

UNITED STATES OF AMERICA
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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CIRCULATORY SYSTEM DEVICES PANEL

+ + +

June 2, 2016
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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ALFRED STAMMERS	Temporary Non-Voting Member
JEFFREY RILEY	Temporary Non-Voting Member
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MEETING

(8:00 a.m.)

DR. YUH: I would like to call this meeting of the Circulatory System Devices Panel to order. I am obviously not Rick Lange, who is the Acting Chairperson of this Panel. He is, I've been notified, on a flight on the way here and should be here in a couple of hours. So I guess I would be the Acting Acting Chairperson of this Panel. I'm David Yuh. Again, I'm the Chief of Cardiac Surgery at Yale University. My expertise is in minimally invasive cardiac surgery and computational modeling of the heart.

At this meeting, the Panel will discuss and make recommendations on the effectiveness of cleaning and disinfection methods for heater-cooler devices; the amount and type of premarket data and information needed to demonstrate validation of cleaning and disinfection of heater-cooler devices in support of labeling claims and technical instructions; appropriate risk mitigations to be implemented by manufacturers of heater-cooler devices and/or hospital facilities to ensure patient safety during surgical procedures where these devices are used; and appropriate guidelines and/or criteria based on risk stratification schema for notifying patients who may have already been exposed to nontuberculous mycobacteria during prior cardiac surgeries.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. As we go around the table, please state your name, your area of expertise, your position, and affiliation. Why don't we start with Dr. Schwartz at the end of the table.

DR. SCHWARTZ: Good morning. My name is Suzanne Schwartz. I'm the Associate

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Director for Science and Strategic Partnerships at FDA's Center for Devices and Radiological Health. I'm also the Acting Director of Emergency Preparedness/Operations and Medical Countermeasures.

MR. AGUEL: Good morning. My name is Fernando Aguel. I'm the Branch Chief of the Circulatory Support Devices Branch in the Division of Cardiovascular Devices, Office of Device Evaluation in CDRH.

MR. RILEY: Good morning. Jeff Riley. I am a perfusionist. I work at the Mayo Clinic in Rochester, and I'm past president of AmSECT, the American Society of ExtraCorporeal Technology.

MR. STAMMERS: Good morning. Al Stammers. I am a cardiovascular perfusionist and the Director of Quality and Research at SpecialtyCare.

DR. GALLAGHER: Good morning. Colleen Gallagher. And I'm an ethicist working at the University of Texas MD Anderson Cancer Center as professor and Executive Director of Integrated Ethics.

DR. ZENILMAN: Good morning. I'm Jonathan Zenilman. I'm an infectious disease physician, and I'm the Chief of Infectious Diseases at Johns Hopkins Bayview Medical Center, and professor of medicine in the medical school and the school of public health.

DR. ARDUINO: I'm Matt Arduino. I am a senior advisor for environmental hygiene and infection prevention at the Division of Healthcare Quality Promotion at CDC.

DR. CHRISTENSEN: I'm Bryan Christensen, CDC's Division of Healthcare Quality Promotion. I am an industrial hygienist with a background in aerosol science.

DR. GIVNER: Larry Givner, Professor of Pediatrics, Pediatric Infectious Diseases at

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Wake Forest School of Medicine in Winston-Salem, North Carolina.

DR. LEGGETT: Jim Leggett, adult infectious disease, Providence Portland Medical Center and the Oregon Health & Science University.

MS. WASHINGTON: Good morning. Evella Washington. I'm the DFO.

DR. ROSELLE: I'm Gary Roselle. I'm the National Director for Infectious Diseases for the VA, and recently I've been looking at the microbiology of the built environment, with a specialty really in water. And in the past, I actually have run sterile processing.

DR. HOPKINS: Richard Hopkins. I am a pediatric congenital cardiac surgeon at Children's Mercy Academic Medical Center in Kansas City. We're the academic medical center for the University of Kansas and University of Missouri, among others. My scientific area of expertise is in regenerative cardiovascular biology.

DR. EVANS: Good morning. My name is Scott Evans, senior researcher, biostatistics, at Harvard.

DR. ALLEN: My name is Keith Allen. I am a cardiothoracic and vascular surgeon at the Mid America Heart Institute in Kansas City, and Director of Structural Heart and Director of Surgical Research.

DR. FENNAL: Good morning. My name is Mildred Fennal, and I am a retired nursing professor from Florida A&M University, currently the Director of the International Nursing Education Consortium. My background is critical care nursing.

MR. McGLAMERY: Good morning. I'm Raymond McGlamery, and I'm the Patient Representative. Both of my parents were recipients of multiple bypasses, and my sister was a heart transplant patient.

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MR. THURAMALLA: Good morning. I am Naveen Thuramalla. I'm working as a Vice President of Regulatory Affairs at ARKRAY, Incorporated. I'll be serving as the Industry Representative on this Panel.

DR. YUH: Thank you very much. As you can see, we have a very distinguished Panel of experts with us today, and very fortunate to have them take some time out of their schedule to make it with us today.

If you've not already done so, please sign the attendance sheets that are on the tables by the doors outside this room.

Ms. Evella Washington, the Designated Federal Officer for the Circulatory System Devices Panel, will make some introductory remarks.

MS. WASHINGTON: Good morning, everyone. Before I begin, I would like to state for the record that Dr. David Naftel was unable to attend due to travel issues.

I will now read the Conflict of Interest Statement.

The Food and Drug Administration, the FDA, is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are 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.

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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.

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 financial conflicts 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.

For today's agenda, the Panel will discuss recent reports and epidemiologic investigations of nontuberculous mycobacteria (NTM) infections associated with the use of heater-cooler devices during cardiac surgical procedures. FDA is convening this Panel to seek expert scientific and clinical opinion related to contamination of heater-cooler devices, associated patient infections, and mitigation strategies based on available scientific information.

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.

Mr. Naveen Thuramalla is serving as the Industry Representative, acting on behalf of

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all related industry, and is employed by ARKRAY, Incorporated.

