 emergency room visits annually.

As an infectious disease physician, I know firsthand the importance of ensuring that physicians have access to sterilized products for patient care. Every single patient that is admitted to one of our hospitals or visits one of our emergency rooms requires at least one sterile product as part of their medical care, whether that be a needle used to draw blood for lab work, an IV to provide fluids, antibiotics, and other essential medications, a tube to provide nutrition to a neonate, or a stent to treat a heart attack.

The recent closures of sterilization facilities have not impacted St. Luke's thus far in terms of our supply chain of these products. Other systems throughout the country, however, are not as fortunate and have reported disruptions of critical life-sustaining supplies such as intrauterine catheters, tracheostomy tubes, and surgical staplers, to name

a few. As a result, they've had to allocate additional time, labor, and financial resources to sourcing alternatives so that they can continue to offer patients the highest quality of healthcare possible. St. Luke's may not be so fortunate in the future if this trend continues. I am concerned that should sterilization facility closures continue throughout the country without adequate warning or contingency planning, that patient safety will be at risk and unnecessary patient harm will occur. Additionally, this would almost certainly translate into increased healthcare costs and strain a healthcare system in the U.S. that is already under financial pressure.

We must work together to find a solution that appropriately balances the risks associated with ethylene oxide sterilization and the urgent need of sick patients in our country. I applaud the FDA for initiating this discussion and thank you for inviting me to share the provider and health system perspective.

My comments today focus on three main points. First, internalization of sterilization by hospitals and health systems would be prohibitive in terms of cost and logistics. Second, inadequate sterilization would be catastrophic for patient care and threaten modern medicine as we know it. And, third, changes to sterilization methods must occur in a coordinated and systematic manner to minimize unintended consequences.

My first point today is that internalization of sterilization by hospitals and health systems would be prohibitive in terms of cost and logistics. St. Luke's has ethylene oxide sterilization capability at 2 of our 10 hospitals that is used in a very limited capacity for the sterilization of some of our GI scopes, as well as reusable supplies used in the intensive care unit, radiation oncology, and cardiac catheterization lab. While we have other methods for sterilization in our network, including steam and gas plasma, these specific products are not validated for, appropriate for, or stable with these alternative sterilization methods. To minimize ethylene oxide emissions and staff exposure, we process only full loads when

possible and use a self-contained system with adequate aeration. Our annual emissions are estimated at less than 30 pounds. Overall, our internal sterilization capabilities are miniscule compared to the number of sterile products we use daily for patient care.

If we were forced to sterilize every product within our health system ourselves, number one, it would be cost prohibitive to build the necessary infrastructure and hire and train the necessary staff to operate such a facility; number two, it would create additional risk to us as a healthcare provider, as it would shift the liability of ensuring product sterility from the manufacturer to our hospitals; and number three, it would increase the regulatory burden to our hospitals, which would lead to an additional increase in costs and legal resources to ensure compliance.

I imagine that the impact would be even greater for systems that do not currently have sterilization capabilities or community facilities that are often the only healthcare provider for their vulnerable rural or underserved populations. For them, the financial burden would likely be so great that it would threaten their ability to remain operational and provide care at all.

I am also concerned that moving away from a centralized sterilization system and fragmenting sterilization would lead to increased patient risk. Currently, a centralized process of sterilization ensures a high level of quality control, reliability, and product confidence. In a decentralized system, every hospital would be left vulnerable in terms of its ability to provide consistent patient care should sterilization operations at a facility be compromised or need to be temporarily shut down, as in the case of a natural disaster, inclement weather, or a highly infectious disease outbreak. While contingency plans may be feasible for larger systems to develop or implement, our smaller and more lean systems may not be able to support such backup plans and therefore would have to temporarily cease patient care if sterile products were not available.

Finally, while our goal is to decrease global ethylene oxide emissions, I worry that a decentralized process might actually increase these. While emissions would occur in smaller pockets spread across larger geographic areas, diluted, if you will, we might actually see an increase in overall emissions due to more inefficient processing.

My second point today is that inadequate sterilization would be catastrophic for patient care and threaten modern medicine as we know it. As a healthcare provider, I never want to be in a situation where I question the sterility or safety of a product that I am using for a patient. Or worse, I never want to be in a situation where I cannot care for a patient due to a shortage of a critical product.

As a resident in internal medicine, I had the privilege to work in an underserved public hospital in Botswana. I witnessed firsthand how our ability or inability to care for sick patients hinged on such basic factors as product availability. If we had no endotracheal tubes that month, patients could not be intubated and were left to die of respiratory failure. Unfortunately, if the sudden closure of sterilization facilities continues, this may become a reality in our own country and threaten modern medicine as we know it.

The potential risk to patients is real. We cannot risk placing potentially contaminated devices into and causing infection in already compromised sick patients whose loved ones have entrusted us to heal them. We cannot risk canceling surgeries or other necessary medical procedures or being unable to care for patients in emergent situations because we lack the necessary supplies.

Product contamination or lack of availability of sterile medical devices will absolutely lead to prolonged hospital stays, increased cost of care, worst patient outcomes, and even unnecessary deaths. In essence, sterility issues and product disruption could completely disrupt healthcare as we know it.

My final point today is that changes to sterilization must occur in a coordinated and

systematic manner to minimize unintended consequences. As a physician and an epidemiologist, I understand the importance of not only caring for the sick but also protecting the health and preventing illness in our general population. It is crucial to ensure that in our efforts to help people we are not causing unintended harm to others.

I believe the answer to our current situation is to work together to find the appropriate balance between the risks associated with current sterilization techniques and the medical needs and safety of the sick in our communities; however, that balance cannot be struck overnight. A coordinated and systematic approach to addressing sterilization concerns is necessary to minimize disruptions to the supply chain and prevent potential downstream harm to patients.

To achieve this, it is imperative that we approach sterilization of medical devices collaboratively such that all stakeholders have a seat at the table and work together to develop a cohesive strategy. We must align our future plans to incorporate federal and state requirements across all appropriate agencies, marrying environmental concerns with patient safety standards. We need to permit sufficient time for change and compliance and allow existing entities to continue current sterilization methods as they work towards instituting change.

In summary, I urge the FDA to continue to work collaboratively with all stakeholders to develop a coordinated, cohesive, and systematic approach to addressing the concerns with ethylene oxide while carefully considering the unintended negative consequences that sterilization facility closures would have on patient care. We can change and perhaps should change the status quo, but we must be thoughtful in how we make that change.

Again, I thank the FDA for the opportunity to provide these comments.

DR. LEWIS: Thank you, Dr. Mascitti.

We'll now discuss reducing ethylene oxide emissions in the use of medical device

sterilization. Mr. Phil Cogdill from Medtronic will kick off this portion and provide us with an overview of the EO sterilization process and engineering to optimize ethylene oxide use.

Mr. Cogdill, please proceed.

MR. COGDILL: Good morning. I'm Phil Cogdill. I would like to thank the Chair, members of the Panel, and the FDA for the opportunity to present today on behalf of industry on sterility assurance and ethylene oxide with an emphasis on the optimization and reducing of ethylene oxide.

By way of background, I've been involved in sterilization since 1983. I'm on the board of directors of the Association for the Advancement of Medical Instrumentation or AAMI, the standards development organization for the standards in the United States on industrial ethylene oxide sterilization. And I'm the past co-chair of Working Group 1 on industrial ethylene oxide sterilization.

The main points I want to cover today are that sterilization is a complex process that starts and ends with the patient. It impacts manufacturing and distribution of the devices across the entire supply chain. I will review the steps throughout the sterilization process in detail. And the sterilization is not just about eradicating microorganisms; it also involves making sure the functionality or performance of the devices is not impaired considering the device's full life cycle.

Next, EtO sterilization is a highly controlled process, and because of the unique advantages, EO is used to sterilize approximately 50% of medical devices worldwide, including devices that treat conditions such as coronary artery disease, diabetes, and instruments used every day in operating rooms, ICUs, and emergency rooms.

Lastly, I will discuss some potential approaches that at any time may allow us to reduce the amount of EO gas used during sterilization.

Let me begin with the sterilization sterility assurance process. The sterility process is

a robust and lengthy one; it starts with research and development, or R&D, and goes all the way through to the patient. We define the continuum as the end-to-end sterility assurance approach.

Initially, the R&D organization works with customers, patients, and consumers to identify what product design should be addressed, the specific clinical and patient needs. Once the design is developed, the product undergoes the planning, sourcing, making, and delivery phases. Sterilization is considered during each and every one of these phases to ensure that the chosen modality is both effective and does not compromise the product structure or performance over the product life cycle.

It is important to emphasize that each area on the continuum is linked. If we make a change in one area, it will impact all the steps in the process. Let me walk you through each of these areas in more detail.

The first part of the R&D process is product design. When a new design is developed, it must effectively address the specific clinical and patient needs. Once the general design is identified, the engineers must evaluate the type of materials that are available and select those which achieve the desired product performance and design specifications. Consideration also must be given to the type of packaging, as most of these products are sterilized in their final packaging. I will come back to that topic later.

During the material selection phase, sterilization needs are carefully evaluated to determine what method can be used to achieve the desired sterility assurance level. In order to consider a device sterile, it is required to show that the probability is less than 1 out of 1 million that the device is contaminated with one organism.

There are two broad categories of sterilization modalities. The first are traditional. These are well-understood methods which have a great deal of experience and data supporting their use and for the use of which international and American standards have

been developed. The second are non-traditional. These are newer methods for which data are more limited and for which industry standards have not been developed. These methods must be validated under the ISO-14937 standard which requires greater testing to understand the microbiocidal efficacy.

Next, we consider the materials that are going to be used in the device and determine how those materials will react with different potential sterilization modalities. The chart on this slide is taken from the AAMI Technical Information Report 17, and it provides a high-level overview of the relationship between certain types of materials and specific sterilization methods.

The far left column shows the materials, and all the columns to the right show the different sterilization modalities we need to consider. As you can see, these relationships are complex, and no single method works for all materials. This is further complicated by the fact that most modern medical devices are made up of more than one type of material. As a result, sterilization options must be carefully evaluated for each product and validated to ensure that they are compatible with a product and do not adversely impact its performance. It is also important to note that many of the nontraditional methods are not compatible with cellulosic packaging used with most medical devices sterilized today.

The next step is to validate the methodology. Specifically, we need to determine whether a conservative or optimized validation process will be used. The conservative validation process uses double the required sterility assurance of one in a million. The optimizer bioburden method assesses the average amount of microorganisms on the product and utilizes that amount to obtain the assurance of sterility of one in a million. If a bioburden validation method is used, additional environmental and microbiological controls are required.

Finally, we decide on the ultimate sterilization modality. This decision will impact

whether the sterilization can be done directly at the manufacturing site or it will need to be performed at a third party location. After the sterilization process has been finalized, a new product must be validated for functionality, biocompatibility, and stability across its entire life cycle.

When the R&D portion is complete, we move into the plan and source phase. The plan phase of the device, of the product, typically identifies where and how the product will be produced along with understanding where and how the product will be sterilized. This will include an evaluation of the manufacturing technologies that will be used.

The source phase focuses on identifying the supplier of the raw materials used to manufacture the device. As part of the process, we need to make sure that the raw materials meet the design specifications for the product and are produced in a manner that ensure the bioburden is low.

Next, we move to the make or manufacturing phase. As shown on this slide, we have programs in place to ensure that the manufacturing process is controlled and that appropriate bioburden specifications are achieved. If a change is proposed in manufacturing or sterilization methods, a planned process must be documented and reviewed to ensure that that change does not impact any of the end-to-end processes, the product or the packaging.

Sterilization is the execution or delivery of the sterilization process and may occur as part of the make or between the make and deliver phase. During the sterilization process, a number of steps are taken to ensure that the final product is sterile and undamaged. Specifically, we verify that sterilization was effective and conduct a quality review on the final product before it is released for delivery to the healthcare provider and the patient.

The last phase is the delivery phase. This phase is where product moves from manufacturing facilities to the customer, patient, and consumer. The primary responsibility

of sterilization in this phase is to work with the packaging organization to ensure that the sterile barrier is not compromised during the delivery process. Furthermore, environmental controls must be in place in storage and transportation to manage the temperature and humidity of the product.

This complex process which I just described needs to be individualized for each device to help ensure that it is safe and effective over its life cycle.

With regards to ethylene oxide, these same steps must be performed. Device manufacturers look at the new product development and determine if we use the existing sterilization process or if we need something new. We perform an assessment of the sterilization facility, we evaluate the raw materials, processing components, and manufacturing aids against ISO standards. We perform the sterilization process which may be internal or external depending upon the capabilities. We do periodic checks to ensure that it meets all validated parameters, and we follow the ISO 10993-7 to ensure the EO residuals meet the standards. We monitor and manage the EO residuals for loads arriving at the distribution center, and finally, we ensure all standards are met for patient safety with regards to sterility assurance and residuals.

Let me now turn to the benefit of EO. Like other sterilization methods, EO has both advantages and disadvantages. However, some of the unique characteristics of EO make it the preferred method for a wide range of medical devices and instruments. Currently, the medical device industry uses EO for approximately 50% of products sterilized because of these unique benefits. One unique characteristic of EO is that it is a lower temperature process than dry heat and steam. This is important because lower temperature is less likely to degrade the materials. Another is that EO is not just a surface sterilant; rather, it is able to penetrate easily into complex medical devices such as oxygenators and respiratory circuits and can be used to sterilize procedure kits such as those used in many operating

rooms.

I would like to leave this example of an oxygenator. During the break, you can come up and look at it and see the complexity and the number of materials that are required to make a device a lifesaving device like this.

EO will also sterilize cellulosic materials such as paper packaging used for most medical devices. This allows us to sterilize a final packaged product and deliver it more quickly to the healthcare provider and patients. And EO sterilization can be performed at any size chamber, and this allows EO to be used in large manufacturing processes which in some cases can produce over a million products a day. And just imagine, you know, tens of thousands of these devices going into a chamber that's almost the size of the area that you're sitting in here right now and being sterilized at one time.

Responsible use of EO sterilization is a highly controlled process that involves sophisticated equipment and monitoring. The primary goal of this process is to deliver a sterile device for patient use while minimizing the potential risk to employees and the environment.

A typical sterilization cycle will have truckloads of fully packaged product being delivered for processing in the chambers. The first step is the preconditioning phase, which requires the load to be brought up to a specific temperature and humidity level as these are essential for proper sterilization.

The second step is the EO processing phase, and this requires the removal of oxygen to allow the gas to fill the chamber. For this to take place, numerous safety measures and controls must be in place. Continuous monitoring of numerous parameters, such as temperature, humidity, pressure, gas concentration, and time, are done throughout that process.

The third step is the aeration phase. This is when the product has completed the EO

process but still maintains the absorbed EO residuals. During this phase additional processing is performed to reduce the residual levels at a minimum to the required ISO standard. To minimize any potential risk, we have numerous environmental and worker safety elements built into the facility to monitor EO emissions and capture and destroy the EO gas.

Let me now discuss the ways of which we are working to better utilize EO. Looking at potential options, modifying product packaging is one of the first things we can consider. While EO can be used to sterilize paper materials, paper absorbs EO gas resulting in higher EO residuals. Reducing the amount of paper material in product packaging and eliminating paper IFUs would allow the reduction of the amount of EO used in sterilization devices and also decrease EO residuals. I'll pass around this instruction for use, which is for this device that's on the table, so you can see what goes through the sterilization process in addition to the package product.

So, for example, paper IFUs could be replaced with a 3-D barcode that would allow the user to obtain the same information electronically with significantly less EO. Traditionally, manufacturers have used a conservative approach of EO sterilization that involves long cycle times and high EO levels. While the conservative approach provides a high degree of confidence that the sterility assurance level has been met or exceeded, it requires larger amounts of EO and results in higher emissions.

An alternative method that has already been recognized by the international and American standards is the BI/bioburden or optimized cycle which involves the use of shorter exposure times and lower EO levels. The graph shows both conservative and optimized methods. As you can see, both methods are capable of reaching the standard sterility assurance of 10^{-6}.

While using the optimized approach may reduce EO levels and emissions, this

method is far more complex than the conservative approach. Converting products from the conservative to the optimized method is not a simple process, and it requires a significant amount of time, including extensive validation and regulatory approval. Currently, studies are under way to evaluate whether we can reduce exposure times to EO while achieving adequate sterility assurance levels.

In this example, traditionally only 120 minutes of the exposure time has been used to control the EO process. However, the total exposure time is 230 minutes, which includes an additional 55 minutes of gas inject and 55 minutes of gas removal. This provides twice the amount of sterility assurance that is required. Calculations above show that the impact reducing this exposure time by 25, 35, and 75 minutes would have on the sterility assurance level and still result in a sterility assurance level of at least 10^{-6}, meaning that there is a less than 1 in 1 million chance of a single microorganism remaining on the product.

However, before these methods can be implemented, extensive validation and testing are needed to ensure that the methods are both effective and safe across the entire life cycle of the product.

Another way to potentially help reduce EO emissions is to lower the concentration of EO gas used during the sterilization process. As I said earlier, the majority of EO validations use a conservative method which uses larger amounts of EO gas. Historically, this is because EO gas was not viewed as a limited resource and because it was thought that larger amounts would increase the speed of sterility. We now believe that we can reduce EO gas to approximately 400 mg/L and still obtain an equivalent sterility. Again, however, studies have to be conducted to evaluate how making this change will impact the safety and effectiveness of the device throughout the life cycle.

And, lastly, we can potentially reduce the number of cycles we are using. Each of the colors in this figure represents a product family that is sterilized using a separate

sterilization cycle. Efforts are currently under way to determine whether some of these families can be sterilized using a single optimized cycle reducing the number of sterilization cycles being performed and thereby reducing EO use and emissions. Later on you will hear more details from Brian McEvoy of STERIS on how industry is working together to implement this.

So, in closing, EO sterilization processes are complex and lengthy. Each of the functions and the sterilization end-to-end approach are critical and can impact the sterilization process and ultimately the patient.

Sterilization is not just about eradicating microorganisms; it also involves making sure that the functionality or performance of the devices is not impaired and needs to consider the device's full life cycle.

Because of its unique advantages and its applicability to a wide range of materials, EO is used for sterilization, about half of the medical devices worldwide. At this time only a very small portion of products currently sterilized by EO can move to other sterilization modalities.

Changes to the sterilization process are difficult to make and take time to implement responsibly. This includes time for validation and testing over the expected lifetime of the product. This is even more complex for non-traditional methods for which there are no nationally recognized standards.

Finally, there are a number of potential approaches that we are working on to better use EO, including reduction of time, gas, and the number of cycles used. However, all of these approaches will require time to evaluate and implement responsibly.

Thank you for your attention.

DR. LEWIS: Thank you, Mr. Cogdill, for that comprehensive review.

We'll now hear from Mr. Brian McEvoy and Dr. William Brodbeck from STERIS

Applied Sterilization Technologies. Mr. McEvoy and Dr. Brodbeck will address the reduction of ethylene oxide emissions by changing cycle design and validation methods.

Gentlemen, if you'd please approach the podium and begin your presentation when you're ready.

MR. McEVOY: Thank you for providing us this opportunity to present today specifically on EO validation and on a program that we launched with STERIS in 2017 in terms of sustainable EO. And by means of an introduction, my role is a technical lead within STERIS, and I've worked in this industry for some 19 years, predominantly in EO sterilization. I'm a microbiologist by original qualification, and for my misfortune or fortune, I'm doing a part in a Ph.D. in sterilization microbiology at present, and so it's a topic very close to my heart.

The scope of the presentation: Upon receiving the invite to attend here today, we were asked to address three questions, and I'm going to attempt to do so in the context of our sustainable EO program. And I've ordered the questions in the following manner, which is how can an acceptable assurance of sterility be maintained as we reduce EO concentration going into our processes? What cycle parameters can we therefore change to reduce EO use or emissions? And a discussion on the challenges for implementing and, you know, novel cycle design or validation methods as we've experienced in the industry over the past number of years.

So the key points I'd like to share today is in validation, we have a scope to improve. We have room within our methods fully described in ISO standards to actually be more efficient with our processes. And we have, I would say, taken, you know, a very advantageous view of what process parameters we can adjust and for the benefit of the overall process and predominantly EO concentration.

And, you know, this is the presentation we've actually given throughout industry

over the last number of years in different formats because it's something, again, fully defined in global standards that I've put here on the slide, and so this is something available for all and manufacturers, all sterilization companies to avail of. And, really, I think as you heard this morning, it's about connecting some of those standards and utilizing some of the guidance or normative reference within those standards to actually be more precise and efficient in how we do EO sterilization.

So the first question, and probably one of the most pertinent questions is, how can we provide assurance that that strict assurance level is being provided to the product? Our goal in sterilization is to provide a product that's sterile, that's safe for patient use, and if we change our validation practices, our approach at how we do validation, we must ensure that we are still delivering those products sterile and safe for patient use.

The last speaker, Mr. Cogdill, talked about conservativeness and that we have in our validation practices. I'm also going to use the word "overkill" because that's how it's described in the standards. And often when we think about the conservativeness, we think solely about, for instance, the validation approach referred to earlier as the half-cycle validation where we, you know, we use an 10^6 biological indicator with a million bugs, we kill it, and in the routine process, we double to achieve a sterility assurance level. What we sometimes fail to recognize is there's multiple layers, additional layers of conservativeness built into this process.

And to describe it on the slide here, for instance, the biological indicators, again, getting back to the last presentation, we talked about end-to-end sterility assurance. The step before sterilization is the manufacture. These products are coming out of clean rooms with actually, more often, very low bioburden levels and very low levels of challenge for the sterilization process, but it's actually something we sometimes fail to recognize in our validation practices because we use a biological indicator with a million bugs on it.

Secondly, when we do the approach in the validation -- I'm going to touch on some of these points a bit more in the upcoming slides -- our validation practices are around creating what we call process challenge devices. Now, again, I just create those process challenge devices in response to having a relationship to the product, but the nature of the validation is we add more layers of conservativeness. So if you look at the slide, our target is to hit this 10^{-6} SAL. In reality, we hit far in excess of that. Again, these multiple layers of conservativeness. I'm going to really focus the remainder of the presentation, really, on this selection of the process challenge device, which has been the essence of our sustainable EO program and because we believe it's -- if you like that layer of the most immediate opportunity to us, we still maintain the conservativeness in the use of the half-cycle validation, etc.

So the next slide is, if you like, taking the previous slide, it's showing a slightly different way, and again, it looks somewhat familiar to, I think, a slide that Mr. Cogdill presented in the previous presentation and -- but really, it's to show that in the graphic the blue line shows our product challenge. I'm showing a product with a bioburden level of a thousand microorganisms. Why did I pick a thousand? Because, actually, in radiation processing, that's a very typical limit, and as you've heard throughout the day, many manufacturers are manufacturing products equally for radiation and EO and commonly coming out with the same clean rooms. So, again, if you think about that limit of cleanliness in the product, often we would see it at a maximum of this thousand CFU level.

Again, focus on that blue line. If we inactivate the challenge, if you'd like, from the product, we can see our end point. I've labeled it minimum SAL. What happens in reality in our validation is, again, we use a biological indicator, so it has three more logs of growth on the indicator. We then place it in a challenge device, we change the resistance, and now our endpoint becomes the red line. And if you look, then, across the x-axis, what that is

doing is increasing the amount of inactivation that's required in the process, and if you extrapolate downwards, you will then see we're far in excess of that SAL that we need to achieve.

So a key consequence of this I would call an exaggeration is that it results in additional process that may be unnecessary, and this has really been the focus of our sustainable EO program is to, you know, maintain conservativeness but actually look to be more precise in what we're doing with the sterilization process.

So what does that look like in reality? In essence, you see now the revised chart where I've drawn the green line, and really, what we're trying to do here is still use a process challenge device, still use a 10^6 BI, and so we set up these layers of conservativeness, but now we want to demonstrate the relationship of the challenge, the process challenge device to the actual requirements of the product. And, again, the methodology behind this approach to validation is fully described in ISO 11135.

The other thing I want to highlight on the graphics that I'm showing, and I'm purposely not labeling the x-axis, just time, and I'm calling it inactivation time because it's a factor of the process parameters, again, which is going to be an important point when we start talking about EO concentration.

The next question we were asked to address is what cycle parameters can be changed to reduce EO use or emissions? So, again, the reason I focused on SAL first is it's our first point of call. It's the first thing we most ensure we have in the process. Once we have that established and we're confident we are achieving our SAL, then our opportunity is to look at process optimization and a common opportunity.

In my own experience in this industry, often we think of process optimization, we look at parameters such as those listed: temperature, humidity, time, vacuum, number of washes. But often what we fail to forget is these parameters are consequences of the

amount of sterility we put in, in the first place. And we typically have not looked at the EO concentration. One might ask why. And this was a question we asked ourselves when we started into our sustainable EO program.

In 2016 we spent time gathering data from our processes; we looked at 160 processes globally, and as you can see from the graphic, we plotted EO concentration from those 160 processes. The average concentration was 612 mg/L. This was not a surprise. We actually expected somewhere around 600. One may ask why did we actually anticipate 600? Because that's how BIs are qualified under the ISO standard for BIs, which is ISO 11138 part 2, the 2017 version. So, again, that use of that concentration and qualifying the BIs has somewhat translated into our industrial processes. And to provide more clarity, I'm talking about a BI qualification in the biological indicator, where the BI is killed in a matter of minutes versus an industrial process where we're spending 3 or 4 hours trying to kill the same BI. So, again, that disconnect opened our eyes to the opportunity to address this parameter of EO concentration.

By addressing this parameter, we sought to reduce EO concentration because, again, some of the benefits from doing that can be realized in being able to optimize process time, the number of washings, aerations, etc., and all of this while still fully compliant to ISO 11135 and measuring residuals in accordance with ISO 10903 part 7.

We at STERIS set ourselves a goal in this program of a 50% reduction in the amount of EO that we're using, and we've worked very collaboratively with some of our customers to see what is that 50% reduction in the input of EO sterilant, how does that translate into product outcomes, and I've talked a little bit about reduced time, reduced process, but in this slide we've actually done some studies to look at the effect on the product residuals.

So this is the residual amount of gas remaining on the product after our process, and interestingly, it's a limited study, some of this work is still ongoing, but we're seeing, you

know, far in excessive of 50% reduction. For instance, the second bar is PVC tubing, and you can see after our optimized process we are now at 43% of the original level. So we believe this focus on EO concentration has wide-ranging positive impacts on product outcomes from EO sterilization.

The final topic we were asked to discuss and explore is the challenges that we've experienced implementing novel designs, and I spent some time thinking a little bit about this, and then one of the things I did was I took the word "novel" and I just consulted the Collins dictionary, and if you bear with me, I'm just going to read that. "Novel things are new and different from anything that has been done, experienced, or made before." Now, I'm sure to most people that gives connotations of, I would say, a nervous resistance to change when you think about doing something new or novel and probably, you know, yes, we've tried to bring a new approach, but one of the things we're emphasizing is it's not new that we're following an ISO standard that was published in 2014. We're utilizing the standard now to its fullest to achieve these better outcomes.

Again, we felt one of our biggest challenges was going to, if you like, bring our customers, our industry on board into this program we created and our SEO scorecard to basically try and create awareness of where we are, as an industry, around EO concentration in our processes and where we should strive to get to, and this is something we've shared across our own sites within STERIS globally and we shared with many of our customers to show where their processes are currently sitting, again, to create that motivation for change.

The other point I want to make is, you know, a value we see in this EO sustainability program is our focus has been on reduction and reduction means what was in the past; legacy probably still remains the worst case. So we're hoping that really focusing on, like, trimming down a legacy process that hopefully eases that change management process for

our customers as they go to document and describe those changes in their quality management system and for regulatory approval.

Probably the biggest challenge that we've experienced is the recognition that the standard has progressed but some of our practices haven't. And this is a busy slide. I'm going to really paraphrase what's in the three boxes. So the three boxes are essentially the ISO standard from 1994, from 2007, and 2014. And in 1994 the ISO standard talked about you will place a BI in the worst-case location in a product. In 2007 it talked about worst-case location or a PCD of equivalent or greater challenge; 2014, it provided a lot more guidance as to what that equivalent or greater challenge could be and how you would demonstrate it against the product. I would say many of our practices were probably still in the 1994 version, and really, what we've been trying to instigate and create conversation within industry is following the 2014 guidance a lot more closely for the benefit of these processes.

The last part of the text that was on the previous slide highlighted the natural bioburden at the most difficult-to-sterilize location. Again, this graphic is showing some of the ways we would've approached that and that validation in the past where we had BIs, you know, put in particular locations inside a product; there are issues with that approach because we're making assumptions about where our worst-case location is. When you look at the product, do you ask is it a matter of gas pathway, is it a matter of where the natural bioburden resides, or is it a matter of where's the lowest humidity? So there's many factors that can affect the lethality in an EO process.

The current standard is now moving towards the use of a test of sterility, and this is something we use in radiation processing as part of the validation process where we're using that test of sterility to compare the product with the challenge device that we use to demonstrate SAL. And, again, there's only advantages of doing that test because you're

looking at the entire product from a microbiology perspective.

So, again, by taking these validation approaches, we believe we can be more accurate in what we do, but we still have many layers of conservativeness. But, again, by just approaching this single layer around the process challenge device, we can see the outcomes of being able to optimize processes.

And this slide really shows the outcomes that we've experienced within STERIS since we launched this program in 2017, and today we've initiated 160 validations with this approach; we've completed 64 and 40 of which are in routine production. But the most important number on this slide is these new processes are now operating at a concentration of 356 mg/L as opposed to our legacy of 512.

So, in summary, how do we achieve? By selecting an approach challenge that has a demonstrated relationship to the product itself, by following the current standard and to make the reduction. On the right-hand side of this slide, you know, our goal is not necessarily to arrive at a single point of a new concentration. We recognize products can be very complex like the one here. Or it could be quite simple. We still expect a normal distribution, but our goal is to shift that normal distribution to the left.

And, in conclusion, I think we've heard it all this morning; the sterility of medical devices is essential to ensure their safe and effective use. EO is used, as we've heard, to sterilize approximately 50% of those medical devices.

We at STERIS continually strive to expand our technology neutral solutions offerings with developments and alternative technologies and creation of sustainable EO sterilization services. And, again, the main part of the presentation this morning was around the sustainable EO program, and we, as a sterilization provider, take our responsibility seriously as to how we are committed to delivering for our customers and to the communities and the environments in which we operate.

Thank you for your time this morning.

DR. LEWIS: Thank you.

Dr. Brodbeck, did you have any comments?

DR. BRODBECK: No further comments to add, thank you.

DR. LEWIS: Thank you.

We'll now hear from Mr. Denny Christensen from SVC, Incorporated. Mr. Christensen will present on reducing ethylene oxide use in sterilization cycles by changing the load configuration.

Mr. Christensen, please continue when you're ready.

MR. CHRISTENSEN: Thank you. Thank you to the Advisory Committee for inviting me to be here today. I certainly appreciate it. I own a contract EO facility in California. It's different than most contract EO facilities in that my facility sterilizes primarily in the primary package; it doesn't sterilize in cartons or pallets. It's a different approach for high-volume/low-volume medical products.

A little background on sterilization: I first got started in sterilization when I graduated from college in 1967. I went to work for a medical device company doing EO sterilization. The way we sterilized back then was entirely different than what we're doing now and hopefully different than what we're going to be doing in the future. Back then, an EO sterilization process was about 8 hours; an hour and a half to get the product ready to sterilize, 6 hours of EO exposure, and about an hour to an hour and a half to get the EO out of the product. Product residuals weren't a concern. Employee exposure to ethylene oxide was not a concern.

The way we actually tested the product was you put a number of biological indicators in a package along side with the product. After every sterilization process we tested a number of biological indicators, after a full cycle now, and also we did a product

sterility test on 40 product. I don't remember in the first 15 years of ever having a biological indicator positive. However, you can imagine if we're testing something like this, we had sterility test positives. So sterility test was what drove cycles. There was no formula; there was no recipe. We based the method of sterilization on what the product needs were.

About 1982 we were notified that we were going to begin validation of our sterilization processes and validation made sense. It required us to run half-cycles; it required us to make sure that we use a scientific approach. We used statistics to make sure that the product had that one-in-a-million probability of a non-sterile product.

My subject today is reducing EO use by sterilization cycles, by changing the load configuration.

I won't spend much time here, Brian and Phil have talked about this, but yes, we do need to put a biological indicator in a place that represents a difficult place for the gas to get to. If we can't put a biological indicator in there, we need a simulator device to show that we can still sterilize the device.

Now I'm going to go back to Phil's device here. Here's a fairly simple device, a syringe. Where's the most difficult place to sterilize? Is it inside the stopper below the plunger? Is it around the ribs of the stopper? Or is it inside the luer tip where you have either a non-vented or a vented cap? This all has to be determined before we start our validation.

So the most important cycle we do in any validation is the fractional run. That documents our ability to sterilize the natural product bioburden. Natural product bioburden on most medical devices is probably less than 500 CFU from products I've seen, and we created an internal process challenge device -- here again, Brian and Phil talked about that -- to simulate something that's more difficult to sterilize than the natural

product bioburden. So we test data documents that the natural product bioburden is sterilized by doing a product sterility test and that the biological indicator has survivors, so it's more difficult to sterilize than the natural product bioburden.

And, also, we need something to use for routine manufacturing, so we have what we call a master challenge product or a process challenge device. In your fractional run, your data should establish that the master challenge product or the external process challenge device are equal or more difficult to sterilize than the product itself.

Everything we do to add layers of packaging or whatever adds difficulty and increases the difficulty of sterilizing products. Product packaging, is it single or double pouch? Is it a PETG tray with a lid, like this? There's pouches that have breathable strips. It minimizes the ability to put ethylene oxide and humidity inside where the product actually is. A lot of companies use shelf cartons, and the placement in the shelf carton adds another barrier. Instructions for use, as Phil showed you his instructions for use. This particular product here, I had a customer that was putting their instructions for use on top of the Tyvek, which is a breathable surface, making it more difficult to sterilize.

Palletizing, cardboard box: A lot of people aren't aware of it, but there's different weights of cardboard boxes. The heavier the cardboard box, the more difficult it is for ethylene oxide and humidity to penetrate and easier to sterilize.

The pallet configuration: Since sterilization is a fairly expensive product, we try to put as much products we can into the sterilizer. That may be good from a cost standpoint but not necessarily good from a microbiology ability to sterilize. So sometimes you can change the number of cartons and make it easier for humidity and EO to penetrate the cardboard and give us a shorter cycle.

Stretch wrap: A lot of companies use stretch wrap. Some people use clear stretch wrap like Saran wrap, others use open-weave stretch wrap, but every layer of stretch wrap

you add here again impairs our ability to get ethylene oxide and humidity inside the product where we want it, again increasing our sterilization cycles.

I owned a process challenge device company, and I had a customer complain one day that my process challenge device had changed, they couldn't sterilize them, and they said we've done nothing wrong, we've done nothing different. So I hopped on an airplane, flew to Chicago, and went to the facility. They were placing the challenge device below a layer of stretch wrap, which is fine, that's how they validated. What they had done, though, was they had changed the person running the stretch wrap machine, and he thought if one layer is good, I'm going to put on six layers. So that was why we were getting process challenge device positives on production runs.

I like the open-weave stretch wrap. It makes it much easier to get humidity and gas in. It also makes it much easier to get humidity and gas out, which is important.

I'd say probably 90% of the products, at least in the United States and most every place I've ever been, are sterilized using the overkill. Overkill, as you find, is a fractional cycle from three half cycles. I've talked about the fractional cycle being a very short exposure and the importance of that. The half-cycle, most places in our past have taken a very conservative approach. If you get a biological indicator of survival at 15 minutes, I don't want to be anywhere near the edge, I'll estimate a half-cycle of 2 hours. I can't have any IPCD positives grow in a half cycle. I can have a few EPC positives grow. But now I go to my production cycle, I double it again. So I might run a 15-minute fractional cycle, a 2-hour half cycle, and a 4-hour full cycle. A lot of safety built into the cycle, like my previous speakers have said.

So end of the day, do we have a 10^{-6} sterility assurance level? I agree with the previous speakers, we're way beyond 10^{-6}. We can do better; we need to do better.

This is a typical overkill validation. You can see the fractional cycle, how fast the

time is in terms of being able to get a product kill to reduce the natural product bioburden. In this particular instance, we went to a 2-hour half cycle and a 4-hour full cycle even though we killed most of the biological indicators in the product with a 5-minute exposure. Conservative?

Here's an example of cycle development that I just finished. This is a product carton where the customer has spent $90,000 and 8 months, they were trying to develop an EO sterilization cycle. The product went inside the cardboard box and inside the closed cell foam. At the end of $90,000 and 8 months, with an 8-hour EO exposure, they were still getting BI positives inside the product. They approached me, knowing that I was sterilizing without the carton, without the closed cell foam, and when they came to me, I eliminated the box, I eliminated the closed cell foam using the exact same internal product with the exact same BI location and the exact same EO parameters, and we had a 1-hour exposure with complete kill of biological indicators.

Here's the actual data for the process product cycle development. Temperature the same, humidity the same, EO concentration the same. I could've validated a cycle less than 3 hours long. If I had kept the box and the closed cell foam, I would've had a cycle with greater than a 16-hour exposure.

One of the choices we have is to go to the BI/bioburden validation method. I like the method; I like the approach. I think we need a better definition on how to implement this before we switch over to this method. There's not enough guidance, in my opinion, in the 11135 document. It requires a lot more samples, a lot more technical challenges, and I do believe it would end up in significantly shorter cycles. I believe it would end up with reduced EO usage. I believe it would end up with reduced employee exposure to ethylene oxide and patient exposure to ethylene oxide. So the benefits would be exposure time is much shorter than the overkill and the product residuals would be significantly less.

The same curve again. I've actually started on a cycle development for a new product, and based on this with the process challenge device, external process challenge device, I can probably validate a cycle that's less than an hour long and reducing the EO concentration 40%. I'm going from 750 mg to 450 mg. So now not only have I reduced the time by more than half, I've reduced the EO consumption by 40%.

So the benefits: We use less EO per cycle. For the manufacturer, it's a significant cost savings in terms of dollar, resulting in shorter EO cycle times, which gives us more available EO capacity. Less aeration time is expected because we're putting less EO in and we're using shorter exposure times. And we would expect lower product EO residuals. And, potentially, we could lower employee exposures.

My concerns with the method are that we need to develop a process challenge device that works at the much shorter EO exposure times than overkill cycles are currently doing now. That's certainly doable, but it does need to be developed.

My second concern is the auditors understanding that if we did a full BI/bioburden approach, we use statistics; we use Stumbo-Murphy, we use Spearman-Karber, Limited Spearman-Karber-Holcomb. I'm not sure auditors will understand how that justifies that our full cycle still gives us a 12-log spore reduction. When I refer to auditors, I run a contract facility; it could be FDA auditors, it could be ISO auditors, it could be any of my 50 customers that I process for. They all have to understand how the BI/bioburden approach works and buy into the concept and the reality that it does work.

So my facility in 2020, I'm estimating that I'm going to run around 2,000 cycles, and if I could do BI/bioburden validation that was successful, the weight of EO processing for my facility would be reduced from 750 pounds to about 500 pounds or about a 35% reduction. Available sterilizer capacity would increase about 25%. The discharge from the abator would be reduced. However, I'm in California; I have six sterilizers, and my maximum

discharge from my facility is less than a pound a year. So even though I reduce my EO consumption, it doesn't change my emission limits.

Once a product is validated, many times a company needs to make changes to the product, add existing products, whatever; there's a document, 11135, that addresses some of it, and then AAMI Technical Information Report 28 does. How do we show equivalence that the changes to the modified product or new products are equivalent to what we've already validated? You can't do a full validation every time you make a change to a product or add a new product. This is how we address this. The guidance that's here on how to document package changes and product changes. Important when you do this, you document any changes to show that your modified or new product is not any more difficult to sterilize than what you've already validated.

So some of the possible actions for a validated product would be a letter to file. We looked at the product, and based on our technical review, it's no more difficult; we can sterilize that product going forward. You might do an additional fractional cycle or a half cycle to show that you get equivalent results. Sometimes you may end up having to do a full new validation. And one of the things you want to do is repeat your residual work. You may need a new dissipation curve or maybe just a single point to show that your residuals are still within the acceptable limits.

Something to consider, and this is for us going forward. We talked about a D value as being the time it takes to reduce the spore population one log. And almost all medical products have a bioburden of 500 CFUs or less. The overkill requires that you put a million spores in our product for our validation. Maybe we should reduce that number from a million spores; maybe that should go down to a thousand spores. Now instead of needing the 12-log spore reduction, we need a 9-log spore reduction. You want to reduce cycles; we have a lot of conservatives built into the validation of the cycle. So I'd like to see

consideration given to possibly lowering that million spores, particularly if we're going to put it in the most difficult-to-sterilize location.

Here again, going back to D values, a D value for a biological indicator used for ethylene oxide sterilization ranges from 3 to 5 minutes with, say, an average of 4 minutes. The D value used in alternative sterilization methods is usually 1 minute or less. Can we consider lowering the D value for biological indicators for EO sterilization? If we reduce cycles by reducing resistance, another way to achieve reduction.

And that's all I have. I thank you very much.

DR. LEWIS: Thank you, Mr. Christensen.

We have one further presentation before we go to the clarifying questions for the Panel, and we'll have about 30 minutes for those questions, so I would urge all of the Panel members to be thinking at this time about questions that they want to direct to these presenters.

We'll now hear from Ted May from Andersen Sterilizers, and Dr. William Andersen from Andersen Products, who will discuss flexible chamber ethylene oxide sterilization.

Gentlemen, if you'd begin when you're ready.

MR. MAY: Thank you very much. My name is Ted May. I'm the President and CEO of Andersen Products. I regret that Dr. William Andersen was not able to accompany me today. I've been asked to speak on the subject of ethylene oxide flexible chamber systems. This is a very traditional ethylene oxide sterilization, and it's one with a lot of application to our conversations today.

Specifically, I'm going to be talking about the characteristics of this system, how it differs from traditional chambers. I will be going over three case studies, and these are not hypotheticals; these are case studies of medical device companies that are using the process today and to show how this method can be applied very effectively to different

parts of the medical device community. Lastly, I'm going to talk about how this system is unique in its high efficiency. And at a time when ethylene oxide emissions are under very close scrutiny, I think this method has particular promise.

I'm going to start off by talking a little bit about the history of flexible chamber systems. For those of you who are students of ethylene oxide history, I'm going to go back to Dr. Charles Phillips, who is considered by most people to be the godfather of ethylene oxide sterilization, and Dr. Phillips, in one of his papers from the 1950s, describes using a flexible chamber in some of his early experiments. So this method goes back to really the very beginnings of ethylene oxide sterilization.

Practically, the first ethylene oxide sterilizers were developed by the Andersen companies in the 1960s. They were used in healthcare facilities and for industrial sterilization starting in the early '70s. These early systems are recognized by the Agency as pre-amendment devices. Subsequently, flexible chamber technology has been recognized by the Agency as a Category B sterilization system, and it has an AAMI guidance document, TIR56, that describes this method in detail.

This slide shows flexible chamber systems at their most basic. You've got a flexible chamber, a bag that is made of an engineered material. In our case, at the Andersen companies, this is a proprietary material. You've got a range of single-use gas cartridges, and I apologize for the small font there, but these cartridges range in size from 5 g to 18 g, and I call your attention to that because this is a full order of magnitude less than any other cartridge in use today. This is a very, very efficient system. On the right you see a sterilization cabinet, and the purpose of that cabinet is to maintain a consistent sterilization environment while the bags are being processed.

The characteristics of flexible chamber systems are themselves special. The bags are limited in size to about 60 L. If they get larger than that, they become awkward and other

problems present themselves. The original bags were gas permeable. We are now using bags that are also gas impermeable that mimic the lethality characteristics of traditional fixed chambers. The single-use cartridges that I mentioned.

This is a particularly delicate cycle. We are not drawing a heavy vacuum, we are not injecting steam, and so this is a cycle that offers unique advantages for very, very delicate medical devices.

The applications and scalability I'm going to go into in greater detail a bit later, and also the low emissions.

This slide is a fairly simple graphic showing the difference between a traditional chamber and a flexible chamber, and on the left you've got a traditional chamber, which as I believe everyone here knows you must fill with a fairly large quantity of ethylene oxide, and you've got to use that same large quantity of ethylene oxide whether or not that chamber is full. On the right you see a graphic of a flexible chamber cabinet with individual sterilization bags. And the thing I want to emphasize here is that with this method, you're able to scale your sterilization to your production needs. You're only using as much ethylene oxide as you need to for a particular sterilization challenge.

And this next slide shows the chambers in practice. On the left is one of a series of pallet chambers that the Andersen companies operate in Europe. We are very familiar with this technology. And on the left is one of our larger EO gas cabinets with a 10 sterilization bag capacity. The key thing again is on the left, you've got to fill all of the dead space around that pallet. On the right, each one of those sterilization bags has a vacuum drawn on it at the start of the process. So the flexible chamber, which is a sterilization vessel, collapses around the items that you're sterilizing. It ends up looking vacuum tight. And, again, there is no dead space, so you can sterilize with a remarkably small amount of ethylene oxide using this process.

And I'm not going to read this process description, it will be available later, but it's largely redundant to what I've already described.

I'd like to talk about applications and scalability of this process, and I'm going to start off with the recognition of the fact that this process is more labor intensive than traditional pallet chambers. You've got to load individual bags, and as such, this process is not going to be able to achieve the raw volumes that you can in a traditional commercial chamber. However, I would suggest that this method still presents a very valuable piece of the puzzle going forward.

We're going to look at three case studies; the case studies are going to involve, again, customers that are using this process today. The first would be in-house sterilization for specialty device manufacturers, and in that group I'm going to include companies that are performing device development, that are performing compatibility studies, that are producing specialty devices such as custom implants, things that are produced in very low volume.

In the second case study we're going to talk about small and medium device manufacturers, and in this case, I'm defining small and medium by the quantity of medical devices that they are producing.

And in the final case study we're going to look at a third-party commercial sterilization facility using this technology.

A number of the previous presenters, Mark Leahey and, I believe, a panel member, have talked about not just the availability of medical devices but the pace of medical device innovation. And this is critical. I've seen an estimate in the last couple of years where 95% of all new medical devices come out of the United States. And so while we're concerned about the availability of medical devices, we've got to be concerned about maintaining the pace at which innovative, disruptive technologies come to market.

This first case study addresses that. We offer a small footprint flexible chamber system that is easy to install. In this picture, below the sterilizer you see the abator that goes with that sterilizer. It's a very compact, very affordable system, and it's being used to great effect right now for this type of manufacturer and particularly people that are developing the next generation of medical devices.

This particular process, the EOGas 4, uses a 17 g cartridge. I'm not going to go through the slide in detail, but I'll draw your attention to the bottom line, which is a case study for heavy use, running a couple of cycles a day in this process. In this case, running the sterilizer basically 7 days a week, you have the potential of using about 20 pounds of gas per year. With our abatement system, you're going to be releasing a teenie fraction of a pound into the environment. So this is not just a simple system, an affordable system, but it's one that offers great potential in terms of emissions.

My second case study, I believe this is where things get really interesting, and I thank Denny Christensen for an excellent discussion of the advantages of sterilizing product in the final product packaging. As I guess all of you know, in a pallet chamber you are sterilizing product that is in the box, that is in the carton, that is shrink-wrapped, and in this case, we're going to be looking at small and medium-sized manufacturers who are sterilizing as part of their production process. And there are a number of advantages to this. You are reducing transportation costs, and I've heard horror stories recently of companies shipping product a thousand miles to get it sterilized. You are establishing greater control over your inventory because you're not losing access to product for weeks on end. And, lastly, this is immensely scalable. You can start off with one cabinet and begin to add cabinets as your production demands increase.

And going through this case study in detail, this particular manufacturer purchased a single EO gas cabinet with a 10-bag capacity, and again, by sterilizing devices in the final

product packaging, in this case Tyvek plastic pouches, the customer estimates that they can sterilize the equivalent of approximately a half pallet of finished product per day. And so operating 7 days a week, they can sterilize about two and a half pallets per week or about 10 pallets per month. That's pretty good.

This customer, over 10 years, kept adding cabinets, and today they are operating 10 of these 10-bag cabinets, so they've got 100-bag capacity per day. Their estimated volume is the equivalent of 25 pallets per week or a hundred pallets per month. And so this process, if you are using it as part of your manufacturing, has the potential to sterilize very significant quantities.

Looking at emissions from this process, the chart that I provided lays out the emissions for a single 10-bag cabinet, and again, looking at the bottom line there, which is heavy use, and that's running a fully loaded cabinet 7 days a week, you have the potential for annual gross emissions of about 85 pounds a year. With our abatement process, that works out to less than a pound a year. And so this customer that is running 10 of these cabinets and sterilizing the equivalent of hundreds of pallets of product is releasing less than 10 pounds of gas into the environment.

My final case study involves a third-party commercial facility that is using a flexible chamber method, and here, we're trying to do an apples-to-apples comparison with a traditional commercial facility, and by that, I mean we are sterilizing in the final -- well, not the final product packaging, the final shipping configuration, so the product is in the box, the box is in a case, and in this case, we estimate that a finished pallet is going to be the equivalent of about 50 of our sterilization bags.

A traditional ethylene oxide pallet chamber is going to be using about 6 to 8 pounds of gas per cycle, and I will defer to some of the earlier speakers who were talking about low concentration cycles, I suspect they've got that down, but I'm going to use six to eight for

the purpose of this comparison. That works out to a bit over 3,000 g of ethylene oxide per pallet. Using a flexible chamber process and 50 bags, you're going to be using between about 525 and about 880 g of ethylene oxide depending upon the cartridge size. And so this process is about 70 to 80% more efficient, again, in a straight apples-to-apples comparison.

Now, I have to emphasize that, as Mr. Christensen described, if you're breaking the product down into the final product packaging, you're going to be able to achieve multiples of this processing throughput.

This chart here looks at emissions data, I'm not going to belabor this point, but the flexible chamber process uses, again, 70 to 80% less gas than a traditional pallet sterilizer, and so the ethylene oxide emissions to the environment are correspondingly lower.

This is an examination of throughput in one of these facilities. Again, I draw your attention to the bottom line, as it were. In a straight apples-to-apples configuration, we're looking at about 24 pallets a week. We can achieve multiples of that by breaking the product down into its final packaging configuration. And so, again, we're not going to be able to achieve the raw volumes of the large commercial facilities. However, we are able to provide very significant throughput, and I believe that as municipalities start to enact stricter and stricter laws on the use of ethylene oxide in their areas, this type of small footprint, a very low emission commercial facility may be the only thing that you can put in different parts of the country.

So, in summary, I'd like to emphasize the fact that flexible chamber ethylene oxide systems are an established method; they've been around for a long time. This is a very gentle method. In fact, I would argue, it's the most gentle sterilization method offered today. It's ideal for a wide range of devices. It's a very attractive option for small and medium device manufacturers. And it's the most gas-efficient system currently available.

As this discussion continues, I would argue again that flexible chamber systems are a very important piece of the puzzle that we are trying to figure out.

Let me end by thanking FDA and the Panel for this opportunity to speak. I am particularly grateful for everyone's forbearance, this being the final presentation before lunch, and I will end there. Thank you all.

DR. LEWIS: Thank you, Mr. May.

May I ask the last seven presenters who have given us information this morning to please assemble before the desk here so that we can ask them some questions?

Actually, I would lead off with the question myself to all of you and invite whomever wishes to respond to it. Each of you has presented some unique ideas for how to reduce the impact of ethylene oxide, reducing concentrations, changing exposure times, changing validation methods, using different packaging, etc., and your presentations have sort of suggested that each of these has great potential. On the other hand, each is associated with a specific private organization and has been developed presumably in some isolation. I guess my broad question is what is the best method by which these different suggestions might be implemented into the industrial process in order to achieve practical utilization? If you have suggestions for that. What, for example, would be the role of the FDA, EPA, or other organizations in facilitating that, because that hasn't really been addressed by anyone, and I invite any of you who wish to respond to that.

MR. COGDILL: Phil Cogdill with Medtronic.

We've submitted three innovation challenges to the FDA, and we are also working with, collaborating with a number of industry leading companies to publish some papers that will get put out and recognized, because while this issue is hitting the United States, it also impacts us. We're all international companies, and we produce products around the world, and we need to get them approved by regulators around the world, and if it's not

published, a lot of times it's difficult to get recognized. So we believe that the innovation challenge is a great way to start getting this recognized not just in the United States but around the world.

DR. LEWIS: So is it your opinion that the current studies are adequate, that a simple publication is going to do this without needing a greater degree of oversight and management of the processes?

MR. COGDILL: Well, I think, you know, to not be -- I think that the benefits that we presented are expensive enough to get the companies to want to do that. And we also care about our patients, and we care about our, you know, workers and the environment as well. I mean, that goes along with our mission. So anything we can do to reduce the potential exposure and the emissions is a benefit, and that falls within our mission statement.

DR. LEWIS: Thank you.

Dr. Kim.

I'm sorry, did you wish to respond?

MR. McEVOY: Yeah, Mr. Chairman, just regarding your question and the presentation that I presented earlier on today, as I said in the presentation, we at STERIS are following very much what's described in the ISO standard, which is methods that are available for anybody to adopt them, and if anything, we've been presenting across industry and quite openly about our approach with the sustainability program, if anything, trying to encourage industry to adopt similar practices. And we've also been part of a presentation program, bringing it out to notified bodies because our program is really global at the moment. And, again, our focus has been very much to follow the ISO standards that are available for everybody to use.

DR. LEWIS: Thank you.

Does anyone else wish to comment?

(No response.)

DR. LEWIS: If not, Dr. Kim.