For the record, the Agency notes that Dr. Joseph Falkinham, III, who is an invited guest speaker with us today, has acknowledged financial interests in the form of consulting arrangements with Cincinnati Sub-Zero, Sorin North America, and LivaNova, whose products are under discussion.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

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

I will now read the Appointment to Temporary Non-Voting Status Statement.

For the duration of the Circulatory System Devices Panel meeting on June the 2nd, 2016, Mr. Raymond McGlamery has been appointed to serve as a Temporary Non-Voting Patient Representative, and Dr. James Leggett, Jr. has been appointed to serve as a Temporary Non-Voting Member. For the record, Mr. McGlamery serves as a consultant to the Oncology Drugs Advisory Committee in the Center for Drug Evaluation and Research (CDER), and Dr. Leggett serves as a consultant to the Antimicrobial Drugs Advisory Committee in CDER. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be

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considered at this meeting.

These appointments were authorized by Jill Hartzler Warner, J.D., Associate Commissioner for Special Medical Programs, on May the 19th of 2016.

For the duration of the Circulatory System Devices Panel meeting on June the 2nd, 2016, Dr. Yuh will serve as a Temporary Non-Voting Chair in place of Dr. Lange.

Before I turn the meeting back over to Dr. Yuh, I'd like to make a few general announcements.

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

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Ms. Deborah Kotz.

I would like to remind everyone that members of the public and the 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 today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

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

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

Thank you very much.

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Dr. Yuh.

DR. YUH: Thank you very much, Ms. Washington.

We will now hear a brief introduction from Dr. Suzanne Schwartz.

DR. SCHWARTZ: Thank you, Dr. Yuh, and Designated Federal Officer Ms. Evella Washington.

Good morning. And on behalf of FDA's Center for Devices and Radiological Health, welcome to the Circulatory System Devices Panel of the Medical Device Advisory Committee.

The subject of this Panel meeting is nontuberculous *Mycobacterium* infections associated with heater-cooler devices during cardiothoracic surgery.

My name is Suzanne Schwartz. I'm the Associate Director for Science and Strategic Partnerships at CDRH. I also serve in the acting capacity of the Center's Emergency Preparedness/Operations and Medical Countermeasures program.

Over the next two days we'll be discussing a public health concern that has emerged over the past year. In Europe and now in the United States, invasive nontuberculous mycobacteria, or NTM, infections have been identified in patients that have previously undergone open-chest cardiothoracic surgeries involving cardiopulmonary bypass, sometimes with a delay in symptoms or signs and in diagnosis for as long as 4 years from the time of exposure to the organism. These NTM invasive infections, while rare, have caused serious illness and death. Through epidemiologic investigations and laboratory analyses, these NTM infections have now been linked to prior exposure to heater-cooler devices used during cardiopulmonary bypass procedures. We'll refer to these heater-cooler

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devices as HCDs, going forward.

It's important to note that HCDs are closed, non-sterile circuits, and there is no contact with the patient's blood or body fluid at any time. These are therefore considered non-patient-contacting devices.

And yet, although these are non-patient-contacting, evidence now demonstrates the potential for water contained in the HCD tanks contaminated with nontuberculous mycobacteria to transfer from the inside of the device into the operating room environment and ultimately into the patient via the open chest through aerosolization. This airborne route for intraoperative transmission of NTM from contaminated HCDs is newly described, and it was not anticipated when HCDs were previously cleared by the FDA.

FDA has called this meeting to bring together an exceptional Panel of subject matter experts across multiple disciplines in order to help inform and provide effective recommendations to industry, hospitals, doctors, and patients to help mitigate this public health concern.

It's important to state here that we, FDA, believe heater-cooler devices remain critical to patient care and that the risk to the individual patient of acquiring an NTM infection is extremely low. In most cases, the risk from delaying needed cardiothoracic surgery is likely to outweigh the risk of acquiring an invasive NTM infection.

As you will hear in the ensuing presentations, this is a multifaceted challenge, and it involves an entire class of devices, infection control measures, as well as the need to consider the environment of use and the end user. And overlaid on these complex factors are difficult questions associated with patient identification and patient notification. FDA

has therefore taken a broad and multi-pronged approach to investigating and responding to this public health concern.

Indeed, the composition of this FDA Medical Device Advisory Committee meeting reflects the crosscutting nature of this issue. Participants include Panel members and invited speakers who represent expertise in aerosolization science and industrial hygiene; microbiology and in particular NTM biology; hospital infection control; cardiothoracic surgery and perfusionist roles and responsibilities; clinical and molecular epidemiology; and the ethics regarding disclosure.

The Panel will hear directly from healthcare facilities that have been impacted by this public health concern, from manufacturers of these medical devices as well as from state and federal public health agencies who play a critical role in this investigation and response.

We remind the Panel participants and the audience that this is not a device-specific Panel. To be clear, the Panel is asked to refrain from discussion and deliberation that singles out any one product or any one manufacturer. Our questions to the Panel are aimed to address an entire class of devices that are identified as cardiopulmonary bypass temperature controllers, also known as heater-cooler devices.

To that end, FDA's objective is to elicit viable, actionable recommendations that can be universally applied across the breadth of this device class, and in the future, to similar device classes such as water-based thermal-regulating systems.

In keeping with FDA's public health mission, we believe it's important to have an open and transparent dialogue with all stakeholders to review and discuss available data

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regarding the benefits and risks associated with the use of heater-cooler devices during cardiothoracic surgeries where cardiopulmonary bypass is required, and to generate evidence-based recommendations on how to best care for patients undergoing these lifesaving procedures.

FDA is therefore convening this meeting to seek expert scientific and clinical opinion related to the following topic areas:

- Number one, the effectiveness of heater-cooler device cleaning and disinfection methods
- Secondly, premarket data and information needed to demonstrate validation of cleaning and disinfection of heater-cooler devices in order to support labeling and technical considerations
- Third, protective measures and risk mitigations to ensure patient safety during procedures where these devices are used

And here we will be asking the Panel to consider the adequacy of mitigations for devices in current use, in order to minimize aerosolization. And we will also ask the Panel to make recommendations regarding future design considerations that would aim to remediate the route of NTM transmission.

- And finally developing risk stratification schema to inform guidelines for notifying patients who may have already been exposed to NTM during prior cardiac surgeries

I'd like to thank all of the Panel members and invited speakers for taking time out of their very demanding schedules to participate in what are extremely critical discussions,

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and to the FDA staff that have worked so diligently on this issue in preparation for this Panel meeting.

And now I'd like to call upon my colleague, Nicole Milligan, who will provide a comprehensive picture of the heater-cooler device.

MS. MILLIGAN: Good morning. My name is Nicole Milligan, and I am a biomedical engineer in the Circulatory Support Devices Branch in the Division of Cardiovascular Devices. I will present an overview of heater-cooler devices, which will be abbreviated as HCD for the remainder of the presentation.

I will start with a background on HCDs and discuss device design, then a background on nontuberculous mycobacteria, and finally review the challenges that affect this issue.

I'd like to draw your attention to the HCD in this image labeled heater-cooler unit. The HCDs provide heated (the red line) or cooled (the blue line) water. HCDs can be connected to oxygenator heat exchangers, cardioplegia heat exchangers, and warming or cooling blankets. The blankets can be reusable or single use and can be used in the operating room. The water circuits in the HCD are closed circuits and shouldn't come in contact with the patient or blood.

These devices are Class II devices and can be cleared under two regulations: cardiopulmonary bypass temperature controller, which heats temperature-controlled water to the oxygenator and cardioplegia heat exchangers, or thermal-regulating system, which feeds temperature-controlled water to blankets. However, this Panel will focus on the cardiopulmonary bypass temperature controller as it is mainly during open chest procedures where extracorporeal circuits are being used that we have seen the infections,

as Ms. Bauer will discuss later.

It's important to note that some HCDs can be connected to the blanket, oxygenator heat exchanger, and cardioplegia heat exchanger.

In the regulations, cardiopulmonary bypass temperature controller is defined as a device used to control the temperature of the fluid entering and leaving a heat exchanger. Primarily, the heat exchanger is either connected to an oxygenator or a cardioplegia system and is an integral part of an extracorporeal circuit used for many open chest cardiothoracic procedures.

Now, a little information about the regulatory history of these devices. HCDs have been on the market since at least the '60s. Successful cardiopulmonary bypass was performed in the '50s, and more complex procedures led to longer surgeries, which then led to hypothermic bypass starting in the '60s, requiring the use of the HCD. Hypothermic bypass became standard of care probably in the early '70s.

So what does this mean for FDA review? Class II in regulatory terms means that the manufacturer needs to submit information to FDA to demonstrate that the device can be compared to another similar device on the market, what we call a predicate device, and also needs to demonstrate that it meets certain performance criteria. FDA review for these devices generally includes a review of device technology, performance, and labeling as compared to the identified predicate device, as well as a determination as to whether any differences noted between the devices can affect safety or effectiveness. Within the labeling is the cleaning and disinfection procedure to be followed for the unit.

Since the temperature-controlled water circuit is a closed circuit with no intended

patient contact and the device is non-sterile, the health risk to the patient was considered very low. As such, in the past, the cleaning and disinfection protocols were not required, but instead FDA relied on the manufacturer's quality system regarding validation of these procedures; that is, the manufacturer had to have these validated data within their own files but did not have to provide them to FDA in their premarket submission.

The possibility of aerosolization of contaminated water from the tank was not anticipated back then. FDA is now actively working with the manufacturers to appropriately validate their cleaning and/or disinfection procedures, including human factors testing, to demonstrate that the labeled procedures result in a product that meets appropriate inputs and outputs with respect to contamination and can be effectively followed by the anticipated end user.

It is important to note that cleaning and/or disinfecting the HCD outside the manufacturer's labeled procedures may result in a damaged device and is not recommended.

Here are the manufacturers of the cardiopulmonary bypass temperature controllers in the U.S. and a snapshot of their products. As you can see, the devices are all very similar to each other and include vents, fans, and water tanks.

As will be discussed in more detail later, the aerosolization of nontuberculous mycobacteria and disruption of the protective airflow in the OR may both play critical roles in these infections. Aerosolization of the nontuberculous mycobacteria may result in bubble creation within the water tanks. And all of the HCDs have design aspects which might include mixing components, water returned being higher than the water level in the

tanks, and pumps that agitate the water and create bubbles. In addition, as we saw in the last slide, they all have fans and vents which have the potential to disrupt the laminar flow in the operating room.

So what is nontuberculous mycobacteria or, as we call it, NTM? This diagram breaks down mycobacteria into NTM and into tuberculous mycobacteria. We are interested in the NTM branch, specifically *M. chimaera*, which was separated from *M. intracellulare* in 2004. It should be noted that while *M. chimaera* has been identified in many of the cardiac surgical patient infections to date, infections have also been attributed to *M. abscessus*, which is also an NTM.

NTM can be further categorized into rapid growers, meaning they grow in solid media in 5 to 10 days -- an example would be *M. abscessus* -- and slow growers, meaning it may take 6 to 8 weeks to grow in solid media, with an example being *M. chimaera*.

All of these waterborne bacteria have the ability to form biofilm. This is important from a contamination standpoint because once biofilm has formed inside the tank or circuit, chemical cleaning and disinfection of a device becomes extremely difficult, if not impossible, at the present time.

Now that we know what NTM is, where can we find it and how is it infecting patients? NTM is widespread in nature, and it can be found in natural and tap water and in the soil. Historically, NTM infections have been found in patients with preexisting conditions such as cystic fibrosis or AIDS. In these populations, transmission occurs via inhalation of aerosols with NTM, leading to pulmonary disease.