DR. KIM: Thank you.

My understanding now is that in these industrial sterilization units, a lot of different devices are being sterilized at the same time, perhaps a one-size-fits-all sterilization technique. Is there an opportunity to tailor, based on the material that's being sterilized, the size of it, the packaging, as we described, bundling like products to potentially overall decrease the amount of EO use and exposure?

MR. COGDILL: What we found is a lot of the cycles that we have were through acquisition, and they weren't utilizing the chamber to its fullest capacity, so they weren't being used a hundred percent. And so what we've actually found in my presentation is we're trying to combine those products into one cycle and that way we get full utilization of the chambers every time. And we're also optimizing that cycle at the same time, which Brian McEvoy talked about where we're going from about 700 mg, 600 mg down to below 400. And so that's reducing the quantity as well, and we're using those techniques, and so that's actually improving our ability to not only maximize the chamber utilization but also move that product to different sites if need be, because they validate into 1 instead of, let's say, 10 cycles.

DR. LEWIS: Thank you.

I would ask, as each of you answers a question or approaches the microphone, just please reiterate your name so that everyone has for the record who's commenting.

Dr. Burr.

DR. BURR: This may be a hard question maybe for Mr. McEvoy, but for a typical industrial EO installation, what's the annual consumption of EO in tons, and do you have any sense of the aggregate annual EO emissions from such a plant? That would be rather

different, I think, than the flexible.

MR. McEVOY: Yeah, Brian McEvoy, STERIS.

Yeah, it's a difficult question to answer and probably something outside my arena, but what I would say is your facilities and their size, their containment of chambers, the number of chambers, etc., can vary greatly. So, again, I think it's something that you look at on a facility-by-facility basis. As I said, our presentation this morning is about reducing that EO sterilant input into facilities irrespective of their size.

DR. BURR: There's got to be a medium facility that you guys have a sense of. That would be helpful, also. Or if you could express the EO input versus the amount in the annual effluent as a percentage of the input, that might be interesting. If it's 1% in the flexible chambers, I'm curious about a more typical industrial facility.

MR. McEVOY: Yeah, unfortunately, that's data that I just don't have at hand at present.

DR. BURR: It's pretty important data, actually; it would be good for us to have that.

DR. LEWIS: Dr. Tung.

DR. TUNG: A question for Dr. Mascitti. You know, I work in the OR and ICU, and sometimes I do worry about the amount of sterile plastic I deploy every day to do my cases. Do you see a lot of opportunity to reduce hospital use of sterile equipment that maybe through less waste we could get to?

DR. MASCITTI: I mean, I think there certainly is. I think it's just with the standards in the United States in terms of, you know, we often have patients in the ICU that are on contact precautions because they have a contagious disease, and any product that was in their room we dispose of in the fear of spreading it to other patients. I mean, I think there's certainly room for improvement in those areas, but I think it would take sort of some national societies or guidelines to come out to give us guidance on how to do that because

currently, you know, the guidelines that we follow don't support that kind of -- you know, at least avoiding waste in those scenarios.

DR. LEWIS: Dr. Yaszemski.

DR. YASZEMSKI: Thanks, Dr. Lewis.

Mr. May, I'd like to address this to you and at the same time, the topic, please, anyone else who is knowledgeable, please answer. You mentioned a 99% abatement. So I'm assuming this is post-treatment of the ethylene oxide after the sterilization is done, so if that's not true, stop me now and then explain that. But what is abatement? Do you chemically change the ethylene oxide and release 99% of it as something less toxic? Do you hook it to something else chemically? What do you do? And then anybody else who can answer a different way, I'd like to hear it because that sounds like a really good strategy.

MR. MAY: Yes, it's a great -- this is Ted May with Andersen Products. That's a great question, and I will defer to some of the other panel members to talk about the abatement process for the larger commercial chambers. We're using so little ethylene oxide that we're able to pass it through a cationic resin that chemically captures the ethylene oxide and converts it into an inert material so that what comes out of the stack, what comes out of the emissions of the sterilizer is air, and this greatly reduced quantity of ethylene oxide. There is no byproduct. And I'll defer to one of the other panelists to discuss the abatement process for a pallet chamber. Denny?

MR. CHRISTENSEN: Thanks, Ted. Dennis Christensen.

My sterilizers use a heated catalytic bed. It has a 99-plus percent efficiency of converting the ethylene oxide into water vapor and carbon dioxide. It's a very efficient system, and it gets tested on an annual basis.

DR. LEWIS: What is the barrier to wider-spread implementation of an abatement system such as that?

MR. CHRISTENSEN: I believe sizing up would be an issue. Both facilities use what we call a Lesni abator system. Brian, you're probably better able to talk to that than I am. I'm not sure if you use the Lesni.

MR. McEVOY: Yeah, Brian McEvoy from STERIS.

Yeah, there's a number of different systems employed across industry. I think the one that Denny's alluding to is a Lesni abator system, which again is a catalyst reaction of the EO gas, which is one that we do use quite a bit in our European facilities, for instance, but there's a number of other technologies available also.

DR. LEWIS: Thank you.

DR. YASZEMSKI: May I give a follow-on?

DR. LEWIS: Yes.

DR. YASZEMSKI: The cost. How much or how little does the abatement add to the overall cost? Is it very expensive, is it reasonable? How much does it cost?

MR. MAY: This is Ted May again.

It's a matter of scale, and so with our process of starting off with a very small amount of ethylene oxide, the abatement challenge is similarly reduced, and so this is adding 5% to the cost of a cycle.

MR. CHRISTENSEN: In my case, I can run two EO sterilizers on one abator. The cost of the abator itself is around 35-40,000 dollars. The principal operating cost is the electricity to heat the catalytic bag and keep it operating. But the abator bed itself is around 35- or 40,000.

DR. LEWIS: Dr. Wilcox.

DR. WILCOX: You can put this in the category of a dumb question from the human factors guy. It seems to me that the only reason we're here is because the EPA has a problem with the emissions, not a problem with use. So why aren't we just concentrating

on abatement? It seems to me if we could just get rid of the emissions, we wouldn't have to be jumping through these hoops trying to use less and so on. I don't know who that was a question for.

(Laughter.)

MR. COGDILL: Phil Cogdill, Medtronic.

We do use a lot of the same abatement equipment, which was the maximum available control technology, which is in excess of 99%. I think the EPA gentleman referred to some of the challenges with the fugitive emissions, and these are actually the emissions that are coming as you're moving product out of the chamber and through the distribution process and are continuing to off-gas. And so I believe the NESHAP regulations are going to be looking into that, the EPA is going to be looking into that, and industry, we're going to work with them and use the best available, you know, advancements that are going to be proposed to do exactly what you just recommended.

DR. LEWIS: Dr. Arduino.

DR. ARDUINO: Yeah, I was just focusing on abatement and whether current technologies that we're using now are actually adequate to meet the EPA requirements. And if it's about off-gassing of the products, couldn't our exhaust air from that aeration process also go through abatement of some sort?

MR. CHRISTENSEN: In my case, all of the ethylene oxide from the sterilizer goes directly to the abatement system. My process is an all-in-one and precondition; I sterilize and I aerate inside the chamber. I can modify the cycle, increase the cycle time, change the number of washes to reduce product residuals before I actually open the door. In most cases right now, based on product EO residual studies, I can release product as soon as the door is opened, once the biological indicator test results are available. So it's a very efficient method of removing when you're using the primary packages.

DR. LEWIS: Mr. Socola.

MR. SOCOLA: My question is for Mr. Cogdill. Your involvement in AAMI, you were the chairman of the working group for the industrial EtO, and I have an advantage over a lot of the Panel members is that I've been involved in the AAMI meetings since 1992; 1993 I heard about how EtO was going to be replaced; 1994 I heard about how EtO was going to be replaced.

My question is, when I started all those years ago, I validated products at 1,200 mg/L. Then we dropped down to 883 mg/L. I like the slides that I'm seeing in reference from the gentleman from STERIS, where we're dropping these levels down to almost 400 mg/L. So my question is, is the ISO and the American National Standards Working Group from AAMI looking at addressing this EtO issue, because I think there's a misconception that this is something that's been happening in just 2018 and 2019 when the reality is it's really decades old, correct?

MR. COGDILL: Phil Cogdill with Medtronic.

And that's a great question and comment. You know, back in the '70s almost a hundred percent of medical devices were sterilized with ethylene oxide, and to your point, back in '86 when the Montreal Protocol came out and CFCs were going to be banned and most ethylene oxide were sterilized with a blend of Freon and EO, everybody thought that ethylene oxide was going to go away because they weren't using a hundred percent in large chambers in very many locations. And what we saw was that a lot of manufacturers looked for opportunities to move as many of their products away, and that's when you saw the growth of radiation and you saw STERIS and Sterigenics offering up those industrial sterilization facilities so that small and midsize and even large-size companies could take advantage of that technology. And so even with all of that effort, we only saw about 45% of the volume move away.

To your point, yes, the working groups are discussing these changes. I think Denny talked about more informative information on how you implement the optimized cycles and the reduced gas concentrations, and I think that, you know, many of the people that were asked to come speak here today are on those ISO committees and will take that information back and put that into the documents so that it's front and center and people that are coming, you know, after us are going to be looking at optimized cycles instead of these, you know, conservative overkill processes that have gigantic amounts of gas concentration and cycle times built into them just for the sake of creating the safest possible, you know, product.

DR. LEWIS: Mr. McEvoy.

MR. McEVOY: Brian McEvoy, STERIS.

Just to further elaborate on the point made by Phil, the ISO Standard 11135 is actually up for ballot for potential review. We can't predict the outcome of the ballot because it's global. I think expectation would be that it's probably going to go through a review process with the ISO technical committee. And I think, as was mentioned this morning in some of the presentations, there's a number of methodologies in that standard, and we have been predominantly following one because we're probably lacking some guidance on some of the other methods such as the BI/bioburden method, which again will give us opportunities for further improvement. So I think as an industry -- and I think we're highly incentivized now, if the ISO document comes up for review, to work on some further guidance so we can avail of some of these more opportune validation approaches.

DR. LEWIS: Thank you.

Dr. Goldman.

DR. GOLDMAN: Thank you.

First, thank you for my having been invited to participate in this panel. So this is the

first time I've ever looked at this issue, so I haven't been looking at this since 1993, but I have some very, you know, fundamental questions about this problem, I mean, starting from the actual identity of what is the substance that we're calling ethylene oxide. I know, as a former EPA official, that oftentimes there are other substances in products other than the one, the main substance that is what they're used for, especially things like sterilants, and I also see that the EtO does break down into a couple of other substances that remain in our document that are known to me to be toxic, fairly toxic. And so when we're talking about the emissions, I like to think in terms of a mass balance. What's everything coming in and what's everything coming out and the identity of those and what are we measuring. Are we measuring the emissions only of the EtO or also of, you know, toxic metabolites that also might be emitted because that's important. You know, there is evidence that this is a carcinogen, a human carcinogen. It's basically mostly strengthened because of worker exposures in medical facilities and sterilization facilities and cancers in those workers. And so even though that doesn't come from emitting into ambient air, it does come from actual use of the product and not the pure technical chemical that's been purified.

The other thing that I'd like to understand, and it's just intriguing to think 1% of what's supplied is actually found as the "emission." But the way I think about emissions, it's everything that's somehow going into a waste stream and where does it go and what might be the exposures, including, you know, so-called fugitive emissions that might be occurring in a work environment. Whether that is a hospital or a sterilizing plant or whatever that is, even though EPA may not be regulating that, that is a concern because those workers inside those facilities are going to be the most exposed.

The amounts that might be from fugitives emitted not from a stack but in some other way, at least I'm guessing that's what EPA has been going after here, the amounts that might be emitted, and if you have a scrubber system or some system that is trying to

capture the EtO from a chamber and then convert into something else, I need to know what that is before I call it -- if you mean by inert that it's no longer a volatile that's going into the air or do you mean by an inert that it is not toxic. I don't know what you mean by inert, and I'd like to know a little bit more about what is that, and then where does that go, because I think, you know, in terms of sustainability of this, even though right now EPA might be focused on the ambient air and what's going into ambient air or only EtO in ambient air, if there are other toxic substances in other ways being emitted, EPA in the future could be focused on those things. And so I think those things are important to understand in terms of a sustainable technology that's going to work for a long time, especially if people are investing in it.

The last thing I'd say is that some of it evidently remains in the product, you know. The paper was specifically mentioned, cloth, other things, and since EtO is a human carcinogen, that is not without concern that there's a certain amount of that winding up in product. I would say especially, you know, again, considering people who work around these products may have frequent exposures, nurses and others who may be daily exposed constantly to some of these products, that to understand how much of the EtO is there. And so knowing where 1% of it is going doesn't make me feel comfortable that I know what's going on in terms of the health impacts of the use of this. So I'd just love to hear, you know, some comments about that so I can understand it a little better.

DR. LEWIS: Thank you.

Who would like to answer that?

MR. CHRISTENSEN: As Phil said, I'm the canary in the chamber. I've been doing this for 52 years. A couple things we're doing. One of the things we always do in my facility is we monitor for employee exposure to ethylene oxide. We have a recording system, we have alarms, so if the EO concentration in the sterilizer area goes above 0.5 parts per

million, it will ring a bell, light a light. My people are instructed to leave the building or leave the room anyway, the sterilizer room. At one part per million, we get a loud alarm and, you know, nobody goes in until that alarm goes off. I think one of the benefits of what we're doing with reduced EO and the reduced cycles is we can use this increased capacity that's available to us to do even further reductions of ethylene oxide to the product while it's still in the sterilizer. We won't change over a length of the cycle, but we can get more EO out while it's still in the chamber. Is that helpful?

DR. GOLDMAN: It is, although the 1 ppm level, which is the OSHA permissible exposure level, the PEL --

MR. CHRISTENSEN: Right.

DR. GOLDMAN: -- is not a health-based number. It is not. And it's one of the many OSHA PELs that is technology based. And so I'm not quick enough to be thinking about, you know, what the import of that is in terms of health, but I think that that's something, if I were in your position, I would be thinking about.

MR. MAY: There are a number of fairly broad -- this is Ted May with Andersen -- fairly broad topic categories that you brought up. I would suggest that ethylene oxide worker exposure has been in place and under study since the 1980s. If you go into a hospital, everybody knows that you have to monitor for ethylene oxide. The methods for monitoring ethylene oxide are very well established, and there are replacements for ethylene oxide in the hospital workplace that are not being tested for right now. I hesitate to use this term, but ethylene oxide is the devil we know.

And so, again, I would suggest that in terms of worker protections, that is very well established science. In terms of ethylene oxide residuals, there are FDA and ISO residual levels that must be met. I mean, everybody running a commercial facility is familiar with the different residual levels required for different product types, and so again, this is very

well-established science, and running an ethylene oxide sterilization facility, you have to abide by these levels.

I used the term "inert" regarding abatement. In our case, the ethylene oxide is captured, and it's turned into a long-chain polymer, a type of plastic that does not leave. There are no volatiles. And so this question of abatement technology is almost a completely different discussion, and I think we discussed three different technologies here, and I would argue that none of these technologies are releasing hazardous volatiles in addition to the ethylene oxide. But, again, that's a subject that we could get into at fairly great depth if necessary. Thank you.

DR. LEWIS: Thank you.

Dr. Tung, the last question.

DR. TUNG: Sorry, a quick question for Mr. Cogdill. In discussing the supply chain, you mentioned that there are constraints on the deliver phase, temperature and humidity. Is there a limitation to how far you can transport something once it has been sterilized?

MR. COGDILL: Yeah, we have to carry out transportation studies that go through cycling and go through shake, rattle, and roll, we call it, to make sure that the package is not breached and that it's able to handle and the cycling is what determines the amount of, you know, temperature ranges that we can, you know, put on our products that they'll be maintained, because then those are evaluated after those stability, you know, cycles that have been put through. As far as distance, we ship worldwide, and really, the product is acceptable as long as the package is still intact, and that's usually the determining factor.

DR. LEWIS: I thank all of the presenters this morning, you've really done an excellent job of informing us of many of the details and very much appreciate your coming and presentations. Thank you.

We're going to now break for lunch. We have 1 hour for lunch, and we'll reconvene

at 1:30, at which time we'll begin the Open Public Hearing, which will continue for 30 minutes. We'd admonish the Panel members as before to please not discuss this among yourselves or with anyone else. And I would ask Commander Garcia to give us some instructions regarding lunch.

CDR GARCIA: Thank you, Dr. Lewis. For Panel members, if you want to eat in the restaurant, call the Rooks Cafe here. There's a private dining area and some sectioned-off tables. There's also a buffet for not only the Panel members but everyone else for $19 a person. So if you just wanted to get through something quickly, that might be an option for you. That's all I have, sir.

DR. LEWIS: Thank you. We stand adjourned until 1:30.

(Whereupon, at 12:32 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:31 p.m.)

DR. LEWIS: Welcome back, everyone. We'll consider the meeting to now be reconvened, and we will enter into the Open Public Hearing.

For the record, all Panel members have been provided with written comments received prior to this meeting for their consideration. During the open hearing, public attendees have an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Commander Garcia will now read the Open Public Hearing Disclosure Process Statement.

CDR GARCIA: Thank you, Dr. Lewis.

Both the Food and Drug Administration 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 public advisory panel, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by this topic of the meeting. For example, this financial information may include a company or a group's payment for your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have 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.

Dr. Lewis, thank you.

DR. LEWIS: The FDA and this Panel place great importance on the Open Public

Hearing process. The insights and the comments provided can help the Agency and the Panel in their consideration of the issues before them today. That said, in many instances and for many topics, there will be a variety of opinions and a lack of consensus. One of the goals today is for the Open Public Hearing to be conducted in a fair and impartial way, where each participant is listened to carefully with courtesy and respect. Therefore, please listen to the person speaking, and do not attempt to participate independently of recognition by the Chairperson.

Each person will have 6 minutes maximum in which to address the Panel, and we ask each presenter to speak clearly, use the microphone in order to allow the transcriptionist to provide an accurate recording of your comments. The Panel appreciates that each speaker remains cognizant of their speaking time.

Will Speaker 1 step up to the podium now and introduce yourself? And we have Janet Trunzo from AdvaMed listed as the first speaker. Is she here?

(Pause.)

DR. LEWIS: Please proceed when you're ready.

MS. TRUNZO: Good afternoon. My name is Janet Trunzo. I am the Senior Executive Vice President at AdvaMed. AdvaMed is the Advanced Medical Technology Association, and that's my affiliation only. AdvaMed is the world's largest trade association. We represent medical device manufacturers, diagnostics, and digital health technology companies. On behalf of AdvaMed and the companies we represent, I want to thank you for this opportunity to speak briefly about the importance of ethylene oxide and the critical role it plays in helping ensure the safety and effectiveness of devices and in promoting patient care. First and foremost, the industry views safety as being critical; safety is our number one priority for the medical technology industry. AdvaMed members make every effort to ensure that devices are safe and effective throughout the product life cycle. For many

devices, sterility is essential to ensure its safe and effective use.

I want to step back and note that EtO has played a critical role in the sterilization of medical devices since the discovery of it as an effective sterilant way back in 1938. Today EtO is the most common way to sterilize medical devices, and it is now used to sterilize more than 20 billion healthcare products each year in the United States. FDA estimates that more than 50% of all medical devices sterilized in the U.S. use EtO. This prevalence speaks to the unique importance to our healthcare system.

For many medical devices, due to their material composition, their size, their shape, or their complexity, EtO is the only effective method for sterilization. Pacemakers, stents, dialysis sets, feeding tubes, breathing tubes, surgical kits are just a few examples of the many device types that are sterilized with EtO and are central to modern patient care, and they can only be sterilized using EtO.

In fact, EtO's compatibility and effectiveness with the plastics and polymers that are commonly used in medical products allows for sterilization of many medical device types that would otherwise be rendered ineffective or unsafe if sterilized with an alternative method. This is one reason why alternative methods, such as radiation, moist heat, or dry heat, have not replaced EtO.

As with most aspects of medical device safety, both regulators and the industry have a shared responsibility to ensure the safe and responsible use of sterilants such as EtO. FDA and other global regulators play an important role in ensuring that manufacturers' sterilization methods are properly validated to ensure their safety and effectiveness through the use of harmonized international standards. Medical device manufacturers employ teams of experts to ensure that they have standards and controls in place to responsibly manage the use of EtO.

Manufacturers must conduct extensive studies to demonstrate the required sterility

assurance levels that are to be achieved and maintained by their equipment and processes, and they also have to confirm that the sterilization process does not adversely affect the device's performance, its safety or effectiveness over the shelf life of the device.

However, while we recognize the necessity of EtO, at the same time AdvaMed members are committed to further reducing the amount of EtO used for effective sterilization processes by actively exploring methods and processes that reduce the amount of EtO that is used for a sterilization cycle. Industry is committed to investigating alternative sterilization methods, but it is important that these methods, these alternative methods provide the same sterility assurance level and result in the same device performance as EtO. But until there is a safe and effective replacement for EtO, we will continue to pursue our goal to reduce the amount of EtO used.

Optimizing the EtO process itself, the medical device packaging, and the approach to validation are examples of possible ways to minimize the amount of EtO sterilant necessary to sterilize devices. However, any potential solutions to reduce the use of EtO will not be achieved just quickly or easily. Any change to minimize EtO use, if even feasible, would require extensive product and process modifications, validation and verification testing, potentially major facility redesigns, and also the required notifications or clearances or approval by the U.S. FDA.

We appreciate that FDA has recognized this challenge and has raised concerns about the potential shortage of critical medical devices, and there may be a possibility of significant disruption in the current capacity of EtO sterilization facilities.

But in my conclusion, I just want to reiterate that AdvaMed member companies are committed to the safe and effective use of EtO for the sterilization of medical devices for which there is no acceptable alternative method. The commitment extends not only to the patients we serve but to the thousands of workers, engineers, and scientists we employ.

We strive to be not only good corporate citizens but also responsible and conscientious members of our communities. We're committed to reducing the amount of EtO needed for an effective sterilization cycle. We'll continue to research alternative sterilization methods and implement them once they are proven to be safe, effective, and feasible.

Finally, we look forward to working with FDA and other stakeholders on this important public health issue. Thank you.

DR. LEWIS: Thank you for your comments.

The next speaker is Lara Simmons.

MS. SIMMONS: Thank you. And thank you for this opportunity to address the Advisory Panel. My name is Lara Simmons, and I'm the President of Quality Assurance and Regulatory Affairs for Medline Industries.

A little background about Medline: We are the nation's largest privately held medical device manufacturer and distributor. We sell to over 40,000 hospitals here in the U.S.; virtually every hospital in this nation buys something from Medline. A large part of this market force is surgical kits. In fact, we are the largest manufacturer of surgical kits in the world.

We've also been in the middle of the ethylene oxide situation in Illinois as we own a sterilization facility that is located right next door to our surgical kit manufacturing plant. This sterilization facility sterilizes over 16,000 surgical kits per day. So to put that in a little perspective of what we've heard previously today, that's about 260 pallets per day or 91,000 pallets of product per year. The bulk of that product is Medline manufactured kits, but we also sterilize for about 20 outside customers.

These surgical packs, we have about 6,000 different active types of packs, cover all types of procedures for the hospital from trauma procedures, open heart procedures, cardiac cath lab, hip replacements, and many others.

Surgical kits provide several benefits to hospitals. They reduce the amount of items that have been opened individually and placed on the sterile field, thereby reducing the risk of accidental contamination. They improve efficiencies in the hospital, allowing the hospital to treat more patients. They also help reduce the risk that an item will not be pulled for a surgery, thereby minimizing the risk that a surgical procedure would have to be extended while that product is pulled, possibly putting the patient under general anesthesia longer than necessary.

These surgical kits are typically composed of disposable items and used for any given procedure. They are procedure and sometimes even surgeon specific, who dictate not only the specific products that are placed in the kit but the layering and sequencing in which they are placed. I have an example here. For those of you who have not seen a surgical kit, this is what they look like when they arrive at the hospital. So I'm going to take a moment and open this, and I'll leave it up here if anybody wants to look at it. This is an open heart procedure pack. This particular procedure actually has three packs, an A, a B, and a C, because there are so many components needed. Some of these surgical kits can contain up to 200 different components.

Ethylene oxide sterilization is critical for these products because it's one of the only modalities that is not only compatible with the myriad of devices within, so we'll have inside this pack, I'll show you in a moment, cellulose-based products, paper, cotton, plastics, polymers, Teflon-coated products. So when you add all of those together, ethylene oxide is not only the only method that's compatible with these products but also that can penetrate through the cardboard carton, through this breather pouch, this outer wrap which becomes the sterile field for the surgical table, and then down through the layers inside. As you can see, a paper bag filled with many small components --

(Off microphone.)

MS. SIMMONS: So there's a lot of things that go into these kits. Ethylene oxide also is the only method that can sterilize long lumens and coils of tubing that we place inside these kits.

Medline, as a company, is deeply committed to the community where we are located and to the health and safety of the residents and our employees. Many of the local residents work in our facility.

As of right now, Medline has invested almost $5 million in upgrading the emissions controls on our plant. We are essentially setting up redundant systems, and if you look at this block diagram, I've given you a very simplified version of what we have done. The black is the original emissions control process. The red is what we're adding. So if you look at this, basically we're taking emissions, running them through our original abatement technology, and then layering additional abatement technology on top of it. Each one of these technologies has the ability to reduce emissions by 99%. So by layering 99% on 99% on 99%, when we are finished, we will drive the emissions down to the point where they are virtually undetectable coming out of our stack.

The entire facility is under negative pressure. That is being upgraded to comply with the U.S. EPA Method 204 and will be monitored. What the negative pressure does, if you're familiar with it, is it basically makes sure that air is constantly being sucked into the plant so that there are no fugitive emissions. So when you open up a dock door or you open up a door in our facility, there's a gush of air that comes inside. If you've ever been inside a negative pressure facility, you'll be familiar with what I'm talking about.

In addition to this, Medline has always been very aggressive about cycle optimization. We reduce the time and amount of ethylene oxide used as a matter of course. For example, the cycle that sterilizes these surgical packs currently runs about one and a half hours, and we are currently actively looking at ways to try and reduce the level of

ethylene oxide that we use in terms of volume. The challenge with that is that in order to drive a lesser amount of ethylene oxide into the pack, we have to increase the vacuum, add a nitrogen blanket; there's things we have to do to help do that that pose risks. If I pull too deep of a vacuum, some of the sealed products in this pack, the seals will pop.

So, almost out of time. In spite of these efforts in modeling which shows that we will reduce these emissions to the virtual undetectable level, we are still facing legislation in Illinois that will virtually ban ethylene oxide and result in our plant closing. There is tremendous confusion among the general population about ethylene oxide, the availability of alternatives, the impact of another facility closure that are very difficult for us to overcome. Right now one of the big misconceptions is that ethylene oxide is used because it's the cheapest method. It is not. Steam is typically the cheapest industrial method of sterilization.

So the second most common misperception is that by banning ethylene oxide, within the amount of time for the ban to take place, we will develop an alternative to ethylene oxide, because there is confusion about how long development of an alternative will take.