Other means of transmission of NTM is through exposure to the GI tract, for

example, drinking water or showers. Yet, the more recent cases of disseminated *M. chimaera* have occurred in patients with a prior history of open cardiothoracic surgery. These cases represent a very different epidemiological phenomenon. These *M. chimaera* infections also demonstrate a more aggressive pathological profile.

Additionally, due to the slow growing nature of *M. chimaera*, there is a long latency period between the time of exposure, which in this case would be the cardiac surgery, to the onset of clinical symptoms, to the ultimate diagnosis of NTM infection. The infections are non-pulmonary, for example, deep seated within the heart.

While Dr. Falkinham will be discussing NTM in more detail later, there is strong evidence to suggest that the NTM found in the water within the HCD water tanks become aerosolized when the water bubbles created within the water tank, which are rich in NTM due to the hydrophobicity of NTM, upon reaching the surface of the water disperse microscopic water droplets containing NTM into the airspace in the tank. Any unsealed pathway between the inside of the tank and the inside of the HCD unit will permit the aerosolized NTM to travel into the HCD unit, where it may be further carried through the unit exhaust vent, accelerated by the fans, and into the operating room environment and then ultimately infect the chest wound.

Now we will be discussing some potential device-related challenges which may facilitate NTM proliferation, aerosolization, and transmission into the sterile field. These challenges will be further addressed in the following slides. Tomorrow, the Panel will be asked to discuss device design features that could be improved on current and future devices to mitigate the aerosolization risk.

The first challenge is access to the water tank and other circuit components. Tank accessibility by the end user varies by manufacturer. Some HCDs allow access; however, heating coils or pumps located within the tanks may prevent adequate cleaning. Access to the water tank and the ability to mechanically clean the tank prior to disinfecting might be necessary to keep the tanks and circuits at an acceptable level of contamination.

It is important to remember that HCDs are not sterile, nor are they intended to be sterile. So keeping the water circuits at an acceptable level of contamination will be critical. As Dr. Mayhall will discuss further, what level of contamination that will be acceptable is still a question, and the Panel will be asked this tomorrow.

Connection to the other circuit components. As I have mentioned previously, the HCD can be connected to an oxygenator heat exchanger, cardioplegia heat exchanger, and/or a blanket. The blanket and water tubing to these accessories can be reusable and are not typically part of the HCD disinfection process. Therefore, over time, these components might become contaminated. If the accessory components become contaminated, they can reseed a disinfected HCD upon connection.

Now, water agitation within the tanks. A few slides ago we talked about the agitation inside the water tanks created from pumps and the return water inlet. This agitation of water produces bubbles. It has previously been published that the water bubbles generated within the water tanks will attract the hydrophobic NTM. More bubbles lead to an increase for the potential for aerosolized NTM within the tank.

So what about filters? Water and air filters might be helpful to stop NTM from coming into the HCD or leaving the HCD. However, a specific pore size is needed in order to

trap the NTM. For example, the pore size of a filter needed to capture the majority of NTM in flowing water would need to be less than or equal to 0.22 μm . The use of a HEPA air filter within these units creates other practical engineering issues.

Now, fans and vents. All of the HCDs have fans for cooling electronics and/or facilitating the cooling efficiency of the condenser. These fans may also facilitate the movement of NTM, which may be present within the unit, into the operating room environment. There has been a recent publication that suggests that the orientation of the exhaust vent in relation to the sterile field may disrupt the protective laminar flow that is typically found in the operating room.

The operating temperature of the water in these devices ranges from 0 to 42 degrees Celsius, which is the equivalent to 32 to 107.6 degrees Fahrenheit. The literature states that the water temperatures less than or equal to 50 degrees Celsius or 122 degrees Fahrenheit are more likely to harbor NTM as compared to water temperatures greater than 55 degrees Celsius or 131 degrees Fahrenheit. Therefore, the operating temperature range for the HCD appears to be ideal for NTM growth and proliferation.

As we have been discussing, the currently designed HCD may contribute to biofilm formation and might release the NTM into the OR. So new or modified design features should be considered for reducing the aerosolization and biofilm formation.

Now we will discuss a few challenges within the labeling of the devices. Tomorrow, the Panel will be asked to comment on FDA's safety communication and provide other suggestions for devices on the market that may help mitigate these patient infections.

First, water recommendations. In the instructions for use for the HCDs, the

recommendations for water vary and include tap water, distilled water, decalcified water, and filtered tap water. Not only is the water used for the device to function, heat and cool, but facilities rinse the inside of the units with water during the disinfection cycle. FDA recommends using either filtered [sic] water or water filtered with a 0.22 µm filter when filling, creating ice, refilling, topping off, and rinsing the HCD to minimize the amount of NTM being introduced into the water circuit.

Next, cleaning and disinfection procedures. The majority of HCDs recommend the use of chemical agents to disinfect the tank, while cleaning is primarily limited to the exterior of the device. However, cleaning the interior of the tanks and water pathways prior to performing the disinfection procedure might be helpful in keeping the contamination at an acceptable level.

Of note, FDA is aware of the fact that in some cases NTM is still being found in HCDs even after following the recommended disinfection procedures. FDA would recommend that facilities continue to follow the manufacturer's disinfection and cleaning instructions, since more aggressive handling may lead to degradation of the device, such as corrosion. FDA is working with the manufacturers to ensure that the disinfection procedure is validated to an acceptable level of disinfection, as Dr. Mayhall will discuss in the next presentation.

Regular maintenance and servicing. Since HCDs can be used for multiple years, they need regular preventative maintenance at pre-specified intervals, such as service hours or every 6 months, to be performed by the manufacturer or trained representative. It may be helpful for future servicing programs and/or manuals to prioritize these schedules to

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mitigate contamination.

There could be one or multiple sources responsible for the introduction of NTM into the HCD water circuit, since it is found so widespread in nature, for example, the source water at the hospital, ice machines, or even the manufacturing line. Additional challenges with identifying the source of *M. chimaera* include genotyping limitations, the latency period, and tracing the patient infection back to a specific HCD, just to name a few.

Now, let's discuss a few of the environmental challenges. First, aerosolization of NTM within the HCD and into the OR. The tanks in the HCD are not air or water sealed. This means that if there are aerosolized NTMs in the tank, they can escape through any unsealed opening between the water tank and the inside of the HCD unit, for example, a pathway for use of a temperature probe or an unsealed tank lid. Once inside the HCD unit, these aerosolized NTMs have direct communication into the OR environment via vents, and movement of the NTM into the OR environment can be facilitated by the cooling fans.

Next, airflow in the operating room. During operations, the HCD is placed outside of the sterile field, and the patient is under a protective laminar flow of air, which should keep particles from entering the sterile field. However, there has been a publication which suggests that the air exiting the HCD's exhaust vents could disrupt this protective laminar flow, creating enough turbulence to move particles already suspended into the OR air into the sterile field and ultimately into the open chest wound.

Finally, OR infection control prevention. As Dr. Munoz will discuss later, operating rooms currently have infection control prevention procedures in place. Some of these procedures include air quality, air volume exchange, and positive pressure, which may help

reduce the transmission of airborne pathogens.

Dr. Mayhall will be presenting next on the cleaning and disinfection validation.

DR. MAYHALL: Good morning. My name is Elaine Mayhall. I'm a scientific reviewer in the Infection Control Branch in the Office of Device Evaluation. My presentation will cover microbial limits and validation testing of HCD water pathway cleaning and disinfection processes.

HCDs are not intended to be sterile. Therefore, some level of microbial contamination of the water within the HCD will be unavoidable even with rigorous cleaning and disinfection processes. Culturing NTM is challenging, particularly given its long grow-out time, and thus would be impractical to use for surveillance purposes.

However, it may be possible to use existing water quality standards or limits when determining acceptable levels of NTM in the circulating water. For example, these two standards, the EPA National Primary Drinking Water Regulations and the FDA-recognized standard ANSI/AAMI 13959, water for hemodialysis and related therapies, specify microbial limits for water. It is noted that neither of these standards specify limits for NTM.

The Committee will be asked to discuss whether or not one of these standards or another standard for microbial water quality can be used as a surrogate when determining acceptable levels of NTM in the HCD circulation water to minimize NTM proliferation and biofilm formation.

The EPA drinking water standard provides limits for heterotrophic plate count, or HPC. HPC is one of the indicators used to detect problems in the water treatment process or integrity of the distribution system. It is an analytic method used to measure the variety

of bacteria that are common in water. The lower the concentration of bacteria in drinking water, the better maintained the water system. The standard specifies that HPC be controlled at less than or equal to 500 bacterial colonies per milliliter. NTM is not used as an indicator, and thus no limit is specified for NTM in drinking water.

It is important to note that the number of bacterial colonies has no correlation between the presence of or the level of NTM in the water.

Given the outbreak of NTM infections associated with HCDs, is this standard appropriate, and is use of HPC as an indicator at 500 bacterial colonies per milliliter adequate to ensure that NTM levels in the water and biofilm formation in HCDs are minimized?

Or would the microbial limits specified in the ANSI/AAMI standard be a more appropriate limit for microbial counts? This standard describes the quality of water to be used in hemodialysis and sets a microbial limit at 100 CFU/mL. Again, NTM is not used as an indicator, and thus no limit is specified for NTM in water used for hemodialysis.

Similar to HCDs, water purification systems and dialysate delivery systems used in hemodialysis do not have direct contact with the patient or their blood during use. However, the dialysate delivery system with water purified by the water purification system may pick up toxins or other contaminants from bacteria in these systems that may potentially cross the semi-permeable membrane into the blood during dialysis. The limit is based on rates of pyrogenic reactions related directly to the number of bacteria in dialysis fluid.

Water systems used in hemodialysis are monitored for microbial levels and

maintained to reduce microbial proliferation and the potential for biofilm formation. The systems undergo regular disinfection. However, when total microbial counts reach 50 CFU/mL, further action is taken and the system undergoes disinfection so that the 100 CFU/mL limit is not reached.

Can either one of these standards for water quality be used as a surrogate when determining acceptable levels of NTM in the HCD water pathways to minimize biofilm formation, NTM aerosolization, and ultimately patient infections?

To maintain the water quality at acceptable levels, the HCDs must undergo a cleaning and disinfection regimen, and validation of the cleaning and disinfection regimen should demonstrate that the process is effective and that the water quality is maintained at expected microbial levels.

Currently, HCD manufacturers' label instructions provide a variety of methods for disinfection of HCDs and maintaining the HCD water pathways that include chemical disinfection such as chlorine-based products. It is noted that few processes include a cleaning step, physical or chemical, prior to the disinfection step. However, it appears that currently recommended processes and frequencies for disinfection have not been effective in preventing contamination of the HCD water pathways with NTM or preventing biofilm formation. FDA has not previously required validation testing information for HCDs prior to clearance as these devices have no intended patient contact.

The Panel will be requested to discuss how manufacturers should challenge the device in a lab environment that would replicate real-world use.

Before I move into the questions we have on the disinfection validation, I would like

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to explain how FDA determines the appropriate level of disinfection that should be applied to reusable medical devices and how the disinfection of HCDs does not fit within this framework.

Reusable medical devices are cleaned to remove patient material and then either disinfected or sterilized so that they can be safely reused on the next patient. The Spaulding classification scheme, as described in the 2015 FDA guidance document on reprocessing of reusable medical devices, bases the type of disinfection that a device should receive on how the device contacts the patient. Semi-critical medical devices which contact mucous membranes and non-intact skin should be sterilized or receive high-level disinfection before reuse. Non-critical devices which contact intact skin should receive either low- or intermediate-level disinfection. And non-critical equipment surfaces which may have indirect patient contact should receive low-level disinfection.