So our ask here is that we continue to work together to communicate, to be collaborative, to help the industry, to help legislators, to help the communities understand what the actual situation is, what the actual risk of shortages is, and also understand the timing it takes to develop alternatives.

We very much appreciate the Agency's efforts in managing the shortages as well as the innovation challenge for alternative methods. Medline has been actively looking at many of these alternative or newer methods that have come up and are continuing to look at those as alternatives for us.

So, thank you for your time. We greatly appreciate everything that's been going on and thank you for this opportunity to speak.

DR. LEWIS: Thank you.

The third speaker is Kim Nubel.

I'd like to note for the Panel that after this speaker there will be an opportunity for clarifying questions from the Panel, so please be formulating your questions at this time.

MS. NUBEL: Hi, everyone. My name is Kimberly Nubel.

DR. LEWIS: Please use the microphone.

MS. NUBEL: My name is Kimberly Nubel, and I'm from Atlanta, Georgia, and this is Ann Louise Hatfield, also from Atlanta, Georgia, and I'm here representing my community and to stop Sterigenics. I, like many of my residents in my community, we were shocked when we found out about the Sterigenics facility in Atlanta that was emitting EtO.

When I learned this, my family history made sense. I was adopted. My birth mother was pregnant with me in 1972, living near the Sterigenics plant on the Chattahoochee River. I went to a top private school 1.4 miles from the plant. I had learning issues while I was at the school that now seem to correlate with the neurological impacts of EtO. My parents moved me to a different private school about 12 miles from any EtO sources, and my learning issues went away.

By a weird twist of fate, we bought our dream home in Smyrna, 4 miles from Sterigenics, not knowing that I moved to the neighborhood where my family cemetery is and where my family have lived for over 40 years. I learned after moving there that my father died from a sudden heart attack at 46, three of my family members had cancer, three had neurological challenges, and my kids now have severe learning issues. In my godmother's neighborhood alone, where houses sell for an average of 1.8 million, which is 3 miles from the plant, there have been 45 cancers in 33 houses during the last 20 years. Our former governor's wife has undergone extensive chemotherapy for breast cancer and lived in the governor's mansion for 8 years, 4 miles from the Sterigenics plant.

What do all these people have in common? It is that we lived within 4 miles of the Sterigenics plant that is permitted to emit EtO. Even 9 days after the closing of the plant, EtO levels higher than the EPA measurement standards were still present in locations around Atlanta and Smyrna.

The NATA report estimated that around Smyrna and Atlanta, ethylene oxide causes about 70 of the 114 extra cases of cancer for every million people exposed over their lifetimes. The EPA considers the cancer risk from pollution to be unacceptable when it tops 100 cases for every million people who are exposed to a chemical over the course of their lifetime. The reality of my godmother's neighborhood right here was 45 cancers in 33 households out of approximately a hundred people, and that is almost 50%.

These are the cancers that are caused by ethylene oxide on the slide. These are the most publicized cancers from the exposure to EtO, and there are more people affected by these cancers than the probability of chance. And it is not just cancer; it is changes through DNA, and there have been previous studies on low sperm count, neurological effects, genetic alteration, spontaneous abortion, cognitive learning, and retention. These topics affect us all and our loved ones.

So why is there so much EtO being allowed to be released into any neighborhood? From a Canadian research paper, an examination of the fugitive emissions from U.S. ethylene oxide production facilities in 1988 suggests that significant emissions can occur as a result of faulty design and inadequate maintenance or monitoring, as we have seen with the Sterigenics and BD Bard plant in Georgia. Leaking pumps and flanges accounted for 30 to 40% of the total estimated ethylene oxide emissions. And what about the other 60? Could the remaining 60% of emissions result from faulty venting systems that are supposed to be scrubbing the air?

I want to point out these are the schools right here listed. Here are some of the

private and public schools in a 5-mile radius of the Sterigenics plant in 2019, and according to a media outlet, ethylene oxide molecules disperse in outdoor air but they don't disappear for a long time. The chemical has a half-life of up 200 days in the air, or almost 7 months. That means it takes that long for just half of the chemical to break down, and with constant emissions, there is no air without the presence of ethylene oxide. And the amount of this chemical in the air is compounded over time due to constant emissions.

This is a geographical location of some of the schools within the 5-mile radius, and emissions have been found to travel much further than the 5 miles. How many other communities are being poisoned by EtO sterilizers? Not only do we have this problem in Georgia, we also have plants around the United States that also emit EtO.

Manufacturers were put on notice by the FDA in April of 2019 to make contingency plans as the grassroots effort began to show progress. The current statements being made about device shortages by the FDA are highly irresponsible and show undue influence on the FDA by industry lobbyists. Any shortages of medical equipment, if they exist, are the direct result of lack of action by the FDA and the industry after the December 2016 reclassification of ethylene oxide to a Class I carcinogen; 28 months of inactivity is negligent. The cancer-causing factors of this chemical have been cited in research papers dating back to 1981.

By continuing the emissions of ethylene oxide, Sterigenics and other companies are poisoning the air in order to increase their profitability in sterilizing medical equipment. We believe that the use of ethylene oxide in a manner that creates any emissions is unethical. The financial profits of Sterigenics and their competitors should never outweigh our basic right to breathe clean air.

Thank you very much.

DR. LEWIS: Thank you for your presentation.

We now have an opportunity for clarifying questions from the Panel. I would ask the three speakers if you could come to the table, please. And I would like to ask the Panel to begin any questions they have.

Yes, Dr. Wilcox.

DR. WILCOX: This is for Medline. I think you made a convincing case that the systems you have in place at your facility would meet the EPA issue, the problem that EPA has with the emissions; is that right?

MS. SIMMONS: The challenge is that if you look at the IRIS value of 0.2 parts per trillion, the challenge with that is the technology can't measure that low. So although the emissions will be below the detectable limit --

DR. WILCOX: Um-hum.

MS. SIMMONS: -- the actual emissions are based on modeling because we can't measure low enough to determine if we're down to that risk factor or not. Point one parts per trillion, I'm sorry.

DR. WILCOX: So does that mean no?

MS. SIMMONS: That means --

DR. WILCOX: The EPA is still going to consider you in violation of their standards?

MS. SIMMONS: It's not an actual standard, and I defer to the folks from the EPA that are here.

DR. WILCOX: Okay.

MS. SIMMONS: But the IRIS risk assessment isn't a regulatory standard; it's a number that they use for identifying risk in areas of concern to look at for further regulation. So it's not an actual standard. We have been and are compliant with our current EPA and will be compliant with our future EPA permit.

DR. WILCOX: Very good.

DR. LEWIS: Are there are other questions? Yes.

MS. PEKAR: Hi, Carol Pekar.

I was just going to ask, you referenced, you know, changing to an alternate method of sterilization would take years. Would you or Janet have an estimate of what it would take to really qualify, change, revalidate, get FDA approval for an alternate method of sterilization?

MS. SIMMONS: So for a true alternate method of sterilization, so not just switching from one current modality to another -- again, I'll defer to -- the gentleman from Medtronic probably can answer that better than I can. But these methods take a significant amount of time because, in addition to validating that it's effective, the material compatibility and shelf-life studies take years to complete. So that's why we say that a true alternate to EO is going to take a long time to develop. As a manufacturer, we use multiple methods, so we're familiar with switching from one method to another, which also is very time consuming. It requires a lot of work.

MS. TRUNZO: It's very difficult to estimate how many years that would take because of the number of steps. And I think in my testimony I referenced not only do you have to validate and verify that through validation testing that the method works, it has to work for assuring the sterility level. You have to test your device to make sure it is as safe and as effective as it was designed. You have to file a submission to FDA. And even during this development of a new test method, if it's a new test method, the facility may have to be redesigned, your process and your methods for manufacturing may have to be redesigned, and then, after you get all of these of things done, then you have to submit to FDA. So I wish I had an answer of how long it takes, but it's in multiple years.

DR. LEWIS: Dr. Benowitz.

DR. BENOWITZ: I have just a clarifying question for the final presentation from the

community group in Georgia. Your focus was on potential impacts within a 5-mile radius, and I'll just ask you to clarify what the basis is of that area of concern.

MS. NUBEL: Well, I have read studies; the gas actually travels a lot farther than 5 miles, but we concentrated on the 5-mile radius around Atlanta based off of some of what the media outlets were reporting.

DR. LEWIS: Okay. Seeing no other questions, I pronounce this session of the Open Public Hearing to be closed. Thank you all very much for your presentations.

We'll move on to the next phase of this, and in this portion of the Panel meeting, the focus will be on the elimination of ethylene oxide emissions for device sterilizations and modalities with existing industrial infrastructure known to the FDA.

Ms. Emily Craven from Mevex will kick off this portion of the meeting and will address the gamma sterilization of medical devices.

Ms. Craven, would you please begin when you're ready?

MS. CRAVEN: Thank you for the invitation to speak today about gamma sterilization of medical devices as a potential alternative to ethylene oxide. I'm involved with the radiation sterilization industry as the co-chair of the AAMI Radiation Sterilizing Working Group WG-2, and I represent Canada internationally on the ISO sterilization standards working group specific to radiation and assurance of sterility.

I've been working in the sterilization industry for more than 20 years with experience in radiation system design, radiation dosimetry, and sterilization science, including 8 years of gamma process design at Nordion. I presently work for Mevex, which is a company specializing in radiation sterilization systems.

Gamma and ethylene oxide are considered the big two in terms of commercial options for sterilization of single-use medical disposables. As we've already heard today, ethylene oxide is approximately 50% of total sterilized products. Gamma takes up 80 to

90% of that remaining volume.

From a medical device standpoint, the types of products currently gamma sterilized cover a full range of devices used for first aid, blood collection, operating room supplies, implantable devices, and more. Other products which are not classified as medical devices may also be sterilized in gamma, including labware, bioreactors, and other components used for pharmaceutical and aseptic manufacturing. In some cases, subcomponents of medical devices may be irradiated as a decontamination step or in the case of ultra-high molecular weight polyethylene used for orthopedic devices as a materials modification step. Gamma is also used for other radiation processing that is unrelated to the material device industry, including the irradiation of spices and food products.

Radiation sterilization is a conceptually simple process. A gamma irradiator consists of a source of radiation inside a shielded room, a conveyance system to bring products into the room and expose them to the source of radiation and then them back out again, and a control and safety system.

For gamma processes, the source is a rack of cobalt-60 pencils. Products in their final shipping containers are loaded into totes or carriers and circulated around a source in a way that absorbs as much of the radiation as possible, as uniformly as possible within the irradiation containers. The intent is to provide a uniform dose to all of the products, but there will always be a distribution of dose to the process itself.

The process is validated in order to make sure that the lowest dose received will be enough to provide the required sterility assurance level to the products and the maximum dose will not affect product functionality.

How much dose is received by the product is a function of the irradiator design, the amount of activity in the source rack, the amount of time the product spends in position around the source, and the density of the product and the products that are surrounding it

in the irradiator.

Ionizing radiation works on a molecular level by disrupting bonds, which creates free radicals that can react with other molecules. When high-energy photons hit a microorganism, its DNA is disrupted to the point where the organism is no longer viable. Many medical devices are made with plastics.

As we've heard, it's important to consider what happens to the polymer chains when they are irradiated and how radiation can affect these materials and their properties.

Due to the statistical nature and the numbers and types of distribution of bioburden on a product, combined with the random interaction of gamma photons with the materials around it, we can calculate a probability that a certain dose of radiation or number of energetic photons interacting with a product will provide a certain reduction in the population of microorganisms.

There are three methods which are standard now to make this determination. The first two methods, Method 1 and Method VD_{max}, assume a standard distribution of resistances based on a presumed population of microorganisms that would commonly be associated with a manufacturer of medical devices. Method 2 determines the resistance of the population of microorganisms specific to the product itself.

Methods 1 and 2 provide a calculation of the minimum dose required to ensure that the product is sterile. VD_{max} alternatively allows for the substantiation of a chosen dose as long as your average bioburden stays below a certain threshold, the most common dose being 25 kGy. The perceived advantage of choosing a dose to substantiate is that it requires fewer product samples and tests in order to validate the chosen dose.

Additionally, for gamma processes where there's a large volume of product in an irradiator at a given time, processes are more easily and efficiently run when similar products have common dose requirements.

Ultimately, the method chosen is based on the product requirements; does it need a low minimum dose for functionality, manufacturing controls; is the bioburden consistent over time, and the radiation process that's selected.

We just talked about how the minimum dose is determined. Maximum dose is driven by product functionality; this is the critical thing and one of the reasons why ethylene oxide is so popular because it does maintain product functionality for a large number of products. And, again, when considering single-use medical devices, the main components are often polymers.

The three mechanisms in which radiation can affect polymers all may have different effects on material properties. Recombination describes where the polymer chain breaks and then recombines at the breaking point, and this is the most neutral of the processes, as it generally does not lead to material change.

Chain-scissioning refers to the process where the polymer chain breaks permanently into shorter chains, which generally causes a degradation or weakening of the polymer.

But then cross-linking has the opposite effect where new bonds are formed between adjacent chains, which can actually make the material stronger.

Different polymers are more or less radiation resistant, meaning that certain of these effects are dominant. An excellent industry resource for the compatibility of materials subject to sterilization processes, including radiation, is AAMI TIR17. Phil Cogdill already referred to this excellent guidance document, and it provides a subjective measure of radiation compatibility for many different types of polymers.

Additionally, external influences may affect the dominant radiation mechanism on the polymer, including exposure to oxygen and the ozone generated when air is exposed to radiation and which tends to cause more degradation. The presence of radio protectants, which act as free radical scavengers that preferentially react with those ionized bonds, and

temperature, for example, very low temperatures may have a radioprotective effect.

In terms of non-polymeric materials, metals are extremely stable and normally do not pose a challenge to gamma radiation.

In terms of any liquid or other chemical components, the effect of the radiation and the formation of free radicals could potentially change the properties of the components, which can be significant when dealing with pharmaceuticals, and this has been studied extensively. Again, it doesn't mean that gamma necessarily doesn't work, but only that the effect of the radiation needs to be taken into account when considering label claims and potencies and things like that. The same goes for general biocompatibility.

This table shows an order of magnitude level comparison of various polymer materials. Looking at some of the more commonly used polymers, polyethylene, polycarbonate, and PET all show up in the thousands of kilogray range, PMMA and PVC both show up in the hundred kilogray range, all of which are easily above what we'd be seeing in a gamma sterilization process. You will see that polypropylene, another commonly used polymer, shows up in more than one location, and this is actually an excellent example of how radio protectants can take something from being non-radiation compatible to something that can be radiation sterilized. There are variations in compatibility within each of the polymers listed, which have to do with how they're manufactured and specific formulations for each.

Whether or not a product can be transferred from ethylene oxide to gamma depends largely on why it was in ethylene oxide in the first place. In some cases, for example, products that have PTFE or Teflon components or electronics that are radiation sensitive, we've heard about pacemakers, gamma is just not a good option. In other cases, though, it may just be that ethylene oxide was the technology that was available or that the device manufacturer was the most familiar with.

It's also possible that the device showed radiation sensitivity at a maximum dose below what a particular radiation process was able to deliver. So depending on the product, some of the challenges with radiation that led them to go into EO in the first place may be overcome with additional testing and/or product and process changes.

And, again, none of these are easy, but these are some potentially mitigating factors:

- A different choice of materials, so using guidance available in TIR17.
- Testing components to failure for maximum dose determination versus testing up to the maximum that one system may deliver.
- Using radio protectants where available, for example, radiation-stabilized polypropylene.
- Validating lower radiation doses for sensitive materials by substantiating doses less than 25 kGy or using alternative dose determination methods.
- Modified radiation processes to improve dose uniformity through different product loading patterns, using modified environments where they improve material properties.
- We've heard kits mentioned many times today with a few examples as well. For kits where there are multiple components that are sterilized together, remove or replace non-radiation resistant components. Easier said than done, I realize.
- And determine if the maximum dose was set based on cosmetic versus functional requirements. So discoloration or odor may not actually affect the safety or efficacy of the product.

I've talked about some potential changes to the product and how it's validated. This slide compares the process of EO versus gamma and how that might, in fact, impact some of the downstream elements such as final product packaging, turnaround time and other

constraints, and how the product is designed and validated.

We talked about sterilization dose determination for gamma. For EO dose or cycle determination, this is sometimes done as an overkill method or as a bioburden-based method, as mentioned during several previous presentations. For both EO and gamma, an end-to-end approach to bioburden control is required for a validated process, so that's where they're similar. The maximum temperature in both processes is roughly equivalent, so no extra considerations there need to be taken into account.

Similarly, a product package and design that is required to go through humidity and pressure changes should be fine going through a process where these parameters are not changed. Radiation does not leave residuals, so no further testing on this would be required. Biocompatibility, if applicable, would still need to be tested regardless.

Packaging: Packaging for ethylene oxide design needs to be gas permeable in addition to providing a sterile barrier. The packaging requirement for gamma is only a sterile barrier, though the packaging material also needs to be radiation compatible. This is not an issue for Tyvek, which is very commonly used in EO packaging. An assessment needs to be done, but packaging redesign would likely not be required. Additionally, both ethylene oxide and gamma processes are penetrating enough for products to be sterilized not only in the final product packaging but in shippers containing multiple products. It is probable that the shipper may not need to be redesigned for a gamma process versus ethylene oxide.

And then the sterilization time for gamma versus EO is also comparable. The time during the actual sterilization process for gamma is generally less than for EO. But depending on the facility that's being used, be it internal or contract, the time between manufacture and the availability of the product may be similar depending on how the gamma system is scheduled or whether or not the EO system uses parametric release.

Gamma, as we've heard, is a standard sterilization process, and ISO 11137-1 is the consensus standard recognized by the FDA on validating radiation processes with Part 2 on dose setting and Part 3 on dosimetric aspects also realized. Part 4 on process control has passed ballot and will soon be published, hopefully by the end of the year.

Gamma has been a default sterilization modality and a default radiation technology for decades. But the standards and guidance apply equally to all radiation sterilization methods, including electronic beam and x-ray.

Gamma technology comes with a few more regulatory hurdles specific to the use of radioactive sources. All irradiators, machine or isotope source, require licensing to operate. But gamma systems need to follow 10 C.F.R. 37, which requires extra security measures to guard against theft of cobalt-60 sources. The perceived threat of a terrorist using a radioactive source to make a dirty bomb has led the Department of Homeland Security and the U.S. Department of Energy to create specific programs to encourage the use of alternative technologies to these sources when possible.

At one point there was a push at the federal government level to ban or phase out the use of cobalt-60 altogether, but thankfully, a lot of lobbying and education was done to demonstrate the need for this technology and the long history of its safe and effective use for sterilization, so that ban never happened.

That being said, the political pressure is there, as well as the uncertainty that comes with changing political landscapes and decisions being made, not about real safety issues but perceived issues and not about the best sterilization technology but about what's available. What it really means from an industry standpoint, though, is that gamma may no longer be the default radiation technology choice in the future.

There are a few things to consider when it comes to how much capacity is available in gamma. The first is infrastructure. Gamma irradiators have a rack that holds cobalt-60

pencils, which gets added to over time to maintain or increase the amount of activity and therefore the amount of product that can be sterilized. Some irradiators may run with unused capacity, meaning they have more than enough cobalt to process all their volume, but due to the nature of cobalt, this means that the operator will be paying extra in isotope for the opportunity cost of getting new business.

Then the next question is whether or not there's room to add more isotope as required to meet new volume requirements. The room I'm referring to is both how much activity is licensed or allowed versus what is installed and how many empty spaces are available to add more pencils. For irradiators that are more than 20 years old, which represents the majority of the irradiators in the United States, generally, they run up against both limits.

The other question is whether or not there is enough of an increase in demand to actually build more gamma irradiators, and as discussed previously, there are incentives not to do this. Despite this, however, new gamma sites have been built in the U.S. as recently as 2017 by Sterigenics.

The second thing to consider in terms of gamma capacity is the availability of the cobalt sources themselves. The nature of radioactive isotopes is that the amount of activity goes down over time due to decay, which means that you lose roughly 12% of your total activity every year. In order to maintain throughput, you have to add this much activity annually to your site, in addition to any extra for growth or new capacity.

This year has been a challenge for cobalt supply, and a supply tightening was announced, which essentially means that users of cobalt-60 were not able to get all of the cobalt that they were trying to order. And the reasons given for this were many-fold, including an unanticipated decrease in supply coming out of Russia, timed against the general lumpiness associated with reactive dischargers and the refurbishment of the aging

reactor for producing cobalt, and it's anticipated that this shortage is not permanent. But for all the time that the cobalt supply is down, gamma irradiation can't grow. Is it possible to increase the amount of cobalt-60 that's produced? Yes, but this is a long-term proposition.

Can gamma capacity replace EO? Thankfully, perhaps, due to the current capability constraints or capacity constraints, so a lot of thought has actually been put into how to use cobalt more effectively. In the short term, capacity can be freed up by moving products that are not medical devices to other technologies, including labware and products for decontamination like spices, as mentioned. These types of products generally have an easier regulatory pathway to move around and in some cases represent a significant volume. This is actually already being done at many sites as more machine source capability is being built and gamma capacity is at a premium.

In the longer term, we can look at the way we run medical device processes and how validations are performed. We talked about establishing lower minimum doses based on what's actually needed for the product as opposed to using a commonly substantiated dose like 25 kGy. One advantage of gamma is that it's usually able to provide a tight dose distribution. So to make room for potentially sensitive products coming from EO, medical devices that are known to be radiation hardy may also be moved to other radiation technologies. That may result in a higher dose distribution. And, yes, more cobalt-60 could be made, but this is a long-term process, as mentioned.

In all cases, we're talking about incremental changes over a long time frame. There is not a solution that would allow the transfer of a significant volume of EO-sterilized devices to gamma today, which would in actual fact require doubling the current gamma processing capability.

And let's not forget, again, for many products, ethylene oxide is still the best process

available. No single replacement technology will provide a perfect solution.

And on a final note, there are other radiation technologies available that are machine source-based and where infrastructure is in the process of being built up to help some of these demands, and Dr. Thomas Kroc from Fermilab will actually talk more about this in the next presentation.

And thank you very much.

DR. LEWIS: Thank you, Dr. Craven.

We'll now hear from Dr. Thomas Kroc from Fermilab, who will present on x-ray and e-beam based industrial sterilization methods.

DR. KROC: Thank you for the opportunity to --

DR. LEWIS: Microphone.

DR. KROC: Thank you for the opportunity to speak to you.

DR. LEWIS: I don't think it's turned on.

DR. KROC: Thank you for the opportunity to speak to you. My name is Thomas Kroc. I am a physicist at the Fermi National Accelerator Laboratory, and I'm going to talk about electron and x-ray sterilization as potential sterilizers for medical devices.

So I was asked a few questions to discuss. One of them is just an overview of x-ray and e-beam and how are they different from gamma. The operational element in radiation sterilization is the creation of electrons. Electrons are the ionizing agent and do about 99% of the killing. Photons, either x-ray or gamma rays, are a way to penetrate deeper into a product, but then they create electrons which then do the killing in that. And the terminology, x-ray and gamma, refer to how the photons are being produced. Gammas are generated within the decay of nucleus of atoms, and x-rays are generated from transitions in the electrons that are orbiting the nucleus. Outside of that nomenclature difference, though, they are essentially the same.

Because of how they're generated, gammas tend to be more mono-energetic whereas x-rays have a broad spectrum of energies. But, fundamentally, a photon is a photon and an electron is an electron.

This slide compares the energy spectra of three modalities, gamma, x-ray, and electron beams. The green curve there is the characteristic spectrum of the decay of cobalt-60. It has two very prominent peaks, one at 1.17 million electron volts, the other at 1.33 million electron volts. The electron beam in using medical device sterilization is typically going to be 10 million electron volts. That is the dark blue curve, very highly peaked right at 10 MeV. And then the red curve is what's produced with a 7½ MeV electron beam onto a target which converts the electrons to x-rays, and in that process, called the Bremsstrahlung process, you end up with a spectrum of energies much broader than with gamma.

So how does this, then, determine how deeply these various modalities can penetrate into materials? So as referenced, I've got the green curve which is the penetration ability of cobalt-60. This graph is for water, a density of 1 g/cm^3. The dark blue curve is the electron penetration, and that has a depth of only about 5 cm in water. The red curve then is the 7½ MeV x-ray beam, which actually has slightly better penetration than gamma. And so depending on how you set up your system in that, that actually could result in better dose uniformity than a gamma facility.

In generating x-rays you have a situation, though, based on fundamental physics of the efficiency of converting the electrons into the x-rays. At 10 MeV on this graph, the conversion efficiency is only about 12 to 15%, so 85% of the energy that you use to generate the electron beam gets wasted as heat in the target and only about 12 to 15% actually produces useful x-rays. So to overcome this, then, you need high-power electron beams, and that is kind of an emerging situation or emerging opportunity for accelerator-

based radiation.

In generating the x-rays, depending on the energy in this incident, electron beam, this graph shows the angular distribution. So in the red there is the 7½ MeV; it's very forward peaked in that many of the x-rays that are generated are actually generated in the same direction as the incident electron beam, whereas the gamma rays in an irradiator that was in the previous presentation, only about 30% of those gamma rays are actually utilized in irradiating a product because they're emitted in 4 pi steradians in all the various directions, and some of those directions are not -- actually impinge any of the product.

So the next question was what are some of the typical devices? The previous presentation commented on that a little bit. In my response, I'm going to focus on some work that has been funded recently by the National Nuclear Security Administration, and this is in comparing the performance of various medical device materials as a standard for gamma radiation but then looking at the performance in e-beam and x-ray. This was spearheaded by the Pacific Northwest National Laboratory and included a number of medical device manufacturers, accelerator providers, and other researchers.

So their goal was to identify various polymers and elastomers that are used in medical products, measure any physical effects that they would exhibit in the various radiation modalities, determine whether any of those effects would preclude the use of e-beam or x-ray. They're right now engaged in industry and public outreach on the results of some of their work and then to try to encourage the increased use of e-beam and x-ray as a sterilization modality.

Their initial activities here looked at two specific medical devices that incorporate six separate polymers, and what they have done is to produce rigorous data to compare these. So this is looking at the amount of yellowness that is induced in the tube portion of this device, and while there is a dependence on dose here, there is not a statistical difference

between the various modalities, between x-ray, e-beam, and gamma.

So what is required to be able to utilize e-beam and x-ray in terms of infrastructure? The biggest difference between e-beam and x-ray and a gamma facility is much more electrical power. The radiation from gamma is an inherent process from the decay of the cobalt-60. Here you have to generate the radiation itself. But the material handling systems are very similar; the dosimetry and process control is very similar.

There, in the past, has been a perception that the accelerator-based methods are more technically rigorous and require more specialized technical help, although the manufacturers have been working hard on addressing that issue, and now they report that the technical skills required to operate and maintain a facility are comparable to that of a well-qualified auto mechanic.