Thus, the Spaulding classification scheme does not account for HCDs, which have no intended patient contact, either direct or indirect, and for which the risk of infection previously had not been recognized. However, as Ms. Milligan described earlier, NTM found in the water of HCD water tanks can be aerosolized and ultimately transmitted into the OR environment to infect a patient's chest wound. Therefore, the Committee will be requested to discuss how HCDs could fit into this framework and to determine what level of disinfection should be applied to HCD water pathways.

Water purification systems and dialysate delivery systems also do not fit into the Spaulding classification scheme and thus are similar to HCDs. As described earlier, water purification systems and dialysate delivery systems do not have direct contact with the

patient or their blood during use and do not become soiled with patient material. However, the dialysate delivery system with water purified by the water purification system may pick up toxins or other contaminants from bacteria in these systems that may potentially cross the semi-permeable membrane into the blood during dialysis. Therefore, these systems are disinfected on a regular basis using disinfectants that have been shown to achieve intermediate-level disinfection and to maintain the water quality below a specified level.

So what level of disinfection should be applied to HCD water pathways? This slide shows the expected disinfection endpoints for high-level and intermediate-level disinfection as described in the FDA's special controls guidance document for medical washer disinfectors. Note that low-level disinfectants are not effective against and are not intended to kill mycobacteria.

The recommended endpoints for high-level disinfection are a 6-log reduction of vegetative bacteria, which is equivalent to a reduction of a million bacteria, and a 6-log reduction of an appropriate *Mycobacterium* species.

The recommended endpoints for intermediate-level disinfection are a 6-log reduction of vegetative bacteria and a 3-log reduction of an appropriate *Mycobacterium* species, which is equivalent to a reduction of 1,000 mycobacteria.

So the difference between high-level disinfection and intermediate-level disinfection is an additional 3-log reduction of mycobacteria or a reduction of 1,000 mycobacteria.

So what endpoint is appropriate for HCDs? Before considering this question further, I am going to describe how FDA approaches validation testing to demonstrate that a disinfectant will be effective.

From a disinfection validation testing perspective, FDA review of disinfectant effectiveness includes a three-tiered approach including potency testing, simulated use testing, and in use testing. This recommended validation testing regimen is consistent with testing FDA has requested for validation of disinfectants used for water purification systems and dialysate delivery systems, as well as for high-level disinfectants used on semi-critical medical devices.

FDA expects manufacturers to demonstrate a disinfectant's potential for disinfection of medical devices by establishing a broad spectrum of microbicidal activity. Intermediate- and high-level disinfectants used to reprocess medical devices are themselves FDA-regulated medical devices, and although intermediate-level disinfectants are exempt from premarket review, they require EPA registration.

For a disinfectant used with HCDs, FDA expects firms to demonstrate that their proposed disinfectant has activity against mycobacteria, fungi, bacteria, and viruses. A high-level disinfectant must also show activity against bacterial endospores. For HCDs, viruses may not be a concern; however, FDA expects that a disinfectant have a broad spectrum of activity.

Simulated use tests help determine the penetrating capability of a disinfectant and other factors that prevent or limit contact in effectiveness of a disinfectant. These are controlled tests that allow the precise application of a specified and quantified inoculum to selected device surfaces. Simulated use testing intends to establish an adequate safety margin for the use of the disinfectant in or on actual medical devices. FDA expectations for simulated use testing of disinfectants includes the following elements. An HCD that has

been exposed to repeated cycles of use, cleaning, disinfection, and descaling represents a worst-case situation for testing because the components may develop surface cracking or pitting, which will make the surfaces more difficult to clean and disinfect.

In order to simulate actual use conditions, the HCDs should contain an organic challenge that is representative of the use environment.

Validation testing should include relevant waterborne test organisms, including *Pseudomonas aeruginosa*, a nontuberculous *Mycobacterium*, for example, *M. chimaera*.

The most difficult areas of a device for the disinfectant to penetrate should be inoculated, and the inoculation procedure should reflect worst-case use conditions for that system and disinfectant would experience in a hospital setting. For example, if the labeling recommends that the water pathways be disinfected at the end of each week, then the inoculation method should reflect the same time period and use conditions.

The number of each organism recovered from one of the inoculated test devices or systems should be quantified to estimate the actual microbial challenge to the disinfectant. All areas that could become colonized, such as water tanks, tubing, connections, and filters, should be microbiologically evaluated before and after the disinfection cycle. The recovery method should be validated, and the recovery conditions should be documented.

Water samples should be collected at specified sites along the water pathway, and a sufficient volume should be collected to allow for detection of low numbers of organisms and then membrane filtered and cultured on the appropriate media. Those areas of a test system identified as difficult for the disinfectant to penetrate, such as water tanks, tubing, and connections for the HCD, should be swabbed and cultured. Internal surfaces should

also be evaluated for the presence of biofilm. The inoculated system should undergo the labeled cleaning and disinfection process using minimal worst-case conditions.

Given that HCDs have no intended patient contact yet are associated with transmission of aerosolized NTM and ultimately patient infections, and based on our outline of validation testing, what disinfection endpoints are appropriate for HCDs?

FDA is proposing the following disinfection endpoints for simulated use testing with HCDs for your consideration. The first option is intermediate-level disinfection with expected endpoints of a 3-log kill of NTM or a kill of 1,000 NTM, and a 6-log kill of vegetative bacteria or a kill of 1 million bacteria.

The second and more rigorous option is high-level disinfection with expected endpoints of 6-log kill of NTM and 6-log kill of vegetative bacteria.

The Panel will be asked to discuss how manufacturers should develop validated disinfection processes that properly challenge HCDs in a laboratory environment and that would replicate real-world use, and what endpoints would be appropriate to apply in simulated use testing for disinfection of HCD water pathways to demonstrate that acceptable levels of NTM in HCD circulation water are achieved and maintained.