Because of that greater penetration of x-ray that I showed in an earlier slide, a facility might need slightly thicker shielding, but whereas you may have 40 totes or packages in a gamma facility radiation room, because of quicker throughput, which I'll mention in a moment, the irradiation room volume can be less in an x-ray or an e-beam facility. So that might result in a total less amount of concrete or shielding that you have to install. And then because it does not involve a radioactive material, it's potentially a less attractive target for improper use in that.

Another way to look at the infrastructure question, though, is addressed in this slide here, where I have noted the location of 11 contract electron-beam facilities currently in operation in the U.S., and then I've also noted a couple other facilities that are for other uses but do some medical device work also.

So what is the potential of accelerator technology in this area? One megacurie of cobalt in a typical panoramic industrial cobalt irradiator is going to be 2 to 4 MCi. The energy that's released there is about 15 kW of energy, so a typical radiation facility is going

to be 30 to 60 kW. This amount of beam power in an electron-beam facility is already readily available from electron-beam machines.

In my comments earlier about the x-rays, you have this inefficiency of the Bremsstrahlung process, and that needs to be overcome, so that requires 200 to 400 kW of electron beam power.

In terms of capacity, a gamma facility can provide about 10 kGy/hour and so can do about 3.4 m^3/hour/MCi at 25 kGy. An electron beam is many orders of magnitude greater than this. It can produce about 20 MGy/hour, whereas x-ray is about six times, on the order of six times higher capacity than gamma. And so for the same -- that gives you a comparison of about 1 MCi of gamma is equivalent to about 120 kW of electron beam power to produce a comparable x-ray dose.

Currently, accelerator technology, there are three main ways that you can do this. One is linear accelerators operating at room temperature. Right now those on the market can be 10 to 50 kW, although manufacturers are developing new machines that can push it up into the hundreds of kilowatts. Cyclotrons and another similar machine called a Rhodotron can provide between 50 and 350 kW. And then there are super-conducting LINACs that are currently in development; they can start at 250 kW and maybe up as high as a megawatt. And this capability, then, is what provides your direct equivalency to the current panoramic gamma irradiators.

So can x-ray and e-beam be an alternative to ethylene oxide sterilization? The answer to this is very similar to what the previous speaker said about gamma. One difference that can be noted, though, is that because of the shorter radiation times with e-beam and x-ray, any of the detrimental processes that are due to oxidative effects in that, those are going to be less prevalent in x-ray and e-beam because the treatment times are shorter.

Ultimately, it's the medical device manufacturers that decide on the sterilization modality. There are opportunities for more education among the manufacturers about alternative processes, incorporating the choice of medical -- of sterilization modality earlier in the design process because it's more difficult, as many people have already testified to about how difficult it is and how expensive it can be for revalidating existing products.

And that's all I have. Thank you.

DR. LEWIS: Thank you.

We'll now hear from Dr. Jonathan Wilder from the Quality Processing Resource Group, LLC, who will present on moist and dry heat sterilization of medical devices.

DR. WILDER: Good afternoon, everyone. Thank you for having me here. I'm honored to be here. I wanted to talk somewhat about what's on the screen, but I do have a little -- listening to the quality of the other talks, I decided to add a few things that are kind of offline right now.

So to begin with, I was asked to look into the issue of alternative technologies to ethylene oxide, specifically steam and dry heat, and my initial response was "hmmm." One of the advantages of the contract sterilization methodologies that have been discussed, including ethylene oxide, is low temperature. So it took a little thinking to figure out exactly how one might go ahead with this, but there is, in fact, somewhat of a silver lining here.

Basically, I did a sieve search on the capabilities in TIR17, AAMI TIR17, which is compatibility materials subject to sterilization, and there was a rule-in/rule-out process done here. I looked at this from a materials standpoint. I do have some other things that are not in the presentation that I'm going to talk about. And if you look in the TIR, you'll see that there were three dots or four dots, meaning compatibility was tolerable to good, and I used those as the criteria for the sort.

Why do we use EO in the first place? Well, it works, it has worked for many years,

and the product penetration is excellent. The material compatibility is excellent because, basically, the industry has designed around this process for the past 50 or 60 years. And the size of an industrial contract sterilization chamber allows economical sterilization.

And if you look at AAMI TIR17, I do have to give that citation, here's a listing of materials preferentially sterilized with ethylene oxide. Just look at it.

If you pull out those that are preferred to be in ethylene oxide rather than radiation per the TIR, Teflon, PFA, etc., etc., there are a lot of things that just won't work in radiation, so they kind of have to be done with ethylene oxide or something else.

And then when we go to look at the major cut here to what can you not do in steam and dry heat, this is the listing that the standard teaches us.

But there are a number of devices that can be used with ethylene oxide -- I mean with steam or dry heat, preferentially steam because it is a lower-temperature process as long as the moisture content of the sterilization process does not affect the device at hand.

So I took this last list from this slide and looked to see what were some other opportunities for dealing with them. Some, silicone, cellulosics, cannot be done with processes that are typically available on the market. Some can go to hydrogen peroxide vapor, which a lot of manufacturers have been doing on a lower level of volume, shall we say, and there have been hydrogen peroxide vapor sterilization of, for example, implants and so on for a number of years, 20 that I'm aware of, maybe more, and that works very well, and that's a good alternative in a number of cases. In other cases, it doesn't work so well at all. Cellulosics are impossible. That's the best way to get your process to error for a hydrogen peroxide process. And silicones apparently get unusable.

So what are some of the differences between thermal sterilization and ethylene oxide? Well, ethylene oxide has large chambers. Thermal sterilization usually requires a relatively small chamber by comparison because it's a pressure vessel. Anything over 15

psi, the pressure is going to require a Section 8 rating from the ASME; in other words, it has to be dealt with as something that can explode and cause shrapnel. In the worst case, a door will fly through five cinder block walls, that's actually happened once, and land in the parking lot, and the door was only about 4 feet by 2 feet. There's a lot of pressure involved and a lot of force involved, so it has to be dealt with carefully. Ethylene oxide has its own issues for safety, which are well known and discussed by others, I'm sure.

The maintenance requirements are similar to or less than those of ethylene oxide sterilizers. There is no toxic waste except in making steam or dry heat, so therefore electricity or, if you're using a gas-fired boiler, emissions from the boiler. Obviously, thermal burns, pressure vessel considerations are the real hazards here. And steam, as I mentioned, these cycles are somewhat shorter than ethylene oxide cycles.

If you're looking at steam cycles as typically envisioned, say, at 121 degrees Celsius, 250 degrees Fahrenheit, you are looking at a 1- to 2-hour total depending upon the temperature, depending upon the mass of load that's required, depending upon how long you need to heat it up and how much vacuum conditioning you need to do and the drying that is necessary at the end of the cycle. These are parametrically controllable, and typically, they run at 121 to 135 C, and I say typically because I'm going to go off script in a minute and talk about some other options.

If you need to penetrate loads, which we do with ethylene oxide loads, if a prevacuum cycle, in other words one or more pulses of evacuation followed by steam admission to the chamber, if they are in fact used, you will get very good penetration of the load. But then, just like ethylene oxide, although without the same hazard, you have to get the water out after the cycle, so there has to be some sort of drying approach taken which will not be done with compromised sterile barrier materials on the outside of the package. And if a sterile barrier material is wet, it's not a sterile barrier material anymore.

The dry heat cycles are somewhat slower. You do have to get things heated up; you do have to get things measured to create a parametric situation, which is a bit harder because the heat transfer is not as good with air as it is with, for example, steam. So the parametric aspects are less apparent, they run at much higher temperatures and the load will act as its own insulator as you go on, so it's going to take quite some time to get the center of the load, if it's a very dense, large load, to the same temperature as the exterior of the load. Clever packaging, clever positioning of the items to be sterilized can help with that, but it's not as simple as ethylene oxide is now where you just take things, put them on a pallet, and put them in. Not to say that that's simple, that's really involved, but this would be worse, I believe. So I like steam, if we're going to talk about alternatives here.

Material compatibility of mixed materials may be questionable. What do I mean there? As you go from a processing temperature of 55 to 60 Celsius to 121 degrees Celsius, you have doubled the dissimilarity in material thermal expansion coefficients. Therefore, things that hold together very nicely under ethylene oxide might not when you go to a much higher temperature such as is required for steam.

If you do go to vapor hydrogen peroxide, which is not the subject of this talk but somehow I insisted on putting it in, the very deep vacuum may create a problem in some packaging materials. For steam, the vacuums are comparable to what is used in ethylene oxide, so it's not really an issue. Similarly, the packaging that is used for ethylene oxide has been validated, Tyvek has been validated for use at 121 to 127 Celsius, therefore, well in the sweet spot of a steam sterilization process, and clearly, if it can work at those temperatures, it can work at lower temperatures, which is a lead-in. As I said before, some materials cannot be sterilized in these alternative methods.

I did a little calculation of lower temperatures for steam, and as a physical chemist, that's what we do. If you were to look at exposure time as necessary to get the same

accumulated lethality that 15 minutes at 121.1 degrees Celsius, which is a standard cycle and a desired 10^{-6} sterility assurance level for a prototypical load, you get a phone call.

(Laughter.)

DR. WILDER: If you drop the temperature to 118 C, you go out to half an hour from 15 minutes. If you drop it to 115, you go out to an hour. If you drop it to 110, you go out to 3.2 hours. If you drop it to 105, you go out to 10.2 hours. Am I advocating for lower temperature steam sterilization? No, but there's a window of opportunity there. I'm not advocating for anything. I just want the facts to be out there.

So I think that there are possibilities of improving the compatibility of steam with certain devices that can otherwise be appropriately processed in it by going to lower temperatures. Will these temperatures be low enough to make a difference as far as the compatibility of the device? That's another question, and each individual case would have to be dealt with. There's no slam dunk here. None of this is easy. If it were, we wouldn't be having this discussion.

So some materials cannot be migrated to radiation sterilization. Some cannot be migrated to dry heat or steam. Or of steam here, whichever. The effects of high temperature sterilization may make this difficult. Again, the differential coefficients of thermal expansion can be a big problem.

Logistics and equipment would differ greatly from ethylene oxide unless we were to go to very low temperature steam, at which point you might be able to actually migrate existing vessels, but then you have to make all that steam, which is a lot. Sterilizers will not have to change, but the boilers would be enormous. And a lot of capital and time would be needed to implement if devices can be, in fact, migrated to these methods.

Thank you very much.

DR. LEWIS: Thank you, Dr. Wilder.

Could we ask all three of the presenters to come to the table, and we're now ready for some clarifying questions from the Panel.

I would like to lead off with a question either for Ms. Craven or Dr. Kroc. You pretty much stated that the radiation methods are not susceptible to any problems with packaging, implying that they all penetrate equally. But, obviously, if there were some layers of lead in there, that probably wouldn't be true. What about if there's steel in the medical devices or for implants, for example; is the energy of the radiation sufficiently high that it penetrates all those things, or is it just that steel is not included in the devices which are sterilized by radiation?

MS. CRAVEN: This is Emily Craven. I can start answering that. For photon-based radiations like gamma and x-ray, they are very penetrating. So orthopedic devices, hip implants, knee implants, those are all commonly done with gamma radiation now. For electron beam, which is less penetrating, it's still possible; it depends on the thickness of the material itself, and that's driven by the physics of how deeply it can penetrate into different materials. But right now, metal components for sure are being radiation sterilized with photons.

DR. LEWIS: So the issue of absorption or stopping radiation is not an issue in these energies?

MS. CRAVEN: It's not that it's not an issue. You couldn't go through a meter of steel, you know; you're going through a reasonable amount.

DR. LEWIS: Okay.

All right, questions from the Panel? Yes, Doctor.

DR. LI: So with this very large "if" in front of this question, if you had a device that's currently being sterilized with ethylene oxide and the big "if" is would it survive your process; in other words, you have a device that you have in ethylene oxide and you're going

to consider gamma or x-ray or thermal, why would I switch? I mean, what would be the driving force for me to switch? Assuming there's the big "if" that it would survive the technology, why would I switch?

MS. CRAVEN: That's an excellent question, and I think one of the ifs -- one of the whys sort of is why we're here today, in terms of what's available as a technology. If you have something established in a process, it is much easier to stay in that process. However, we're seeing a real push, not only because of the challenges with ethylene oxide and some other methods in the past, where companies want to have the agility to move from one type of modality to another. That being said, that's a financial decision, and that might be a good question for a medical device manufacturer in terms of why they may choose to do that extra burden of validation, because it is a burden; it's a lot more testing, and it's a lot more work that needs to be done.

DR. LEWIS: Dr. Dominitz.

DR. DOMINITZ: I think I know the answer to this question, but I'd like to hear explicit answers from each of the speakers. Since we're talking about toxicity of ethylene oxide, could you each comment on any environmental or occupational public health hazards of the treatments or the sterilization approaches you just discussed?

DR. WILDER: Well, let me do steam, and then you guys can fight over the radiation. As far as steam and dry heat, most of the energy cost involved, aside from welding up strong vessels for steam or creating enough insulation for a dry heat system and a steam system, it's at some cost. You do have to make steam; you do have to heat the air. A boiler -- and these would, by necessity, considering what we're talking about, be clean steam boilers. A boiler is going to cost quite a bit of money, and it's something on the order of the same amount as a sterilizer. So to make that -- to get that much stainless steel and that much engineering involved and to be controlling the process would be difficult or expensive

as far as resource requirements.

Further, the ongoing run costs of having to heat steam, heat water to make steam or heat air to make dry heat are going to be substantial. Steam is more expensive to make because it's about 2,000:1 energy ratio to the water at the same temperature, so you've got to put that much more energy into it. If you're using a locally driven gas-fed, natural gas-fed boiler, that is typically what's most efficient. The ones that I normally deal with in hospitals are basically the size of not quite a tractor-trailer but about half that size. So there's a lot of oomph required there; there's a lot of power required there to make the heat to make the steam.

Dry heat would be more energy efficient, but you still have to get stuff pretty hot, and you still have to make sure it circulates properly so that you don't lose the heat you put into it. I believe that probably is what I've got for you on that.

DR. KROC: So for electron and e-beam, the energies that were chosen to do that are below the thresholds of activating any of your product in that, so there's no issue there. The biggest impact, I think, would just be the electricity generation.

MS. CRAVEN: Yeah, I'd agree with Tom. And it depends on what your electricity source is, of course, right? But e-beam, it's a lot; x-ray, it's a lot, a lot because it's a much less efficient process to create x-ray than it is with e-beam.

One of the byproducts of radiation, which I mentioned in my presentation, is ozone, so there is ozone generation, which is considered a ground-level pollutant. And so when irradiation systems are designed, air handling has to be taken into consideration, and usually the ozone goes out a stack, and it's just, you know, dilution is the solution to pollution. But this, again, is all regulated, and it's well understood and reported on.

The other thing on the gamma side of things is that, because it is using radioactive sources, there has to be a waste stream for those, a disposal path for those sources. And

right now that's all handled exactly the same way that nuclear fuel is handled from a waste disposal standpoint. So there's no special path, there's no special stream, but it just needs to be thought of in that same context.

DR. LEWIS: Dr. Burr.

DR. BURR: Just specifically on the cobalt-60 supply and security question, aren't there gamma generators that will deliver energy that's comparable to cobalt-60 that you can unplug and make them less troublesome that way?

MS. CRAVEN: That's x-ray. The x-ray systems that Tom Kroc was talking about.

DR. BURR: So, in effect, cobalt-60 is simply a material that generates your x-ray energies, whereas you can use generators to simply obviate the cobalt-60 problem --

DR. KROC: Correct.

DR. BURR: -- which is significant.

DR. KROC: Yes.

DR. LEWIS: Mr. Socola.

MR. SOCOLA: My question is for Ms. Craven. You mentioned that there was a new gamma facility built as late as 2017. I would have to assume that with permits, regulations, and holding public meetings, etc., there's quite a lot of time that goes into putting into, you know, the building of a new facility like that. Could you give the Panel an idea of how long that process might take?

MS. CRAVEN: Yeah, generally speaking, there's usually two parallel processes going on. You need building permits. You need radiation licenses. The rate-limiting factor in terms of actually getting a plant built is usually building the biological shield itself because it's a great big concrete structure. Generally speaking, if you're dealing with an established technology and a company that has lots of regulatory experience, depending on which state it's in as well, then the licensing part of it is well understood, and the licensing process and

the building of the infrastructure can happen in parallel. So usually, you know, there's all the thought that goes into saying yes, we're going to do it. But then from the time that you put the shovel in the ground, usually it's about a year.

DR. LEWIS: Yes.

DR. KIM: This is a follow-up, Ms. Craven. So we've heard about how the EtO sterilization facilities are working at capacity. Would you say, in the gamma radiation sterilization field, that that's also the case or that there is additional capacity to take on more?

MS. CRAVEN: What we're seeing right now is that gamma is at capacity due to some of the factors that I mentioned in my presentation. So there has been a lot of pressure. In fact, I was invited to speak at a conference sponsored by Fermilab about this topic, specifically, because there is pressure on gamma supply, which is forcing a lot of products to look at machine source.

DR. LEWIS: Ms. Wells.

MS. WELLS: So just real quick. You had stated that your science right now does 30 to 40% of the sterilization other than what EtO does, and with that, is there any or has there been any community results from where you have built out that were similar to EtO? We did hear from a community representative about concerns, and I would think the concerns would be similar.

MS. CRAVEN: I don't know if I'm the best person to answer that, but I am not aware of community grassroots movements against radiation. Again, radiation has a very long and safe operating record, but also like ethylene oxide, sometimes they're operating in communities where people don't actually know what it is that they do.

Just something anecdotal from the time when I was working at Nordion, which is the producer of cobalt-60: Our facility was built long before the community around it built up,

and then a few years ago they wanted to zone a school for right next to the facility, and Nordion ended up lobbying the city to say, no, we don't want a school zone right next to our facility, and it had absolutely nothing to do with the safety or any emissions or anything like that from the facility itself. It had to do with the fact of the perception of a nuclear plant or a nuclear licensed facility next to a school and what that would mean if Nordion ever wanted to build on to their facility or do anything else and how that might impact their business. But, really, there has been not that I'm aware of any sort of community arguments against radiation sterilization.

DR. LEWIS: Dr. Saubolle.

DR. SAUBOLLE: This is to the whole group. Looking at the compatibility chart and as well as the safety of byproducts, what do you think is the future of using the vaporized hydrogen peroxide? Looking at the chart that I see here, it's the most compatible with most of the material. Is there another issue, the cost, etc., down the road?

DR. WILDER: I did a lot of work with peroxides in the early '90s, and I have a couple of patents to use when I feel I need to make a point. The issue with peroxide, it's a great sterilization technique except when it isn't. It will destroy ionization, for example. If you're going to do it efficiently, you probably are going to be working with 70% hydrogen peroxide as your feedstock, not the 59% peroxide that's commonly in use right now was chosen because that's what the Interstate Commerce Commission allows to be shipped on an airplane. Sixty is no good.

Seventy is a much better starting point. I worked with it. It was trucked in. It came in jerrycans -- not a jerrycan. It came in aluminum canisters like a beer, you know, keg. That's it. It's been a long time since I was playing with beer kegs. And then I got a call from the manufacturer about 2 years in; have you used up all the peroxide? No, I haven't. Well, I want you to very carefully fill it with reverse osmosis to soap water to dilute it down, and

we're going to send a hazmat truck to bring it back because it turned out our preservation of the keg was not adequate and you may have a problem. The problem with high-concentration peroxide is, as was shown in World War II, it's an effective rocket fuel.

(Laughter.)

DR. WILDER: The V-2s were powered by 95% peroxide and, I think, hydrazine, another nice chemical. The environmental effects would be less than ethylene oxide would be if both were allowed to emit untreated into the atmosphere, but it's not a friendly material.

A personal example was I was working during that period in the room with 30 air changes an hour and not exposing myself to peroxide directly that much. After the project ended, it took 3 months for my sense of smell to fully return, and that was 30 air changes an hour.

The environmental controls for peroxide on an industrial scale are staggering, what has to be done, and the safety issues are staggering. If you go to a manufacturer of hydrogen peroxide and you go to their test areas, you find blockhouse thick walls on the buildings and very thin roofs, so the explosion will go up. It's not a nice molecule. It's a really good sterilant, but it has to really be taken care of to be used effectively and used safely.

DR. KRAUSE: This is Dave Krause.

Just a point of information. We're going to have hydrogen peroxide discussed tomorrow, so I mean, we'd like to focus the questions on what was actually discussed today, and we'll save the hydrogen peroxide for tomorrow.

DR. LEWIS: Thank you.

Are there other questions? Dr. Arduino.

DR. ARDUINO: So looking at devices that have electronic components, could you

actually radiate them, or do those kind of fall off the scale?

MS. CRAVEN: It's an "it depends" kind of answer. I pointed out pacemakers as something that is generally not radiation sterilized. Electronics are known to be radiation sensitive. However, I was part of a research project looking at a specific kind of radiation resistant memory, like computer memory, data memory, that showed radiation tolerance up to hundreds of kilograys as well. So I think as a general statement, they're usually not radiation compatible, but for some things they could be.

DR. LEWIS: Thank you.

DR. ARDUINO: Thank you.

DR. LEWIS: Anyone else?

(No response.)

DR. LEWIS: Seeing no further questions, I thank the Panel very much for their presentations and answers.

We will now take a 15-minute break. It's 3:05, so we'll restart at 3:20, at which time there will be another Open Public Hearing. Thank you.

(Off the record at 3:05 p.m.)

(On the record at 3:19 p.m.)

DR. LEWIS: The Panel will now reconvene for this afternoon's session. I would like to go off agenda for just a moment because a question has come up from one of the Panelists that relates to an issue this morning, and before we go into the Open Public Hearing, I would like to just take a couple of minutes and answer this if we could, and I would like to ask if either Mark Leahey, David Gillian, or Kara Mascitti are here to address a question which was raised by the Panelists as to why the EtO facilities have not begun to generate new capacity in the face of the apparent need for that under the present circumstances. Could either of you approach the podium and answer that question? Or is

there anyone else representing the industry who feels they could if those are not the right people? Thank you.

MS. SIMMONS: So I think the answer to your question --

DR. LEWIS: State your name.

MS. SIMMONS: My name is Lara Simmons, sorry. Again, from Medline.

The answer to your question is that generating additional ethylene oxide capacity is a very time-consuming and lengthy process. Capacity is added, and in fact, I'm personally aware of capacity that's been added within the past year, but it's just keeping pace with production, so it's a very tight balance. The lead time on an ethylene oxide sterilization chamber, to manufacture a chamber is at least a year, so to build a facility from scratch is a 2- to 3-year process by the time you get the permits, build the building, have the chambers manufactured, get them installed, get everything up and validated. So the EO capacity that's been put in place historically has just been to manage growth and kind of maintain the very careful balance. When you start closing plants, that balance gets thrown off, and because of the long lead time to add capacity, we just can't respond fast enough.

DR. LEWIS: Okay. Thank you very, very much for stepping forward.

MS. SIMMONS: You're welcome.

DR. LEWIS: We'll now proceed into the Open Public Hearing and have the second public hearing of this panel meeting. Again, all Panel members have been provided with written comments prior to the meeting. During this hearing, public attendees may address data, information, or views relevant to the agenda. Before we proceed, Commander Garcia will again read the public hearing disclosure process statement.

CDR GARCIA: Thank you, Dr. Lewis.

Both the Food and Drug Administration 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 public Advisory Panel, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may 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 the 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.

Thank you, Dr. Lewis.

DR. LEWIS: The FDA and the Panel have placed great importance on this Open Public Hearing process. The insights and comments provided can help the Agency in their consideration of the issues before them. One of the goals today is to continue to conduct this in a fair and open way where everyone is listened to carefully and treated with dignity, courtesy, and respect. We appreciate your cooperation. Again, we will have 6 minutes for each person, and we will need to adhere strictly to the 6-minute limit, so I really ask the speakers to respect this because we have five speakers for a 30-minute period, we have no real excess of time in this session. So, please, for each of the Panelists, be prepared to terminate your discussion at 6 minutes. We ask each of them to adhere to that, and we also ask each of you to be careful to use the microphone, speak directly into it in order to allow accurate transcription of your remarks. We'll -- excuse me?

(Off microphone discussion.)

DR. LEWIS: Okay. The first speaker is Chaun Powell, C-h-a-u-n, Powell, P-o-w-e-l-l, representing Premier.

MR. POWELL: Good afternoon. My name is Chaun Powell, and I serve as a group vice president of supplier engagement for Premier. I have no formal financial conflicts of interest as it pertains to this meeting.

Like many of my counterparts today, I'd like to thank the FDA and the Advisory Committee members for the opportunity to provide comments today. I'd like to start with an explanation of why Premier is here and the three stages of processes that we've gone through to evaluate the impact of EtO closures on patient care. Premier is a leading healthcare improvement company uniting 4,000 hospitals and 175,000 non-acute members across the United States to transform healthcare. Currently, our membership represents 83% of community hospitals across the country.

In my role I'm personally responsible for the contractual relationship that our health systems maintain with over 1,300 suppliers and work side by side with healthcare providers to manage, forecast, and deliver the medical devices needed to offer high-quality care to patients. With the mission of improving the health of our communities, we have been working proactively to ensure the recent sterilization facility closures don't result in supply chain disruptions nor impact patient care.

Premier and our members appreciate the delicate balance between EPA's necessity to protect general populace and specific geography surrounding EtO facilities and the FDA's role in providing the regulatory pathway for products to sustain effective patient care in the United States. Premier is committed to working with the FDA, the EPA, and additional stakeholders to find a sustainable solution that addresses these concerns.

Premier is proactively engaged in three specific initiatives to identify and mitigate the potential impact of previous plant closures as well as those that may be forced by local and state governments.

First, we created a product disruption team to track, mitigate, and respond to device

disruptions. Although there are specific regulations prescribing notification protocols for potential shortages with pharmaceuticals, these same regulations do not exist for devices. In the absence of these rules, Premier has stepped in to fill this void for hospital systems. We created a product disruptions team to collaborate with suppliers, collect real-time information and inventory through the sterilization facilities, analyze product availability, and attempt to determine the time it will take to return to a steady state. The end result is that we, as a group, are stronger, better prepared, but the success of this is predicated on the availability of sterilization capacity, which as I will point out momentarily remains a question.

With our disruption team in place, we were able to engage in the second critical initiative, to quantify the impact of closures on suppliers. As the threat of additional closures became more public, we surveyed 600 suppliers, and we determined the number of locations and suppliers, sterilization activities by state, the form of sterilization used, alternatives, redundancy, contingency plans, etc. Our survey identified EtO sterilization in 21 unique locations across 13 states and 7 countries. The most alarming trend of all of this, however, was that only 3% of respondents declared that there was a legitimate risk of product disruption of their supply chain given their confidence in their redundancy and contingency plans, relying on assumed capacity at other sterilization plants. This statistic was reassuring at first, yet we reasoned suppliers assumed the excess sterilization capacity existed and that sterilization of their products could simply be transferred from one location to another.