In use testing is conducted to demonstrate that the cleaning and disinfection regimen is sufficient to maintain acceptable microbial levels in water and prevent or minimize biofilm formation in the HCD water pathways under actual use conditions. The cleaning and disinfection procedure should be conducted by healthcare personnel that are responsible for using the systems, implementing the cleaning and disinfection processes and maintaining the water pathways, and have been instructed to clean and disinfect the

device according to the device label.

The device should be filled, operated, and maintained according to the label instructions over an extended period of time under conditions that replicate worst-case use conditions for the HCD water pathways, including periods of inactivity.

Water and internal surface samples should be collected over the test period to demonstrate that the cleaning and disinfection procedure and schedule are sufficient to control microbial levels and contamination of the HCD water pathways at specified acceptable levels. The microbial load in representative control devices should be quantified before and after the cleaning and disinfection steps.

It is noted that a paper by M.I. Garvey and others is currently in press for the *Journal of Hospital Infection*. It evaluates three different decontamination regimens for reducing the total viable microbial count (TVC) in the water inside HCDs from greater than 300 CFU/100 mL.

With the manufacturer's method using a chlorine-based solution, the total viable counts remained high, and *M. chimaera* was found.

In Regimen 2, the manufacturer's method was modified and included two consecutive cycles of disinfection. The total viable count in the water was reduced to 1 to 10 CFU/100 mL, but weekly counts increased to as much as 300 CFU/100 mL, and *M. chimaera* was again found.

In Regimen 3, the method used a peracetic acid solution instead of a chlorine-based solution and again included two consecutive cycles of disinfection. The total viable counts in the water were reduced to 0 CFU/100 mL, with weekly counts increasing to as much as

100 CFU/100 mL, but with no *M. chimaera* found. The authors associated the continued contamination primarily with the presence of biofilms in the tubing. After replacing the tubing, Regimen 3 was again undertaken, and the results of testing showed that the total viable count in the water was reduced to 0 CFU/100 mL, with weekly counts also remaining at zero and with no *M. chimaera* found.

It is noted that the compatibility of these regimens with the HCD materials was not evaluated and needs further investigation.

The authors concluded that a decontamination cycle including an initial replacement of internal tubing with weekly microbiological water samples is required to maintain the water quality within HCDs at an acceptable level.

The Committee will be asked to discuss whether monitoring or surveillance of the HCD water for NTM or bacterial contamination should be performed to determine that the microbial water quality within the HCD is maintained at an acceptable level.

In addition to disinfection validation testing, there are other bench tests that should be undertaken. Chemical germicides used to clean and disinfect the HCD water pathways and their frequency of use may damage the HCD. Therefore, testing should be conducted to demonstrate the compatibility of the cleaning and disinfection regimen with the HCD water system materials and components following repeated cleaning and disinfection cycles. The testing should address the effects of the functionality, material compatibility, and specifications of the HCD water pathways.

In summary, here are the challenges we are faced with. NTM are difficult to identify, and the slow-growing varieties require long grow-out times. Standards exist that set limits

for microbial water quality but do not specify limits for NTM.

Can a standard that specifies microbial water quality be used as a surrogate when determining acceptable levels of NTM in the HCD water to minimize NTM growth and biofilm formation? Should the HCD water be monitored for NTM or bacterial contamination in the clinical setting?

Previously, cleaning and disinfection validation information was not required in premarket notification submissions for HCDs because this device type has no intended patient contact. However, NTM found in HCD water can be aerosolized and ultimately transmitted into the OR environment to infect a patient's chest wound. However, these devices do not fit into the scheme used for determining the appropriate disinfection level.

How should a manufacturer challenge the HCD to replicate real-world use and validate the disinfection process? And what endpoints for disinfection should be used in simulated use testing to demonstrate the effectiveness of the cleaning and disinfection instructions?

Now I turn it over to Ms. Julia Marders of the Office of Surveillance and Biometrics, who will describe FDA's investigative process.

MS. MARDERS: Hi. Good morning. My name is Julia Marders, and I am nurse consultant at the FDA in the Center for Devices and Radiological Health. Today I'm representing Emergency Preparedness/Operations and Medical Countermeasures in the Office of the Center Director under Dr. Suzanne Schwartz and will, along with my colleague Kelly Bauer, provide FDA's multi-pronged process to investigate NTM infections associated with heater-cooler devices.

FDA's approach with this issue has involved a multi-pronged investigative process which includes outreach, compliance, communications, medical device report analysis, and information request letters so that we can tackle it from many different angles and gain as much information in an expeditious and timely manner.

We've been very aggressive with our outreach and ongoing collaborations and activities to not only learn from others' experiences, but to also share what we were learning about aerosolization.

We have ongoing weekly teleconferences with the Centers for Disease Control and Prevention (CDC), in addition to frequent teleconferences with state health departments and the Association of State/Territorial Health; regulatory public health agencies outside the U.S.; experts; professional societies, including the Society for Healthcare Epidemiology of America and the Infectious Disease Society of America; and the Veterans Administration.

In addition to our ongoing collaborations, we've also engaged in outreach activities. We've had regular follow-up and frequent outreach to hospitals who have sent us medical device reports so that we can increase our understanding of their experiences and develop collaborative relationships with the clinical community. We've also gone on site visits to several hospitals to further expand our knowledge about the everyday use of heater-coolers in existing operating room settings.

In addition, early on in our investigation in the fall of 2015, we conducted a survey through our Medical Products Safety Network (MedSun) to query cardiothoracic surgeons, perfusionists, and infection control staff about their knowledge of NTM infections associated with heater-coolers, whether they've experienced any at their institutions, and

their procedures and training for cleaning and disinfecting heater-cooler devices. We also asked them about tank water, water filters, and water circuits. Interestingly, at that time, none of the respondents had experienced or were aware of NTM infections associated with heater-cooler devices.