Prior to the first Sterigenics closure in Willowbrook, those alternative facilities likely did have capacity. As additional closures occurred, however, Premier worked with several top healthcare suppliers and verified that they were struggling to find facilities with enough capacities to meet their demand, which brings me to summarize my third and most

profound point. If you're sleeping, this is the part where I'm going to ask you to wake up for a second.

Premier determined it was imperative for us to collaborate with industry to quantify the availability of excess capacity in the United States. We're here today to share that excess capacity across the U.S. is nearly exhausted, and I will now show how dire the situation is.

* Based on our primary research, we identified that most third-party EtO sterilization facilities operate during a steady state of supply chain at 90% capacity. Combined with the fact that the average facility sterilizes 200 million units per year, we established that excess sterilization capacity in the U.S. to be just around just north of one billion units. Following the closure of Sterigenics in Illinois, Viant in Michigan, and Sterigenics in Georgia, the current excess capacity is roughly 520 million units. The estimated volume at Medline in Waukegan, Illinois, and BD in Covington, Georgia, is 550 million units. Simple math shows that if we close those two plants, we exceed the current capacity across the entire U.S. by 30 million units. Two facilities of average size, you name them, that's all the capacity we have today. Exchange any two average size facilities, including the SSE facility in Fulton that made news last week, and the result is the same.

So where do we go from here? Premier proposes two near-term solutions. First, we must create visibility to upstream stakeholders in the supply chain. This includes raw material suppliers as well as packagers and sterilization locations. This visibility will help us prevent, estimate the impact of, and mitigate disruptions of all kinds, including those due to hurricanes, terrorists, raw material shortages, etc. Absent that true visibility, packagers and sterilizer locations, we cannot predict nor effectively address any disruptions until clinical practices are already impacted.

Second, we must leverage the solutions we have that have been successful to

acknowledge drug shortages and apply them to medical devices. The FDA should have similar authority to address shortages for medical devices as they do with drugs. We must work together with the public and private sector to find more effective means of disruption, prediction, prevention, and mitigation.

In conclusion, the threat to supply chain disruptions at the downstream impact to patients as a result of continued sterilization facility closures is real; we only have two more facilities before we exceed the total capacity in the United States, and this tipping point is going to be very real and happen very quickly.

Thank you once again for your time and for your interest.

DR. LEWIS: Thank you for your comments.

We'd next ask Sam Ajizian, Dr. Sam Ajizian, from Medtronic to present.

DR. AJIZIAN: Thank you to the Chair, members of the Panel, the FDA, and members of the public who are here today. My name is Sam Ajizian. I'm Vice President overseeing medical safety and Co-Chair of Medtronic's Medical Safety Council. Prior to joining Medtronic, I practiced pediatric critical care for over 20 years, and during my career I have taken care of our most vulnerable patients for whom device sterility is absolutely foundational. For well over half a century, Medtronic has been at the forefront of innovation in the medical device space, and as a global healthcare leader, we appreciate the opportunity to not only provide our comments on this important issue but to be part of the discussion moving forward.

First and foremost, Medtronic's priority is to ensure that all of our products are as safe as possible for patients, and sterilization is essential to that goal. Healthcare-associated infections are a major public health concern. In the U.S. alone, it is estimated that more than 1 million patients experience healthcare-associated infections resulting in approximately a hundred thousand deaths and numerous additional medical and surgical

procedures. A sudden shift in sterilization practices may substantially worsen these numbers and place patients at significantly more risk for infection-related complications.

Medtronic uses a wide range of methods to sterilize its medical devices and makes every effort to select the most effective and safe method for each device. These methods include steam, radiation, and ethylene oxide. Unfortunately, no perfect sterilization method exists. None can effectively be used on all medical devices, and none of the sterilization processes are without risk. As Phil Cogdill discussed earlier today, EO offers unique advantages over other sterilization techniques, including its applicability to a wide range of devices and instruments.

While EO usage has decreased over time, it continues to be the most widely used gaseous sterilization agent in the world. Indeed, for the majority of Medtronic products, EO remains the only validated method to ensure sterility without affecting the integrity and function of the device over its lifespan.

These devices are in continuous use in hospitals and other healthcare settings across the U.S. They're necessary to treat neonates, children, and adults with a wide range of chronic diseases, as well as to care for acutely ill and injured patients in operating rooms, intensive care units, and emergency rooms across the country. Simply put, EO sterilized devices touch each and every one of us either directly or through our loved ones who are patients.

Medtronic is committed to protecting the health and well-being of all people, including patients who rely on our devices as well as individuals who work near or work in or live near sterilization facilities, and we take recent concerns regarding EO emissions very seriously. Medtronic has processes and controls in place to minimize emissions at our own facilities, and as you heard this morning from Mr. Cogdill, these controls are robust and impact each and every step in the EO sterilization process. The common goal is to use EO

responsibly while maximizing EO capture and disposal to mitigate any environmental effects. When used responsibly, EO is a safe and effective sterilization method.

At the same time, Medtronic is actively engaged in evaluating a number of possible processes and technologies to further reduce EO use and emissions including as part of FDA's innovation challenge. Medtronic supports FDA sterilization initiatives and will continue to work collaboratively with the Agency, the EPA, industry partners, and other stakeholders on this important matter.

However, Medtronic is very concerned about calls to abruptly ban or restrict the use of EO in the U.S. Considering the range of critical devices that exclusively rely on EO, any abrupt decision to limit its use could have a profound effect on device availability and adversely affect the health and well-being of millions of Americans.

Changes to establish sterilization practices will take time as new techniques must be carefully tested and validated to ensure that they are appropriate, effective, and safe for both patients and the environment. As clinicians, we assume complete confidence in the product when we reach for it. We expect sterility for the shelf life of the device, and we expect performance over the product's entire lifespan. Therefore, robust testing is required to ensure that any changes in sterilization practices do not adversely affect these expectations.

While testing and evaluation is ongoing, EO must continue to be available to ensure the sterility and safety of critical medical devices and to avoid acute shortages of lifesaving devices relied on every day by patients and healthcare providers.

Thank you for your time and attention.

DR. LEWIS: Thank you.

The third speaker is Josh Babb, who is Director of Government Affairs for the Health Industry Distributors Association.

MR. BABB: Thank you. Good afternoon. My name is Josh Babb. I serve as the Director of Government Affairs for the Health Industry Distributors Association, or HIDA. Thank you to the FDA and this Advisory Committee for the opportunity to address you on this important topic.

HIDA is the trade association representing medical products distributors. Approximately 600 distribution centers nationwide, HIDA members distribute the full range of medical products essential to everyday medical services and procedures. These products range from surgical kits, which you've seen today, to catheters, as well as gauze and gloves. Distributor customers include over 200,000 physician offices, 6,500 hospitals, and 44,000 nursing home and extended care facilities throughout the United States. They also serve the healthcare facilities of numerous federal agencies such as the Veterans Administration as well as the United States military.

We recognize and appreciate the importance of environmental, public health, and other factors with regards to the use of ethylene oxide for medical products. My comments today, however, are from the perspective of the medical products supply chain supporting the nation's providers. It goes without saying, sterilized medical products are mission critical to healthcare and one that all facets of the industry are imminently concerned about.

Ethylene oxide is used because many products cannot tolerate other sterilization procedures. Today, more than 50% of all medical devices are sterilized using EtO, upwards of 20 billion devices annually. As is recognized by the FDA, there's no viable alternative currently available to replace ethylene oxide sterilization. Should regulatory policy or actions regarding the use of ethylene oxide affect overall sterilization capacity in the United States, the impact on healthcare providers and patients, first and foremost, would be profound.

For this reason, HIDA recommends a thoughtful approach that considers the impact on the delivery of healthcare nationwide. Any changes on ethylene oxide policies must include a realistic and feasible plan to anticipate and address any potential product disruptions.

It is important for this committee to understand that a disruption at a single sterilization facility could have a magnified impact across the entire country and across every healthcare setting. Devices sterilized in one facility often support healthcare providers and patients in every one of the 50 United States. Examples of these essential products which we've heard from today include catheters, surgical kits, and even the ports used for delivering lifesaving cancer treatments. For example, a single facility in Georgia sterilizes 50% of the entire United States catheter market. A single facility in Illinois sterilizes 18 to 20% of the U.S. market of surgical kits used every day in hospitals for both routine as well as emergency procedures.

And FDA's recent statement on the issue was recognized that restrictions on ethylene oxide use could ultimately result in years of spot or nationwide shortages of critical medical devices which ultimately could compromise patient care. Previous experience has also shown that a shortage in one product category can deplete adjacent product categories as providers adjust to meet their commitments to their communities. These products ensure quality healthcare for millions of patients every single day. Industry data indicates that in a typical year, more than 13 million urinary catheters were used across all healthcare settings, and more than 12 million of those were used in hospital settings. Many millions are used in the homecare setting, and access to these sterilized catheters improves outcomes, manages infection rates and avoids hospitalizations, and provides dignity and comfort to patients. These positive outcomes would be diminished, if not done away with, if the supply chain for these critical products is disrupted.

Ethylene oxide sterilized surgical kits are delivered to operating rooms with a full range of products customized for particular procedures. A disruption to a single surgical kit supply has the potential to impact the millions of surgical procedures in hospitals, surgery centers, and doctors' offices each year.

If ethylene oxide use is altered by regulatory shifts or legal decision, there must be both a realistic and feasible plan, including a timeline in place that addresses these significant challenges that would be created for the healthcare system. Without this consideration, the disruption of the provision of healthcare in the supply chain would be immediate and significant.

Contract sterilization facilities support multiple device manufacturers which all have unique specifications for the sterilization of their devices. Changes in sterilization policies or methods will require those specific processes to be altered and revalidated to ensure patient care is not compromised. An additional factor is the sheer number and volume of devices that would be impacted.

For the reasons above, HIDA strongly urges caution and collaboration when considering the use of ethylene oxide for medical device sterilization. The nation's providers and mainly their patients need assurance that access to critical medical devices will not be compromised. We urge the FDA to continue to work closely with HIDA and the rest of our industry partners to ensure that the healthcare supply chain continues to provide safe products to our customers and ultimately the patients they serve.

We appreciate the FDA for convening this meeting and the opportunity to share our thoughts. Thank you.

DR. LEWIS: Thank you, Mr. Babb.

Next, call on Dr. Danielle Walsh representing SAGES.

DR. WALSH: Good afternoon. My name is Dr. Danielle Walsh, and I'm here at the

behest of the Society of American Gastrointestinal and Endoscopic Surgeons, otherwise known as SAGES. I have no other financial disclosures. I thank the esteemed members of this Panel for the opportunity to speak.

It's a privilege to be the voice of the surgeon as we face the challenges of optimally managing the safety of our patients and communities. Board certified as a surgeon, my past 24 years have been focused on providing surgical care to our smallest and most vulnerable population as a pediatric surgeon. It is as a surgeon, an advocate for children, a scientist, a parent, and a citizen of this nation and world that I provide my perspective today. Each day I sit with a family who has a child needing surgery. After reviewing the history, examination, and data, the family must be consented for the intended procedure inclusive of the risks, the benefits, and the alternatives. And it is with this frame of reference that I speak today.

The history is one of ethylene oxide since the 1930s for sterilization, and some complications were noted along the way. Explosions, fires, and risk to healthcare workers were identified, and iterative steps were taken to improve the safety over decades. Under the leadership of the FDA and other governmental bodies, surgeons and other physicians now have access to sterile devices that we trust implicitly. I don't worry that the device I'm taking out of this package to utilize on an infant is unsterile due to decades of reliability. With plenty to worry about in the utilization of the device and how each patient will tolerate the operation, it is critical that doctors, nurses, and patients can unquestionably trust the sterilization of the devices in use.

So I encourage the FDA to continue requiring exceptionally high standards for any sterilization process. A loss of trust in sterility will not only result in patient harm but potentially in patient and physician avoidance of performing procedures over concern of the quality of the equipment at hand.

My obligation as a surgeon is to continuously review the available data on any operation I do to inform consent. Innovation, devices, and new procedures are developed to save lives, yet new and different isn't always better. Please ensure that the safety and the efficacy data in both testing and real-life usage support a change in sterilization that's equal or better to what we have now. Consider the potential harms of these sterilization methods in direct comparison to ethylene oxide before a transition. Will an acute shortage of cobalt one day shut down our gamma radiation sterilization? Is the potential environmental impact of the spent cobalt better or worse than that of ethylene oxide?

The use of hydrogen peroxide to sterilize urinary collection bags was once touted as a safe way to prevent infections from catheters, but data showed it didn't actually lower infections at all. Again, change isn't always an improvement. Please show me the real-life data, not just models.

A decade ago we had high infection rates related to vascular catheters, and we learned that to prevent infection successfully requires a combination of safety steps to provide summative protection. I now open a single kit that contains everything I need to safely place a line in our neonatal unit, and it's packaged with each piece available in the order that I use it and containing a line with antimicrobial coating. This replaces the opening of individual devices and components with the risk of each material being contaminated, dropped, or even forgotten in the process and preparation.

One commentator discussed disassembling these sterilized kits as a strategy of decreasing the use of this chemical, and yet, while every test of sterility might say that they are equivalently sterile, I can assure you it's far from the real-world usage. I don't want to trade the risks of sterilization for an increased risk in breaking sterile technique at bedside line insertion, and for this reason I encourage this body to continue thoughtful, iterative, scientific analysis of the products and processes that come out of this challenge to reduce

ethylene oxide with real-world application and human factors information in mind.

The hardest part of the surgical consent is the description of the risks, as surgery is intentional injury through an incision despite an aim for relief of suffering. In preparation for today, I looked at the risks to the population around ethylene oxide-based sterilization plants. Notwithstanding the concerns about the accuracy of the prediction models and the standards used, the statistic that stood out to me the most was reported this year in the summary, EPA's risk assessment of ethylene oxide surrounding the shuttered plant in Illinois, and it stated the risk is "potentially as low as one in a million," meaning one person out of a million who are breathing the air containing ethylene oxide for a lifetime would develop cancer as a risk of that exposure.

Now, that person is very important to someone, and it could be my own sister who lives in Smyrna, Georgia, where these plants are, but I also have to think of the 23,000 people per year who develop sepsis from central lines and the fact that 12 to 25% of those die of their infection, a rate well exceeding the one in a million lifetime risk of this plant.

At some point equipoise must enter our conversation. Just as a surgical blade induces bleeding and a risk of infection and leads to scar, the incision is needed to remove a cancer of a patient who is to die. Efforts to improve the safety of ethylene oxide must be undertaken but not without assured access to critical devices. Do not throw out the baby with the bathwater.

SAGES and other organizations remain available to assist you in this journey, and we thank you for the opportunity to join the conversation.

DR. LEWIS: Thank you for your comments, Dr. Walsh.

I'd like to ask the four public presenters to please come to the table, and we now have an opportunity for questions from the Panel of these four individuals.

I'd like to begin by posing a question either to Mr. Powell or Dr. Ajizian, since they

both represent large organizations and they're affected by this. I assume you were present this morning and you've heard about many of the mitigation strategies relative to the use of EtO. Obviously, there are at least four or five different approaches to that that have been suggested.

How do you feel the industry is going to move forward and address those given the fact there apparently is an opportunity to retain EtO but to significantly reduce concentrations, emissions, and whatever, and again, as was pointed out, I think by the Panel earlier, it was not specifically addressed, but specifically, scrubbing or mitigation of EtO emissions from the sterilizing plants is an option that has not been explored to a great extent but clearly exists as a possibility. Can you address or project how the industry may be responding to this and what sort of a time frame they would have for adopting strategies to reduce EtO in some way or at least the public exposure to EtO?

DR. AJIZIAN: Sure. Sam Ajizian from Medtronic.

I think Medtronic's position is one of responsible use of EtO. When used responsibly, it is safe and it is effective. So even the changes that you propose with increased scrubbing, increased retention, we need to work with our sterilization partners and internal experts to make sure that that does not compromise the product in any way. That is a key message here that has to come across, is what is the effect on the product for its entire life cycle? We put patient safety as absolutely first in our mission, and we back it up with scientific rigor so that even a perceived change that may sound like it's relatively easy must be put through that rigor so that when that device is used, there is no disruption in its performance, not to mention its sterility.

MR. POWELL: And briefly to add to that -- Chaun Powell from Premier -- I think the primary thing to consider is how quickly can we create a solution here that is sustainable long term? We've got the current challenges that I think the mitigation and some of the

solutions proposed earlier today would certainly create a near-term solution for. I think the extreme jeopardy we face here is if we continue to force these facilities to shut down prematurely without having an alternative long-term solution in place.

And so to answer your question directly, I do believe that industry is quickly recognizing that this is not something to laugh at, but they are taking very seriously these concerns. As an example, the $8 million investment that the BD plant was hoping to make, but there's other examples of that as well. I think those are the near-term solutions that we need to help push through in the near term. Long term, there's obviously alternative sterilization models that we need to continue to explore that haven't been verified as alternatives today. But, ultimately, I would say the key point is we cannot jeopardize an entire nation of patients for even those that are in immediate proximity to EtO facilities with respect to the fact that we do want to be concerted to those lives.

DR. LEWIS: I think, however, both Dr. Walsh and Mr. Babb addressed issues about the FDA or other regulatory agencies potentially acting precipitously without due consideration of the consequences, but I think we should recognize that, for example, in Illinois it was the state which took action, it had nothing to do with any regulatory agency at the federal level, and I believe in Georgia, that also is what's moving forward. So I think we have to consider the issue here that this is not being driven currently by regulatory agencies but by state concerns, and that's not controllable either by the FDA or anyone else, and so the industry needs to recognize, I think, that there is a movement which has begun here because of public concern about the hazards, and industry needs to move fairly quickly to address some of these issues.

MR. POWELL: If I may just very quickly comment on that. I do want to represent several large manufacturers that we've interviewed; some of them have presented today and others have not. They all indicated that your statement, the FDA's statement on the

28th was very helpful at assuring some of the concerns, and increased cadence of communication similar to that is at the request of those organizations, so thank you for your leadership there.

DR. LEWIS: And thank you.

Dr. Goldman.

DR. GOLDMAN: Yes, I just wanted to ask each one of you to reflect -- I believe that it was in 2005 that the EPA actually proposed a rule to shut down ethylene oxide sterilization facilities across the country, I believe, and I believe that they did not finalize that rule because of the kinds of comments that they received at that time from people just like all of you, the medical community, the industry, also the FDA, to the extent that there would not be a way to quickly move forward to replace those facilities with other technologies and the essentiality of having the capacity to be able to sterilize these items.

And I guess my concern is that I hear in these comments a lot of the same kinds of comments that came forth, you know, those many years back and, you know, how would things really be different? This is not actually a new issue, you know, that there is an environmental concern. Now it's coming from a state.

At one time I worked at EPA. I can tell you that generally states, which have much smaller environmental regulatory staffs than the federal government and far less muscle than agencies like the EPA, generally don't take actions like the action that Illinois is taking if they feel that the federal government will do that, and that it's actually a symptom, I think, of inaction when you see a state moving forward to take an action like that.

And while I can't agree more that, from everything I've heard from all of you, that we're not ready to see a transition to a different way of doing business, but I also didn't hear from you clearly, you know, how steps are being taken to bring us to that point where there would be an actual transition to a different way of doing business, whether it's

controlling the emissions or switching to alternative technologies or however you would go about doing that.

DR. LEWIS: Do either of you wish to respond to that statement?

DR. AJIZIAN: Sure. Thank you for the question. Sam Ajizian from Medtronic.

I think your comments are very well taken and understood. I think what is different today is that companies like us, for example, Medtronic is participating actively in the FDA's innovation challenge. There's tangible work being done by multiple stakeholders to not only decrease ethylene oxide input but also increase recovery. The responsible use is clearly safer than the alternative of rushing and not having devices that are sterile and safe.

But as we heard today, the process is not an overnight one, and it will take scientific rigor and many stakeholders working together to solve the issue. Until then, we maintain that ethylene oxide, when used responsibly, is safe and effective and meets the needs of these critical devices being sterile, safe, and available.

DR. LEWIS: Thank you.

Are there other questions from the Panel?

I'm sorry, go ahead.

MR. BABB: Thank you again for that question, and again, duly noted on the concerns. I think I speak from the perspective of the distributor in the sense that we're not here necessarily to debate the science of ethylene oxide. I think the distribution and the supply chain, from our perspective, simply looks at the constraints that are posed on both supply as well as demand, and as it stands right now, the supply chain is both unique as well as fragile, and the supply chain has a lot of other demands outside of just sterilization needs that are placed on it. And so we look at the compounding forces that are placed here, and we say, you know, aside from the debate of how to move away or into a different sterilization mode, the supply chain simply cannot take a brisk or agile shift in another

direction right now.

I think, when we look at the numbers, solely at surgical kits and catheters alone and the concentration of those products being sterilized in individual facilities and the sheer force that they would have on the market should ethylene oxide, you know, not be an option to sterilize, the market simply cannot take that shift regardless of the science or regardless of the debate over ethylene oxide as a whole, and I think our urge as the distribution component of the supply chain is careful consideration because it is a very delicate and fragile and complex distribution system that exists today.

DR. LEWIS: Thank you.

Yes, Mr. Socola.

MR. SOCOLA: Thank you.

It's my understanding that the Sterigenics plant in Illinois was ahead of schedule, and it spent millions of dollars on the risks that were going to be mitigated by their upgrades. Then the legislature of Illinois had a couple of laws introduced that would basically shut down EtO facilities in the state. Have your organizations reached out to the legislature of Illinois, and if so, are they receptive to speaking with you?

MR. POWELL: Chaun Powell from Premier.

I can share that we work hand in hand with several of our facilities, our member facilities there that have worked with the legislature. I, personally, have not reached out to them, so I can't speak to the receptiveness.

DR. WALSH: I am not aware of the -- Danielle Walsh.

I'm not aware of the house of physicians or organizations reaching out explicitly. I know that this came to our attention because a physician member in the state of Illinois brought it to the American Medical Association as a resolution to close down these plants and the house of surgery at that meeting noticed it and started looking into it and realized,

wait a minute here, if you do this, we might have a way bigger problem.

And so, ultimately, we asked that that get tabled and sent to a committee, which it did, and it led to a group of physicians starting to look at it, and that's how it got to me. I didn't learn anything about ethylene oxide in medical school, I didn't learn anything about the process of sterilizing the devices, but it did come from that state that it was brought to our attention. We're very concerned about it now. It's like this secret meteor that's about to hit Earth, and we didn't even know it was coming. But we do take it very seriously, and I do think we need to go back to the state level, but our body doesn't have a lot of state activity like that. We work more in the national arena, and that's why I was happy to come today to this group to have these conversations and learn more.

MR. BABB: I would echo her --

DR. LEWIS: Ms. Wells.

MR. BABB: I'm sorry, Josh Babb from HIDA.

Echo her sentiments in the sense that we don't have a lot of state-level activity. We do a lot of work in the federal arena, and so we have not personally spoken with the state legislators, although we have a number of members who obviously do business in the state of Illinois, sterilize in Illinois, and we have worked hand in hand with them as they work on advocacy down there.

DR. LEWIS: Ms. Wells.

MS. WELLS: Thank you.

So just a real quick question: I know, Mr. Babb, you had talked about the crisis that we are in right now, that if we even shut down two of these plants, that we would really be putting patients in serious condition really at risk. So I do know Mother Nature sometimes, especially in Texas and Georgia, if that was to occur, if we're in this much of a crisis, what is the plan for socioeconomic defunct? What is planned for Mother Nature in case Mother

Nature decides to land a nice hurricane through Texas and take out several? What would our circumstances be? And do you all have a plan in case that happens, because we are in a crisis, correct?

MR. BABB: I would say that the supply chain, again, is fragile and it is complex, and to your point, I believe HIDA tries to work at its best to be proactive in this front. I can't speak from a sterilization component because I'll admit to you I am not a sterilization expert. Product supply chain and healthcare supply chain is more my business. I will tell you that we work very hard and have spent the last several years working directly with a number of facets of the federal government in trying to be more proactive and protecting the supply chain from the natural vulnerabilities that do exist.

When you look at big hurricanes that have hit Puerto Rico, Florida, Texas, they're all unfortunate, they're unavoidable, and as you pointed out, there are a number of very fragile communities that deliver large quantities of medical devices to those sections of the country. And so our association has spent a lot of time working both with the strategic national stockpile, ASPR, as well as the CDC in trying to plan a more proactive public-private partnership and looking at how do we better prepare the supply chain to weather these bumps in the system, if you will, because quite frankly, the supply chain is much more, I think, fragile than any one of us would like to admit or talk about.

And so we try to have those conversations both on the Hill as well as at the agency level and have tried very hard behind the scenes to develop a number of different programs that are, you know, still in progress, if you will, to better prevent the hiccups from causing major disruptions. I'm not going to tell you it's an exact science, and I'm not going to tell you that we've necessarily got it all figured out, but I am telling you that, you know, we are aware of a number of the bumps in the system that can occur, that can occur from natural phenomenons as well as manmade phenomenons and shutdowns like we're talking about

right now, and it's just a very delicate balancing act. It's a fine line we're towing. We're not sitting back and letting it happen. This is one of the many areas that we're trying to be proactive in, if you will.

DR. LEWIS: Dr. Li, last question.

DR. LI: A question that's been kind of bothering me: It seems like there was almost a reluctance to add more capacity. I don't know if that's just a feeling I'm getting or if it's something real, but my question is why isn't supply and demand working? You know, all the demographics are that the number of medical devices that are going to be needed over the next 20 years are going to increase. Joint replacements alone are going to increase 15 to 20% within the next 15 years.

So it's a guarantee that the number of implants that you're going to have to sterilize is growing, so there's a demand. So it's a little bit like a situation where there's a housing shortage but the builders don't want to build any buildings because it'll take too long to build the house. So with this known demand in hand and coming, why isn't there a more aggressive plan to expand your capability?

MR. POWELL: Chaun Powell from Premier.

In our calculations, we again estimated that in a steady state, most EtO facilities, third-party, I want to be clear, third-party sterilization facilities operate at 90% capacity. That capacity equates to roughly 1.1 billion devices to be sterilized. Prior to the Sterigenics activity earlier this year, which keep in mind was within this calendar 12 months, that excess capacity, I think, would afford us the opportunity to be a little bit more forward thinking about the increase in the baby boomers and the hips and the knees, etc.

I think it's been a bit of a surprise to the industry that we saw this grow from one state, in Willowbrook, Illinois, to include Viant in Michigan and now Georgia. I know California and several other states are also close behind, so I think it's been -- I want to be

clear, I don't have an answer for your question as to why they haven't increased capacity outside of the fact that I think they're also looking around and saying is this even going to be viable? Should we make let alone an $8 million investment for BD to clean up our stacks if this is going to get shut down anyway, let alone expand our capacity, so that's conjecture on my behalf, but that's my belief.

DR. LEWIS: In view of the time and the need to move forward, I want to close this session and thank the speakers all for their presentations and for responding to the questions.

We now will proceed to the addressing of the FDA questions which have been presented to the Panel. There are six questions which we need to address today, and we have approximately 90 minutes in which to do so, so I would like to more or less address 15 minutes or so to each question as needed. Dr. Ortega of the FDA, I believe, will be presenting the questions. I would ask him to step forward. After each question is presented, the Panel will discuss it for the requisite time in order to hopefully arrive at some consensus. As to the Panel, we will ask Dr. Krause to evaluate that, and when the responses are adequate, we'll move on to the next.

Mr. Ortega.

DR. ORTEGA: Thank you.

DR. SCHWARTZ: Dr. Ortega, before you begin -- this is Suzanne Schwartz -- we have the wrong slide deck that's up. This is for tomorrow for duodenoscopes.

(Pause.)

DR. ORTEGA: And so FDA's first question to the Panel today is: If EtO sterilization is reduced, eliminated or replaced to a different sterilization modality, how can the impact to healthcare delivery organizations be minimized?

DR. LEWIS: Floor's open for discussion from any panelist.

DR. MYERS: So for representation of the Veterans Administration, we did look back in 2005, and we looked at our facilities, and we started to mandate a reduction in our EtO. We reduced our national EtO by 80%. So I think it can be done. I do think that it is something that has got to be measured and perhaps looking at facilities that are utilizing the EtO and looking to say, is it needed?

We discovered that a lot of our EtO use was utilized for items that were old and that they were preference based, so we enticed with newer models, education, training, and opportunity for advancement. With that being done, once again, out of my 20% that I have that are utilizing EtO, there's only roughly 5% that use it on a daily basis. So I know it can be done, and maybe that could be our first look is at the hospital facility level. What can we do to begin our reduction there and then move it out to our vendors, and in the meantime, they need to be looking in the same direction. But that is --

DR. LEWIS: But reducing the use of EtO at the hospital level would not affect this nationwide shortage. It would be useful locally for perhaps extending capacity, but I don't think you would address what the FDA could do in order to help the process.

DR. MYERS: Totally agree with you. I think, though, we would have to set up a system where we have to say at X date this has got to occur, but we have to set that system and that plan up through a contingency plan of what are we going to do today, and just like I said, if a hurricane comes or a tornado, what is our contingency plan? And so we have to look, I would think, in segments and then go out long term. We also have to look at the environment, and what is that concentration load? Is that concentration load like Illinois believes, to be so large that it is affecting communities? Then I have to say I agree with what they did. But I know, as a large institution, it did take us time. It's not something that we can just shut off today. I think that we need to look at it and say how much time can we allocate.

DR. LEWIS: Yes.

MS. PEKAR: This is Carol Pekar.

I mean, this is a complex issue, and I think it's going to require every, you know, entity involved to take some steps. You know, sterilization plants have to start putting in the best scrubbers that they can for abatement, and what can they do to help industry with mixed loads, that's the way that looks kind of easier. Industry itself has to get some incentives, and maybe the carrot and the stick from FDA in terms of maybe new devices have to have alternate sterilization. I do think we need to look at these less conservative -- you know, forget the overkill, can we do the BI/bioburden? So I think that everywhere you look, the FDA can help support the medical industry in terms of this, and I think the EPA has to clearly support. We need some better science around, you know, something that's having such a potential huge impact on us.

DR. LEWIS: Dr. Goldman.

DR. GOLDMAN: Well, first, we heard earlier today about, you know, numerous ways, I'm not going to list them all, that people are already working to minimize the quantity of ethylene oxide that's required for sterilization without impacting on the efficacy, and since it's basically all going to end up in the environment somewhere, this is my opinion, that's a good thing. That will reduce the burden on communities.

The second thing I'd say, the FDA sterilization challenge, which we heard that one of the companies is participating in, I looked that up, they're judging, you know, the competition right now, that it seems to be a really laudable effort, you know, to actually bring in proposals for new technological approaches and then that FDA would actually help to accelerate the R&D because we know a lot of the barrier to bringing new products out on the market is the FDA itself. So that seems to me to be very much worth supporting, that FDA would be really behind that effort.

DR. LEWIS: Your suggestion is a little different than the impact of the question. The question actually doesn't ask how the FDA might change the speed of elimination of EtO or be involved in that. It presupposes that that might occur and is asking how the FDA can reduce the impact on healthcare delivery institutions, which is really a different question and --

DR. GOLDMAN: Well, I think by incentivizing reducing use and also helping to bring on board substitute technologies, FDA certainly -- because from the standpoint of a healthcare delivery organization, it's that they can obtain the devices they need and that they are sterile, you know, that is however they're made that way and that FDA has a role in hopefully, you know, incentivizing, that that continues to happen through reducing use.

And I think I'd also say that I think that there is -- part of this problem is one of public confidence and whether the system is working for the public and being able to show the public that real efforts are being made to reduce the use of EtO in their communities and to find replacements that work as well, better, safer; that should go a long ways toward helping to make that happen. And I think the thing we heard from a couple of people who represented communities, that is a message, I think, that they need to hear.

DR. LEWIS: Dr. Li.

DR. LI: I'm a little confused over the question. It seems to read, as I read it, if ethylene oxide sterilizer is reduced, eliminated or replaced, in all three cases it seems like you're asking for -- is it asking if there's somehow some other technology other than ethylene oxide comes in, how will that impact the healthcare delivery? Is that the question?

DR. LEWIS: The question, as I read it, says if these things happen. It's not asking what can the FDA actually do to modify it.

DR. LI: Oh, I understand that. So I was just asking, so if somehow there was this

other process --

DR. LEWIS: Yeah.

DR. LI: -- or processes, you know, how would they, in fact -- well, it's hard -- I think it's a hard hypothetical for me because, one, we don't know what those processes are and, two, is the replacement going to be the same as EtO? Is it going to cost the same, is it going to be as fast, is it going to be as effective? What about delivery, what about packaging? I'm actually one who's actually gone through this process of taking a product from a lab bench and taking it out to commercial sale through the sterilization process, and it is not an easy task. I've yet to find a product where I get my choice of sterilization methods because the design or the material of construction or the packaging dictates the sterilization method that I can use. To pick a sterilization method and design a product around that is a tail wagging the dog, in my feeling.

So in this one it's a little hard to answer the question because unless the replacement technology is similar to EtO and its practicality of cost and delivery and everything else, then its impact is going to be negative. It can't be anything else. So if you want something with no impact, the replacement has to be performed equally, not just in sterilization but in all the other practical standpoints. So in the absence of knowing what this magical new process is, I don't know how I answer this question.

DR. LEWIS: Well, Dr. Krause or Dr. Schwartz, could you perhaps clarify the FDA position as to exactly how you view this question, because I think the Panel is struggling a little bit with the issue. Other than telling the institutions that the sky is falling, what other things could you do?

DR. SCHWARTZ: Thank you. This is Suzanne Schwartz.

Let me see if I could do a little reframing and clarifying of the question as we intended it, because, you know, clearly the Panel is struggling. If EtO sterilization, let's say

its capacity is reduced or it's eliminated as a result of various bans that are put in place, so what we're saying here is we're taking the situation as we have it as present, and if this were to continue, the trajectory that we're on potentially continues so that the availability of EtO sterilization were to go away or to be inadequate, how can that impact -- what can we be doing from a shortage mitigation standpoint? How do we prevent further disruption within the supply chain?

Similarly, if a different sterilization modality were to be viable, but we know that there is a ramp-up time in order to be able to get that to meet the shortfall, so there is going to be a period of time where the capability of meeting the demands of healthcare are not going to be met, and we're concerned about that. We're very concerned about that, so that's really, you know, the intent behind the question.

DR. LEWIS: Is there a manner in which the FDA might encourage industry broadly to accelerate their efforts to mitigate the exposure of the public to EtO or to in any way encourage the development of alternate methodologies to replace it?

DR. SCHWARTZ: This is Suzanne Schwartz again, and I think that we would point to innovation challenges that have been announced. We would certainly continue working with various stakeholders to determine whether there are other potential incentives that could be viable in order to bring about potential mitigations.

And I think, as we all heard this morning, this is going to take time no matter how one looks at it. From the standpoint of doing the research, the validation, the capability of being able to meet what the requirements would be from FDA's perspective on the regulatory basis and the ability to then get that to scale, that's not a short-term process. FDA's estimation is certainly for a new modality, an entirely new modality, that it would take several years in order to get that from the standpoint of its initial R&D discovery to the point where it's actually operational, which is why, as we've talked about, we're looking

also at what those short-term mitigations are from the standpoint of reducing the exposure, reducing the levels of EtO that would be utilized, as we heard this morning.

David, I don't know if there's anything you want to add.

DR. KRAUSE: Sure. I think it's been mentioned here, and also, if you remember Dr. Cortez's presentation this morning, she showed that only 2% of devices have EtO plus another sterilization method validated for their use. So assuming that things progress as they are and more states eliminate ethylene oxide sterilization, the FDA can only comment and say, you know, jeez, we think it's a bad idea because we think we need to keep capacity up. Whatever we say isn't necessarily going to change, you know, what a state legislature does. So the process of, you know, EtO sterilization becoming unavailable may be something that can't be stopped.

So I think the point of this question is at this time there are, you know, 2% of medical devices that have EtO as well as another validated method for sterilization, and I think it was mentioned that, you know, perhaps companies should also be planning, you know, to validate more than one method, and some of the devices that are out there certainly lend themselves to that process. It may not be simple, it may not be cheap, but you know, it may be something that's important to do.

Another part of the question, I think, was also addressed, and somebody mentioned the fact that we did, you know, we put out the announcement for the innovation challenge to come up with ways to -- you know, other sterilization methods or lower EtO emission, things along those lines, and I think that's the kind of responses that we're looking for. Perhaps someone has some other ideas along those lines that we could institute. The FDA has a limited capacity. We're not a legislative body; we can't go out and make laws. But we can work on ways to more quickly review processes. There's things that we can do, and I think that's the kind of information, you know, perhaps someone has ideas. This is a way of

us collecting experts' thoughts.

DR. LEWIS: Dr. Arduino.

DR. ARDUINO: Have you thought about working with or educating state legislators or the Council of Governors and talking to state governors to say, well, if you close your plants down, here's the outcome for the hospitals in your state and your citizens in your state; this is what's going to happen, you know, in a short term?

DR. SCHWARTZ: So, yeah, this is Suzanne Schwartz.

FDA works through its Office of Intergovernment Affairs very closely on these issues with states, with state legislatures as well as with governors' offices.

DR. LEWIS: Dr. Tung.

DR. TUNG: Say in the anesthesia realm we've worked our way through a number of significant drug shortages over the last several years, all the way from injectable opioids to amiodarone, atropine, drugs that we used to consider essential but now we've figured out a way around it. Is there any -- I mean, does the FDA see a drug shortage as different from what's going to happen when these plants close?

DR. SCHWARTZ: I'm not sure I entirely understand your question. Can you clarify?

DR. TUNG: I guess I'll say working it that way is sort of a demand side question. You know, you let the users know that there's going to be a shortage, and the users work to find a substitute as opposed to a supply side question, which is what I am hearing, you know. I mean, in the drug shortage situations, it has kept us going.

DR. SCHWARTZ: Yeah, so if I do understand the question -- this is Suzanne Schwartz, FDA.

There are some significant differences from an authority's perspective between drugs and devices, and there are authorities that the FDA has with respect to drug shortages that simply don't exist on the device side. That is something that we are working

towards and that we believe that that is very important in terms of being in a better state of preparedness, not just for FDA, obviously, but all of this nation.

Recognize that this is cross-cutting not only with an issue such as the one we're dealing with now but, you know, with regard to hurricane preparedness and other types of natural disasters. So to the extent that we're able to communicate or provide transparency around information on the device side, there are discrete differences between what presently exists for the Center for Devices and Radiological Health because of the way the authorities are.

DR. LEWIS: I guess one could say that in the worst-case scenario, if continued reduction of EtO capacity occurs and if the information we've heard today is accurate as to the minimal level of reserves, that we would fairly quickly get to a situation where there would be an entirely different feedback loop which would be at the local level of the public not being able to obtain appropriate services in a timely fashion at the local hospital, and the public reaction to that which would be manifest at the local level potentially would have much greater potential, if it exists, than what the FDA would do.

Don't know if that's realistic or not, but that would seem to be the potential of what we're looking at. But as far as answering the question, I guess what we're hearing is that the scope of what the FDA can do is limited. It potentially can accelerate, through any influence it has, the adoption of some of these issues for reducing the utilization of EtO or encouraging the adoption of better scrubbing mechanisms to prevent release into the atmosphere. It can publicize the issue to the extent of its ability through other governmental agencies to state agencies, and any direct regulatory authority it might have over standards which could be mitigated in order to increase device availability would be appropriate, but its overall role, given that a reduction is going to occur, is probably limited, and I don't hear from the Panel any great conclusions, otherwise.

Dr. Burr?

DR. BURR: Yeah, let me say something. So it depends on how this happens. You guys are on the cusp of a major medical logistical failure; I mean, that's yes. The consequence of that will be extremely difficult to mitigate, and the Agency is not going to have much of a role in that. If you're looking out 6, 7, 8 years for new technologies to replace EtO, terrific, but that doesn't help you next March. I think it would be helpful to look at this from the perspective that you have two time frames to work with.

You've got one that's right now, what are you going to do right now, and you've got your people working on innovations in sterilization technologies. That will have a payoff 6, 7, 8, 9, 10 years from now, and there are things you can do right now. The things you can do right now don't really belong to the FDA; they belong to the Secretary, and the Secretary can declare a public health emergency and on doing that can simply override the state, can override the EPA; you can get your missing plants back online.

Second, the technology to do abatement is extraordinarily good. They could build industrial plants 35 years ago that could handle sarin, VX, mustard, with no community exposure at all, zero. And if they could've done that 35 years ago, you can do it now. So there isn't any reason why the plants that now don't meet an EPA standard, Medtronic's may, but there isn't any reason why, over a relatively short period of time, investment in abatement technologies can't bring them within standard and reassure people who live in the neighborhood that things are okay.

Those are not long-term solutions. Those are up close and very feasible. Maybe even a public-private partnership where there would be some investment assistance in developing the kind of abatement systems that the plants will require to assure that the EtO stays inside and doesn't get outside. Anyway, that's kind of my thought on this, that we're getting very confused about timelines, and the timelines that everybody out there has been

talking about are very short. The timelines that a lot of the folks on this side of the room have been talking about are very long and don't address the problem that's right here staring everybody in the face.

DR. SCHWARTZ: This is Suzanne Schwartz. Let me comment on that.

We concur at FDA with the two timelines; that is exactly the intent behind the two innovation challenges. One is specifically to address the short term, the near term right now, over the next months, weeks, months, year. And then the second one is more of that forward looking towards the future with regard to alternatives, new research and development. Let me also address, from the Agency's perspective, the question or the comments that continuously come up regarding abatement because that's recognized as something that can have a more immediate impact.

I think it's important to understand that one of the reasons that we have not had direct presentations on abatement, on structural changes that a facility would undertake, is because that really does not fall under FDA's remit. And so while we have observed and we continue to in dialogue receive information from the affected manufacturers or firms that are involved that are taking those steps towards abatement and making those changes, we're still having to deal with, within states, state jurisdictions, decision making as to whether those plants, those facilities will be able to be operational, and that is out of FDA's hands.

DR. BURR: Right, agreed.

DR. KRAUSE: This is David Krause.

I appreciate some of the points and something -- and I think the two timelines, as Suzanne said, is exactly what we're trying to get at, and my question, and I think this question where I discussed, you know, perhaps validating another method, another question -- I mean, there's -- I'm looking for creative solutions, right? I mean, so currently if

you go and you use ethylene oxide sterilization, it's validated to 10^{-6}, okay. Are there products for which 10^{-3} might be adequate, where not as much sterilization is necessary, something that is used in a situation that could by validating it at a lower level advise us if there are products along those lines where we could do something where we would say well, you know, if 10^{-3} is adequate, that might allow industry to free up some capacity because they have to sterilize things for a shorter period of time or use less gas or whatever. Those are the kinds of thoughts that might have a solution in the short term, if there were things along those lines that, you know, we could look at and we could try to implement.

DR. LEWIS: I sense that -- actually, Dr. Goldman, do you have a comment?

DR. GOLDMAN: Actually, Ashley had her hand up and then I did.

DR. FAULX: I just wanted to make a comment as a clinician and been practicing GI for about 15 years is, you know, more and more things are being required to be sterilized, like we use sterile gauze to put lube on to do a colonoscopy. I mean, that makes zero sense. We use sterile water in the colon; that makes no sense. I mean, there's so many things, and every year we get a new inspector that comes in and comes up with a new rule based on we don't know what about what we have to throw away again.

So the amount of medical waste, just in GI, I don't know -- I mean, it's obviously -- we're not working in a sterile space, but there's got to be money and, you know, we're probably taking up -- I mean, the number of procedures I do a day, you know, 12, 15, we have six rooms, I mean, this is a huge volume of stuff that's getting sterilized that it's not really clear why we need to be using sterile things in the GI lab for non-sterile. Or in the mouth, which is really dirty, we're in the colon.

So I think, you know -- I mean, not that it's something necessarily -- I don't know if it's under FDA purview, but these inspectors that come in that make up stuff, I mean, we

are throwing away tubing in between each colonoscopy, like the whole -- everything gets thrown away. We roll colonoscopies in, they come now in a new plastic bin that has special -- I'm sure the covers are sterile, that they're either green or red that say whether it's, you know, dirty or clean, and then there's something -- I mean, there's so much stuff that's going on in this sterile process going into a colonoscopy.

So I think that there are really -- I mean, our trash cans are just overflowing every day with just garbage of things that were sterile that are no longer sterile that never needed to be sterile. So I would say, as a clinician, there are many things that we could look at just in GI that could decrease the volume that's going into these sterilizers.

DR. LEWIS: Dr. Goldman.

DR. SAUBOLLE: I agree with both Dr. Burr and Dr. Faulx. I think our problem is if you stop immediately, like tomorrow, there would be a big, big problem. If that were to happen, though, you'd have to really prioritize, what are you going to be using when, which things need to be sterilized, and who's the patient population, because you're going to be dealing with immunocompromised patients who may have to have sterile equipment, and then those that are not immunocompromised, you don't have to have it.

For example, at our hospital we had one leukemia patient bathing, showering all 2 weeks; that was his way of getting his emotions down. He came down with lichen sclerosus. Nobody else came down with lichen sclerosus; they're using the same water, so it is the quantity of organisms that's on there also makes it very big and important. So I think prioritizing, if that was to happen. I hope that's not going to happen. I hope that we can move forward by progressing, talking to the manufacturers; everything was said today, moving forward with, you know, what are we going to prioritize, where, which equipment can we do different methods, how can we change the processes.

Everything I've heard today, I think when you get there, I think we need to work as

partners. I think FDA, even though it doesn't have jurisdiction, can work with the state health departments as partners, bring them in now by saying this could be really problematic, can you work with us, let's move forward, instead of saying what's going to happen? And I think then you get them on your side as well. You talk to the public health people; they understand. I've worked with public health in Arizona. I work with them very closely. They listen to us all the time. We work together as partners. I think that's what needs to be done right now.

DR. LEWIS: Dr. Goldman.

DR. GOLDMAN: Yeah, so I've got three ideas, but now a couple of other people have said similar things, so I'm going to say them more briefly. But I mean, one is and all of what Ashley mentioned, you know, some kind of a risk framework, you know, that not everything needs to be a 10^{-6}, but you know, can you get experts in infectious diseases together and surgeons and all together to agree on a framework, what are the things that have to be at minus six, minus -- etc., and then you could triage, you know, things out of the system.

As a piece of that, something that occurred to me, that enormous pack that was unpacked for us here and had so many items in it, and I would guess, I'm not a surgeon, but I would guess that the person doing the procedure does not actually utilize all those items, and a lot of those things end up going straight from the pack into the garbage and that a lot of the volume that might be taken up is with -- it's the convenience of having a pack where everything is in one pack, but does each of the items in that pack actually need to be at that level because the volume, it's creating the demand for the EtO.

I also thought of the innovation of collaborating, and I was really happy to hear Michael say that, too, that it's not the way FDA usually works with states, but there's nothing in the law that prohibits it, and FDA and EPA and state health people rather than, you know, going to their governors and legislatures and trying to get them to push them

down, to work with them and even representatives from communities on how do you solve these problems together, and because I think that they're going to listen to communities, the politicians will. That's my experience in public health. They will listen to the communities. And so if you can collaborate with them and bring in the experts from EPA as well, and the states, I think you might be able to get past some of these problems with confidence in a little different way than simply going to the governors and saying, you know, squash this.

And then I was very concerned, as a couple of others have been, about the overall supply chain issue regardless of what happens with the politics, with these plants, because I saw some of these plants in what appear to be in earthquake areas on the West Coast as well as hurricane areas on the Gulf, and if the data we heard are correct, and I think that the FDA needs to do its own kind of digging down into that, but if those data are correct, I think that that's a health security issue that is a very important issue for the country, and it adds, perhaps, more fuel to the fire to say, well, let's develop a framework around where do we really need this technology to be applied where is it most critically needed, because tomorrow there could be a major earthquake that could take out a couple of plants, so it seems to me. But maybe, you know, maybe the data are -- I don't know if the data are really correct. I can't, you know, say that, but it certainly is a concern if this is true.

DR. LEWIS: We need to move on. I would ask the FDA if they feel they have as much information as we can get here.

DR. KRAUSE: I think we got some food for thought, thank you. Appreciate it.

DR. LEWIS: It appears that the suggestion made by several people of potentially looking at requirements and seeing where reductions can occur would be one potential area, but I don't sense that the Panel can deal with any specifics in that. That requires, obviously, looking at individual things, issues such as Ashley has suggested, about sterile

supplies for colonoscopies makes little sense, and to the extent that such things exist that could be looked at in your regulations, that potentially would have some impact.

Dr. Ortega, could you present Question 2?

DR. ORTEGA: Our second question for the Panel is: What can FDA do to help mitigate and prevent device shortages due to reduced device sterilization capabilities?

DR. LEWIS: That seems to me to be the same question rephrased from a different direction, and I would ask if any panelists wish to address it otherwise, but it looks to me like the same question.

Dr. Pekar.

MS. PEKAR: I was holding back a few thoughts so, you know, I think the FDA can do a lot around this, even this idea that there's a risk-based framework for sterilization and that for companies to essentially revalidate to reduce ethylene oxide, and here's some ideas, you know; maybe your device needs 10^{-3}, you know, maybe you don't need overkill, maybe you start from the bioburden. And I think what the FDA could really do is, first of all, put it out there because that's going to be a really novel idea, you know, and include the idea that you don't ever really want to be much more than 10^{-6}.

You know, we've seen 10^{-12} and, you know, right now we would all think that's great, you know, go for the 10^{-12}, but there's a cost. So some of the things the FDA could do is put that out there, you know, and whether it's a guidance or just a communication. Secondarily, maybe do some sample validation protocols. A lot of companies just don't know where to begin. If they had a template, that would help. You know, thirdly, can this be a special 510(k)? And then, fourthly, can you give it a quick review? I mean, so there's some things that I think are completely within FDA's control that would be very helpful.

DR. LEWIS: Mr. Socola.

MR. SOCOLA: I think it would be very helpful if the EPA or the FDA, who have

statisticians that are available, could get together and do a risk assessment, because I would really like to know if we didn't have EtO, what risk we would have to the public as compared to the NATA data, which is this could be or a probability, you know, based on their modeling that they did and, you know, that risk assessment would show us some hard information that could possibly be used to go to our legislature and say, hey, guys, if you care about the public, maybe we should introduce a law to give our FDA a little more freedom like we have with drugs in order to step in if we have a huge device shortage like we may see. So I would suggest we take a look at doing a risk assessment against their data and then what we believe could occur if we didn't have EtO available anymore.

And the second thing I want to just mention on is the 10^6. The 10^6 makes all the sense in the world if we're dealing with reusable medical devices, right? We're going to talk about that tomorrow. You have the ability to have accumulation of soil; if you don't clean it correctly, you can have super bugs, so we want to have a very robust validation process. We're talking about single-use devices here. Mr. Christensen mentioned that his data shows we have, you know, 500 colony units. We're dealing with a million.

So I do believe we could definitely reduce it to a 10^3 or even, you know, whatever the bioburden level would be. We don't need to have a panel to discuss that; that's already in the standards. All that's been decided internationally. It's all there. It's just a matter of following it and if the FDA would allow those things. So I think that definitely that could be something that could be done pretty quick.

DR. LEWIS: Are there other points to be made? I believe that this question really is the same question and pretty much I think the same responses.

DR. KRAUSE: That's good, thank you.

DR. MORGAN: This is Charity Morgan on the phone.

I guess I do believe that there's a lot of overlap with the previous question, but I

would say one thing that hasn't come up yet, is in the Executive Summary they talked about when Willowbrook was closing, they identified a cardiac device that was in danger of being in a shortage, and so they fast-tracked the approval of moving sterilization of that device to a new location. So that's something that is a short-term solution to some of these plants closing in certain locations due to, you know, the government in that state having an issue with the problem. It won't solve anything long term, but the FDA can help by sort of fast-tracking, moving things around as they can.

DR. LEWIS: All right, thank you.

Could we move to Question 3?

DR. ORTEGA: Our third question for the Panel is: Can changing EtO sterilization cycles or sterilization loads reduce EtO use while maintaining effective sterilization? Can the Panel provide a recommendation for which methods appear to be the most promising?

DR. LEWIS: Are there members of the Panel who wish to address that, because we heard about several issues, and someone who's more expert in that than I could better address it. Yes?

DR. SULLY: Hi, I'm Dr. Sully. I'm the Consumer Representative.

One other thing that I think we haven't really discussed just to that end, from the other two questions, is that some materials do yield and increase in parts per million from EtO after that processing than some other materials, and maybe research into which of those materials can yield a lower ppm might be beneficial in this endeavor.

DR. LEWIS: Any other comments? Does anyone feel that, of the three or four different ways of reducing EtO use, that you feel that some of those are more likely to be effective or more easily implemented than others?

Yes, Dr. Pekar.

MS. PEKAR: You know, the instructions for use, we could do that tomorrow, and I

think industry would be hugely happy not to be putting those booklets in.

DR. LEWIS: I guess the issue here also I think is a little difficult to deal with is we've heard a couple of times now that implementing methods for scavenging the EtO gas are readily available, implementable. We didn't really hear anything about the cost of those, but conversely, we hear that the FDA doesn't have jurisdiction in that area. So we're in a little bit of a bind in trying to address this as a comprehensive problem when the FDA only has jurisdiction over a limited number of things that perhaps are not the most effective, so I'm not sure if there's any way FDA can address this through collaboration with other agencies that do have jurisdiction or not. Obviously, there's a lot of legalese in that, and I don't think most of us have the expertise to know exactly where it goes, so we might ask if the FDA has any comments about that.

DR. SCHWARTZ: Suzanne Schwartz, FDA.

And FDA has been working together with U.S. EPA on this broad issue, and where there's opportunity for us to collaborate, you know, we certainly pursue that. I would say the same goes to a remark earlier with regard to states, in our discussions with state entities, that FDA's approach with states has been how can we help be a resource, how can we help deal with this challenge, as opposed to imposing, you know, what our specific needs are, but it's really been more about informing, educating, and how can we work together.

DR. LEWIS: Yes?

MS. WELLS: So I think one other way that we could -- and I very much agree with our expendable packs, that why are we utilizing packs that some of those products in those packs do not absolutely have to be EtO. Why don't we move to only products that absolutely have to be EtO'd are EtO'd. The rest then move toward towels, for instance, bowls, for instance. Those don't necessarily have to be under EtO. Why not make those

packs more efficient and ensuring that what is going into EtO is a necessity, breaking down those packs, expendable products, because that's really what we're talking about, is expendable products but looking at them and categorizing them properly perhaps.

DR. LEWIS: Yes, Dr. Arduino.

DR. ARDUINO: So if we're going to look at sterilization cycle, so using less EtO, maybe a longer time, that still has to go through validation. We're still going to have to validate that to even come up to being able to recommend whether those methods appear to be promising or not. I don't think we have enough data. And even reconfiguring loads within a sterilizer, that's still going to require some sort of validation to go through.

DR. LEWIS: But it could be a recommendation that the FDA, in fact, initiate some of those things to look at reducing the concentration, reconfiguring --

DR. ARDUINO: Sure.

DR. LEWIS: It's not a quick solution, but it certainly is an option as far as dealing with reduction of EtO usage.

Yes?

DR. SAUBOLLE: It sounds to me like the issue is a process, and that's why the large packs, everything's there for you, it's easy to take out. So it's not efficient; it's more easier to get into, and I think that's what we have to work with. It's the supply chain, the same issue of the supply chain. I think we have to change that whole concept and do a much better job of how we provide our patients with the material; that's what you said. Otherwise, it's a huge pack, take everything out, but it's also sterile, but it's easy. It's all there. And supply chain sends it over to the -- so I think that's the issue, again, is supply chain.

DR. KIM: And it's also -- Eugene Kim here.

It's also cost effective when you're buying things as a pack; for a hospital it's cost

effective. And I would say, as a surgeon, that we do use almost everything in those packs, and if we don't, we have it removed, and you can customize your packs to just what we need. This is a favorite topic for a lot of quality projects in a lot of hospitals in looking at our kits and removing what we don't need so that we're not unnecessarily washing instruments that never get used. So these projects are going on.

With regards to this question, I would say that, you know, what we've heard this morning with regards to industry decreasing the concentrations over time from 800 to 600 to 400, I think as far as the short term, I think that needs to continue going on. That's the fastest thing; that's what's already going on, and validating that may be probably the most effective thing right now.

DR. LEWIS: Dr. Li.

DR. LI: Just saying it in a slightly different way, it seemed like the companies that do the sterilization should already be doing these things because basically, quite frankly, it will give them a bigger profit. But if they can process more things with less time, and we heard today how they're shortening time and trying to improve their process on their own, it seems like actually there's a financial incentive as well as public service and patient incentive actually to improve the process that's going on now.

I think it's good that the FDA has basically signaled its strong interest and support in that they continue to do that, but my message to industry was this is a problem where you can make a big leap all by yourself and make money while you're doing it. So it's not clear to me why that isn't happening faster. So I'm not sure what the FDA role is in this because there's a very practical, if you will, just plain business sense to making this more practical, using less EtO, having less EtO being emitted in the emissions. You know, if you don't have to sterilize it to 10^6, then you can go to a shorter time. All these things are not only beneficial for the medical industry, but it helps them make money. So it seems like the

incentive is there, and the FDA inspiring to do them, I think, basically adds to that. So I'm not quite sure what the FDA role is in this because these companies, if they're run well, should be doing it already.

DR. KRAUSE: So this is David Krause, FDA.

A lot of good points. I think the reducing EtO, maintaining effective sterilization, sterilization cycles, we heard some very nice talks about ways that the amount of EtO could be lowered. We heard some nice talks, showed some nice graphs about the curves. Sitting behind me here are some guys that are just chomping at the bit to get a hold of the validations for those things; they would love to look at that stuff. These guys are ready, they're ramped up, they're ready to go.

So we are encouraging, you know, submissions of Q-Subs, and you know, this started in February and March when we got these reports, and you know, even though you may think we're just sitting around, we're actually already working with companies on some of these things. These guys have been working really hard, they know what they're doing, and you know, we love ideas, we love submissions; we are, you know, ready, willing, and able to work with companies on these thoughts and these ideas. So, you know, just tell us your thoughts and what you think works and how we can make this happen faster and, you know, that's what we're asking.

DR. LEWIS: Well, I don't think the Panel can tell you which of these methods is preferable. I mean, that's kind of a technical issue; costs are involved as well as a number of other factors, and I think, if I sense the feeling of the Panel, it's that we encourage you strongly to move forward with these, and of the various options presented, reduction of the concentration, reduction of the parameters of sterilization, repackaging, looking at the potential for entirely different packaging options, all were presented here as potentially useful strategies. They're all highly technical. This Panel is not going to be able to tell you

which one works better than another, so I think all we can do is recommend to you that you do move forward with experts and as quickly as possible in an attempt to find things that would be useful.

Dr. Dominitz.

DR. DOMINITZ: If I heard correctly, only 2% of products are duly approved for sterilization --

DR. LEWIS: That's right.

DR. DOMINITZ: -- and it seems that, you know, there would be an incentive for industry to have dual approval given what's going on with EtO. So, you know, maybe there's nothing more that needs to be done, but if there's anything the FDA can do to incentivize additional sterilization approvals, maybe fast-tracking them or other incentives might be available so that there is this capacity for switching more rapidly, I think that would be helpful.

DR. LEWIS: Are there other comments?

DR. SAUBOLLE: I have one question, actually. We're talking about lowering EtO. To what capacity? I mean, I heard this morning talking about a safe threshold; do we know what a safe threshold is? I think it would behoove us to find out a little bit more about that so that we can look at it and say, all right, looking at, you know, the risk factors, at what point is it a risk, at what point?

I also heard this morning, talking about ambient air detection of EtO, ambient air without any known source. How prevalent is that, and is that a risk factor itself? Is that just something coming from California to Arizona, because we don't have any places that do EtO there, but you see what I'm saying?

DR. KRAUSE: Yes. This is David.

That was the EPA comment, but the safe threshold, I think Steve mentioned that. Do

you want to elaborate on what you were referring to on your graph about the safe threshold? Go to the microphone.

DR. ELLIOTT: Hi, Steve Elliott.

Yeah, in terms of safe threshold for the purpose of that particular diagram, we were referring to residuals remaining on devices, so it wasn't directed specifically towards emissions, although at the conclusion of the cycle where you're essentially venting your ethylene oxide away from the load, that would be where your most likely points would be to start getting emissions of ethylene oxide.

DR. SAUBOLLE: So without a safe threshold that we know of and since it's a carcinogen, our long-term goal probably would be to get rid of EtO altogether, unless we can set up the risk factors, at what point are we no longer at risk?

DR. GOLDMAN: People have done that, people have done that. I mean, I'm not sure -- I think your point is well taken, but that's something that FDA actually has access to. It's just that FDA does not regulate ambient air, and the way EPA regulates air toxics is not through a risk-based approach but through a max standard, which is what's being applied to these plants, so the maximum achievable control technology, which kind of gets us to the next question because there are things that can capture and remove EtO from emissions, and EPA's standards are based on the application of the best, you know, or the best of the 75th percentile or something like that. It might be 80th.

DR. LEWIS: And, again, it seems to me those technical questions are not something this Panel can answer.

DR. GOLDMAN: No, no.

DR. LEWIS: And I think it's a waste of time for us to really get into that, and I think --

DR. GOLDMAN: And we can't say which scrubber technology. I mean, to the next question --

DR. LEWIS: Correct.

DR. GOLDMAN: -- we weren't shown this technology.

DR. LEWIS: Correct, we'll get there in a moment.

DR. KRAUSE: So just to reiterate, the safe threshold, as was just mentioned, there is an ISO standard that gives the exact amounts that a device is not allowed to have more than that on there, and we require the manufacturer and then, you know, when they submit their product, to show that they have met that threshold, have less than that amount of ethylene oxide and also ethylene chlorohydrin, which is, you know, a product that, you know, comes from the same sterilization process.

DR. LEWIS: So FDA, do you have the answers for Question 3, as best we can do it?

DR. KRAUSE: All right, thank you.

DR. LEWIS: Question 4 from Dr. Kroger. Dr. Ortega, excuse me.

DR. ORTEGA: Our fourth question is: Can new or different methods of validating EtO sterilization cycles potentially result in a reduction of EtO use while still maintaining an effective sterilization process? If so, how?

DR. LEWIS: This is a different question from the one which was published to us, I believe. The one I have in front of me says, "Are there effective methods of scrubbing or abating EtO from the sterilization chamber following an industrial process?" So have you modified that question?

(Off microphone response.)

DR. LEWIS: Oh, okay. So we're bypassing 4?

(Off microphone response.)

DR. LEWIS: Four and four don't agree. So we have a bit of a conflict here, and Question 4, as I have it listed, is not the same as this Question 4.

(Off microphone comment.)

DR. LEWIS: Okay. So we'll answer the slide. Can new or different methods of validating EtO sterilization cycles potentially result in a reduction of EtO use while still maintaining an effective sterilization process? If so, how?

Yes, Ms. Wells.

MS. WELLS: This, I think, is a really good opportunity and just pretty much like what you were saying with being able to look at that Spaulding Classification, we have to follow manufacturing guidelines. When the manufacturing guideline states that that instrument needs to be sterilized, whether it's being used at a clinic to take out, you know, stitches, to which you know you're not going to go below that threshold line, then we're going to send that product to be sterilized. I think that's the same way.

Can we look at manufacturing guidelines and categorize their usage, whether it's for clinics or for non-critical and then do an evaluation on that of whether or not it needs to be EtO'd or steam sterilized or whatever, and in addition, looking at over the years that I've been practicing, I've seen sterilization times go up, up, up, up, up, and now, for some of our products, we're up to 23 minutes. Can we get a standardization process for categories?

Critical RME, must do 10 minutes, you know. Semi-critical, we know it's high-level disinfection. But can we get better parameters on our instruments? Dental's another perfect example. Does it truly need to be in the critical arena? But because that is our instructions, that's what we follow.

DR. KRAUSE: So this is David Krause again.

So this is like Jeopardy. Can you put that into a recommendation rather than a question?

MS. WELLS: I recommend that we look at the validation of 510(k) instrumentation for clinical usage and scale it out very much like Spaulding Classification and you have, in the instrument IFU, a clinic which would be no greater than a semi-critical situation

sterilization process or a care-in-handling process, and then for critical, what that sterilization process would look like. The very same Potts scissors that I use in the ophthalmology department for foreign removal are the very same Potts scissors that I use in, perhaps, my retina surgery, but I don't need that same sterilization process. So for me, that would be what my recommendation is, to look at our sterilization instructions and categorize for clinical use.

DR. LEWIS: So I believe the recommendation is that the FDA look at -- was there another comment? Excuse me, yes.

MS. PEKAR: What if the FDA could, at this point, recommend the BI/bioburden validation method and maybe go as far to set up, you know, a time frame a year from now where it will be mandated for new devices? That would automatically cut EtO emissions substantially.

DR. LEWIS: So it seems to be the opinion that the FDA could look at the processes which are currently required and critically evaluate whether the standards are high and they're necessary, particularly when the area involved or the subject involved is either non-sterile itself or where the consequences are minimal in regard to non-sterility.

DR. KRAUSE: Thank you.

DR. LEWIS: Question 5.

DR. ORTEGA: Question 5 is: Should sterilization of some medical devices to a less rigorous sterility assurance level (e.g. 10^{-5}, 10^{-4}, instead of 10^{-6}) be considered as part of the approach to reduce sterilant use? How do you see this changing the patient risk profile for sterile devices if a different sterility assurance level is determined to be acceptable?

DR. SAUBOLLE: Isn't this the question we just answered?

DR. LEWIS: I believe so.

DR. SAUBOLLE: So we have to go back to Question 4 now; that's a different

question.

DR. LEWIS: Well, no. I think we probably answered this question.

DR. GOLDMAN: I think we answered the question, yes.

DR. LEWIS: I would say that there's a slightly different interpretation because the suggestion that reducing the sterility assurance level increases the patient risk is actually not true because what we heard was that the level could be reduced and still maintain the same assurances of sterility because the actual sterility that was being achieved was several layers of magnitude greater than 10^{-6}. And so I believe the meaning or the issue is somewhat different than stated in the question, and that reducing or increasing the patient risk profile, certainly for some devices, is not acceptable, implants, for example, and endovascular devices, such things. But the issue is are the standards higher than they need to be given the way in which they're being done, and I think, as has been stated, the answer to that has already been stated as yes.

Are there other comments that people wish to make?

Dr. Goldman?

(Off microphone response.)

DR. LEWIS: Okay.

DR. KRAUSE: All right, thank you.

DR. LEWIS: Question 6.

DR. BURR: Could I just add one quick thought on that?

DR. LEWIS: Go ahead.

DR. BURR: So I think if you were to do that so that you would have products that actually might be very similar in form and function but had been prepared to different levels of sterility, you would have to have some way of identifying which is which, perhaps by color or something like that, I think to avoid confusion in use.

DR. LEWIS: Next question.

DR. ORTEGA: Our sixth question and final question for the evening is: Are there large-scale industrial sterilization modalities that can take over a portion of the EtO sterilization performed for medical devices in the short or long term? If so, can the Panel provide a discussion of the path forward for these modalities? And if not, what are the barriers and challenges preventing wider utilization of these modalities?

DR. LEWIS: I'm not sure we've heard about -- Dr. Li, would you like to comment?

DR. LI: A little repeat of what I said earlier. I think this is a hard question again for me to answer because I think it depends on the device and mostly what it's made of. Again, I've seldom had a device where I had my choice of which sterilization method to use. There are some devices, for instance, if it's got Teflon in it, then gamma radiation is out. If dimensions are important, thermal sterilization is out. So in my own experience, in almost every case, the device is dictating the sterilization method.

So this question is kind of going the other way around, given the sterilization method, what else could I sterilize, this EtO, to sterilize the device with when the thought process already had gone into it that it was chosen over the other methods. So unless we're talking about some method that doesn't exist, they've already decided once that EtO is the way to go.

DR. LEWIS: Well, the possibility exists. We were told that there's roughly 2% overlap of devices that can be sterilized in multiple ways. Perhaps that number is too small and it simply is the way it's been done, but it doesn't represent the possibilities that exist.

DR. LI: Well, if you can get 2%, I say go for the 2%, but I would be surprised if it was a lot bigger than that.

DR. LEWIS: Yeah, that's what I'm saying.

DR. LI: Yeah, yeah. Exactly.

DR. LEWIS: I think it may be --

DR. LI: Yeah.

DR. LEWIS: -- a lot bigger than that and that the 2% number has been arrived at because that's what's been selected but not necessarily that that's all the possibilities. On the other hand, the table that we saw where multiple columns addressed the subtle issues of compatibility and other possibilities with the use of different sterilization methods requires, again, that it's a highly technical and highly detailed evaluation which needs to occur. The likelihood is that I think there are opportunities for other sterilization modalities to be utilized, particularly radiation but possibly peroxide and some of the other things we heard about. But, again, it's such a technical issue that it requires, for each type of device, that those be addressed in detail, and it's not something that this committee can arrive at.

DR. LI: I completely agree, and I don't actually mean to be negative. I actually think that there are definitely devices that probably could be sterilized in some other way, and you're talking about gas, hydrogen peroxide tomorrow? I think there are places for those sterilization methods, but I don't really think there's a wholesale decision that can be made and it said, you know, all these products over here we're doing with EtO, we could switch to this. I don't think that possibility is there.

DR. LEWIS: Dr. Goldman.

DR. GOLDMAN: I don't think that we received very much information to allow us to answer this question, but I remember earlier, and I don't remember who from across the table asked, you know, why isn't the market working to take care of this if there isn't enough capacity, and you know, the EtO facilities are -- people could be building more of them, they could be scaling up the ones that they have already, and they're not. And then we did see that there is the availability of alternative technologies; those tables were pretty, for me, persuasive, but I didn't hear that any of them are being deployed in large-

scale facilities that, you know, could kick in today.

And so I don't have -- I can't answer that question, except I do think that FDA may need to give some thought to what is going on with the market and its ability as a regulatory agency to impact that. Now, the innovation challenge is one way to do that, but there might be other things, and again, getting back to the earlier idea about collaborating, you know, is there a way to get into a collaborative relationship with some of the industry, the states, the EPA, others, you know, to address this as a problem, because it's a little bit of a puzzle that we would be in a precarious situation with heavy capacity for this given that there's a market for it.

DR. LEWIS: I think the answer to the question is, yes, that there are opportunities, perhaps not a large number, but that they require detailed evaluation of each type of device and material that's being addressed.

Dr. Wilcox, do you have some other comments?

DR. WILCOX: Stephen Wilcox

So this is not an answer to the question, but I just wanted to say something, and that is every single question assumes that EtO use is going to go down, where I think we all agree it needs to go up, not down. So I think, yeah, it might happen, we might have to live with lower EtO use, but I think we also ought to ask the question of how we can increase capacity. From the healthcare industry point of view, we don't have a problem with EtO, with using EtO; it's coming from the outside and, in fact, it didn't even sound to me like the EPA had a problem with using EtO; they have a problem with emissions, and the emission problem is solvable. At least I was convinced today that that was solvable.

So I think at least in parallel with figuring out how to live with lower EtO use, we ought to ask the question what can the FDA do to increase capacity, to encourage more use, more plants to come online, because that was the prior problem, not enough capacity in the

first place, and then when this state legislature thing happened, it reduced it even more, but the prior problem was not enough capacity in the first place, and I fear that while we're all assuming EtO use is going to go down, then who is going to invest in another EtO plant when we're all talking about how it's going to go away? So I think we ought to make it clear that we're not assuming that that's going to happen; we're asking the question of if it does happen, what are we going to do?

DR. LEWIS: Yeah, I would agree. I think one of the more significant pieces of information that's come out of the meeting today is that, in fact, there are abatement procedures and techniques that are readily available and could be implemented and that that potentially is the biggest short-term fix for the problem we've heard about and that somehow, although that may not be the FDA purview, that they really need to, to the extent possible, take a role in investigating how agencies or the private sector can be encouraged to move in that direction since that would seem to be the quickest way to solve the problems which are apparently bothering the state legislatures.

Are there other comments? If not, is the FDA adequate with this answer?

DR. SCHWARTZ: This is Suzanne Schwartz.

I do just want to comment that the reality that we face today is that there is a lot of movement on the ground across the nation with regard to decreasing the use or eliminating the use of EtO; that is the reality that we face. So we have to think about it at the Agency in that context where public sentiment and concern across communities has significant influence and has raised these concerns within various state jurisdictions, and while we're talking right now about two states in particular -- three, potentially -- our understanding is that this is again a growing movement, and so I don't know that it's helpful for us to be thinking about it from the standpoint of increasing capacity of ethylene oxide sterilization. I think that our main focus is really on what we can be doing to certainly help in decreasing

the EtO emissions through the measures that have been discussed today.

DR. SAUBOLLE: I think I have to agree with you on that. I think, listening to everything that was said today, especially as far as the outcomes are concerned, the problem with abatement or other methods of scrubbing is the process. If the process was so good, then why was all the EtO over the factory that was the industrial area that was using it; it shouldn't have been there in the first place.

So in my estimation, processes break down quite frequently, so if we can eliminate something that is bad, it's much better than trying to bring a process that can scrub it out in the final product itself. So that's the problem, you know; it's what you think you put in place and you check it, it's not really there because you haven't looked at the outcome, the final area there, you think you have it in place. Oftentimes in hospitals we set something, policies in place. A year later, when we check on them, they're no longer the same pothole; they've moved. Somebody's kind of doing their own thing again, so it is difficult.

DR. LEWIS: Dr. Kim.

DR. KIM: With regards to existing large-scale alternatives, there just seems to be one, and that's the gamma radiation, the one with the significant other half of the volume, and it seems like they have their own challenges per Ms. Craven's talk today, particularly with the acquisition of cobalt and all that's required to build it, and so I think that the other half has to be thought about. If EtO is going to be limited in their scope in the future, then you have to think about the other half and how to better remove barriers to expand those facilities.

DR. LEWIS: Dr. Li.

DR. LI: Two things. One, on abatement, we haven't heard really a lot of detail about abatement, so I'm certainly no abatement expert on this, but the emissions that came out, it wouldn't be the first plant that just didn't do a good job with their equipment. It's not

like the technology doesn't exist. For instance, there's no outcry for the companies that make the ethylene oxide gas. I mean, they're making 100% ethylene gas, putting it in tank cars and shipping it out, and they have no abatement issues. So I believe the abatement issue is available. Now, what the expense is and how much trouble it is, that I don't know, but at this point, I got to believe that there is a chance that abatement can be at least improved.

And just a quick comment. I completely understand the notion that things are not going the ethylene oxide's way and that there's a public outcry from that. And I think it's actually a good idea to talk about what to do should that come about, but I don't think we should ever stop saying we don't really think that's a good idea at this point because we have no alternative, and if you take it away from us tomorrow, more bad things will happen than good, and I don't think it's helpful for us to stop saying that while we're trying to look up for a solution.

So I'm going to keep hammering on the fact that we don't really have an alternative solution, right? So even though the disaster may be coming, I'd just as soon just remind people that, hey, you could take that away, but you're going to lose this, too, and I would not like to lose that message.

DR. LEWIS: Dr. Benowitz.

DR. BENOWITZ: I just had a clarifying question about the availability of gamma sterilization. So, you know, we've heard that these challenges with EtO go back to the '80s and that since then the industry has switched to using gamma sterilization for somewhere between 40 and 50% of the devices. What have we done to look at whether that is actually an available option for other devices? Is it that nobody has tried and gamma might work or that we expect that those are materially incompatible and it's just not going to work?

DR. LI: I can answer in my own experience with that question. Typically, you use the

method of sterilization that either works the best or is the cheapest, right. Those are the two criteria, and gamma radiation came to the front because there were certain devices that actually it's cheaper and more effective and more efficient to use than EtO, and those are the ones that are gamma irradiated if the material can stand the irradiation. So, again, these companies, it's not a random choice of which sterilizer they pick, or it's not even a price choice, you know. Price is part of it but, you know, it's as you said, it's a complicated decision. So it's not very often that I run into a device where you can use both methods of sterilization. You know, they say 2%. I would go along with that number. But my experience is there are not very many devices where you have that freedom of choice.

DR. KRAUSE: This is Dave Krause. Steve Elliott can give a little insight into that.

DR. ELLIOTT: I think the last response was very accurate in terms of the challenges with that. It's often the sterilization process that is compatible with the device that can effectively sterilize it or there can be economic reasons for doing that. The problem is the exploratory work that goes with actually establishing another process that works can be very expensive, and that might not be feasible for device manufacturers. Medical devices are very different than drugs in terms of the size of the companies producing them. Some of these are single-person operations, and it's just not feasible to pursue multiple sterilization modality options for processing your device.

DR. ARDUINO: Oh, I have something.

DR. LEWIS: Yes, Dr. Arduino.

DR. ARDUINO: For some of these smaller companies, is there a way to incentivize them or help them move that device to a different --

DR. KRAUSE: This is Dave Krause.

The FDA does have small business assistance where a small company, I think 50 people or less, pays less for certain of the user fees. Those kinds of incentives exist but, you

know, any company, whether they're loaded with money or whether they have no money, can submit a Q-Sub, and we will talk to them and we will see how we can help them out with, you know, whatever project they have, whatever device they're working on. You know, there are numerous FDA programs; for example, if somebody has a really good idea and they have a product and they have a little bit of information that shows that it might work, we have breakthrough product status where, you know, somebody can get into the system. They can get, you know, expedited help. You know, I mean, those are the kinds of things we try to do, so yes.

Also, you know, on the issue of, you know, different sterilization methods, we saw a really nice presentation. There are devices that just don't lend themselves to being irradiated. I know, I started out at FDA as a reviewer and, you know, hydra gels and various plastics just could not be sterilized with radiation because there was just so much energy being deposited in the device that it would break down the device and so you just couldn't do it.

But, I mean, you know, I'm sure there's other products that are, you know, heavy metal or something made out of titanium or steel or whatever that probably could be either EtO sterilized or radiation sterilized or maybe even some other modalities, and then the question is just whether or not, you know, which is the most efficient way to do it and, you know, if a company has been doing it with EtO for, you know, 20 years, it might be cheaper for them to just keep doing it that way than to validate a new process, and so, I mean, those are all things that need to be taken into account.

DR. LEWIS: Mr. Socola.

MR. SOCOLA: In my experience, I've been validating reusable medical devices for 30 years now, if a device manufacturer can validate in more than one sterilization process, they're going to do it. They do not want to have a disadvantage to the competitor that's

selling the exact same device that can be sterilized in much more modalities than they can, so they're going to try to sterilize it as much as they can, as many modalities as possible. The exception, as Steve pointed out, is, you know, the orthopedic surgeon, that it's him and his wife, they developed a widget, you know, they have some limitations.

When we get into these type of devices and the chemical characterizations, you're going to have to follow ISO 10993, it's going to tell you the amount of toxicology and the amount of biocompatibility testing that you do, and these tests aren't $500, okay. So depending on what you have to do, you could be spending tens of thousands, hundreds of thousands of dollars on your biocompatibility testing. So I mean, there's not a lot of incentives for someone to, you know, try to switch, you know, when you're looking at those types of dollars. And, you know, one of the other things -- I'll actually save this for the next one that's coming up, thanks.

DR. LEWIS: Thank you.

Dr. Goldman?

(Off microphone response.)

DR. LEWIS: Okay. Do we have any other questions, or are we done?

DR. KRAUSE: There's more questions for tomorrow, so maybe --

DR. LEWIS: I know, no, but I'm asking for today.

DR. KRAUSE: Yeah.

DR. LEWIS: If not, do you have satisfactory answers?

DR. KRAUSE: I think so, thank you.

DR. LEWIS: I believe Commander Garcia has some announcements.

CDR GARCIA: Thank you, Dr. Lewis.

For members of the audience who plan to attend to tomorrow's meeting, if you want to keep your handouts or public handouts, please keep them because we're going to use

them again tomorrow. And for the Panel members, if you want to keep your folders up here, you can do so as well, because Day 2 also contained tomorrow's panel materials. That's all I have, Dr. Lewis. Thank you.

DR. LEWIS: We'll plan to meet here again tomorrow morning at 8:00, and I thank all the Panelists for their contributions and comments today. We stand adjourned.

(Whereupon, at 5:38 p.m., the meeting was continued, to resume the following day, Thursday, November 7, 2019, at 8:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL HOSPITAL AND PERSONAL USE DEVICES PANEL

November 6, 2019

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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TOM BOWMAN

Official Reporter