Specific outreach activities this year have included a presentation at the Centers for Disease Control and Prevention convened Healthcare Infection Control Practices Advisory Committee (HICPAC) on March 31st, and a 50 states call on May 16th. The three objectives of the 50 states call were to heighten awareness across state departments of health and local, tribal, and territorial organizations of the recent associations of NTM infections with heater-cooler devices in patients who have undergone open chest cardiac procedures; to inform stakeholders of ongoing and upcoming efforts by FDA and CDC to address this public health issue; and to provide recommendations and resources to aid in risk reduction.

Our compliance activities have included inspections and resulted in regulatory actions. Directed inspections at heater-cooler manufacturers are under way. Several inspections have been completed and resulted in actions including a warning letter and import alert. The focus for the inspections is ensuring that firms have strong quality system and reporting procedures in place.

The third area of our multi-pronged investigative process is communications. On October 15th, 2015, the FDA issued a safety communication, Nontuberculous Mycobacterium Infections Associated with Heater-Cooler Devices, to heighten awareness about infections associated with heater-cooler devices and steps healthcare providers and health facilities can take to mitigate risks to patients. It also recommends users strictly

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adhere to the cleaning and disinfection instructions provided in the manufacturer labeling.

On March 28th, 2016, FDA launched a website specific to heater-cooler devices to further alert the healthcare community to FDA's awareness of reports of infections associated with heater-cooler devices used during surgical procedures, provide recommendations to patients, encourage facilities to perform appropriate maintenance on heater-cooler devices, encourage facilities to implement appropriate decontamination procedures and/or remove contaminated machines from service, and communicate FDA's understanding of the issue and action steps proactively.

The webpage provides a new section entitled Information for Patients which contains a long list of frequently asked questions with answers. The webpage also allows FDA to be more fluid in its communications, since we are easily able to update it as new information becomes available.

FDA just released another safety communication that provides new information about *M. chimaera* infections in patients who have undergone cardiothoracic surgeries. This safety communication provides additional recommendations for healthcare facilities, staff, and patients, and acknowledges that as new and important information becomes available, FDA will evaluate the information and update its recommendations as appropriate.

And now I will turn the presentation over to my colleague Kelly Bauer to present two final areas of our multi-pronged FDA investigative process: the medical device report analysis and information request letters.

MS. BAUER: Thank you, Julie.

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Good morning. My name is Kelly Bauer. I am a nurse consultant at the FDA in the Center for Devices and Radiological Health, Office of Surveillance and Biometrics, Division of Postmarket Surveillance. I will present a summary of the postmarket medical device reports, or MDRs, or adverse event data that FDA has received related to NTM and patient infections associated with heater-cooler devices.

I will start with an overview of MDR reporting, then discuss the limitations of MDRs. I will review the adverse event reports received by the FDA on heater-cooler devices related to patient infections and/or device contamination, and I will conclude my presentation with the FDA information request letters to manufacturers of HCDs.

The FDA receives a significant number of adverse event reports for all medical devices. Last year alone, the FDA received approximately 1 million individual MDRs.

There are two groups of events that are required to be reported to the FDA: First, events in which a device may have caused or contributed to a death or serious injury; second, events in which certain malfunctions have been identified and must be reported by manufacturers and importers.

When has an event caused or contributed to a death or serious injury? This would apply in events where a death or serious injury was or may have been attributed to a medical device, or when a medical device was or may have been a factor in a death or serious injury. This includes events resulting from failure, malfunction, improper or inadequate design, manufacturing or labeling issues, and use error. Let's further define what is considered a serious injury in this context.

A serious injury is an injury or illness that is either life-threatening, or results in

permanent impairment or damage to a body function or structure, or requires medical or surgical intervention to preclude permanent impairment or damage to a body function or structure. Based on these definitions, infections associated with heater-cooler devices are considered reportable events to the FDA.

I previously mentioned that certain device malfunctions are also considered reportable events. A malfunction is considered reportable for a manufacturer or importer when the device either fails to meet its performance specifications or otherwise perform as intended, and the device is likely to cause or contribute to a death or serious injury if the malfunction were to recur.

I would like to explain with a little more detail who is required to submit reports to the FDA and what is the timing for the submission of these reports.

Manufacturers, both domestic and foreign, are required to submit reports of deaths, serious injuries, or malfunctions to the FDA within 30 calendar days of becoming aware of a particular event. A manufacturer becomes aware of an event when any manufacturer employee gains knowledge of the event. From that time, the manufacturer has 30 calendar days to send an MDR to the FDA.

User facilities are required to submit death associated reports to both the manufacturer and the FDA within 10 working days of becoming aware of the event. They are also required to submit serious injuries to the manufacturer within 10 working days of becoming aware of the event. User facilities can submit serious injury reports to the FDA if the manufacturer of the device is unknown.

Importers of medical devices are required to submit death and serious injury reports

to both the FDA and the manufacturer within 30 calendar days of becoming aware of an event. They are also required to submit malfunction reports to the manufacturer in the same time frame.

As new information is made available, as in the case of the manufacturer obtaining more information from the end user or evaluation of the device, supplemental reports are required to be submitted within 30 days.

Finally, anyone can submit any type of report to the FDA at any time as a voluntary report through MedWatch. Once MDRs are received and processed by the FDA, they are available to the public within 60 calendar days.

Now I will discuss the limitations of MDRs. MDRs are a useful but limited tool in postmarket surveillance, and for that reason, they are only one of the multiple tools used for this purpose. The results of an MDR analysis provides a snapshot of the data available on the reports at the time the data is pulled. These results can change over time as new information is added by reporters and analyzed.

There is significant underreporting of medical-device-associated events. This underreporting can be due to multiple causes. Some of them include:

- Users that are unfamiliar with the reporting requirements;
- Fear of unintended consequences that could arise if a report is submitted to the FDA;
- Confusion about HIPAA and privacy of reporting; and
- Events where the malfunction or injury may not be clinically apparent and, as such, difficult to associate to a particular device, as in the case of these HCDs

where there may be a long time between exposure and symptoms of infection.

It is also important to point out that certain device malfunctions may not meet MDR reporting requirements; therefore, the lack of submission of MDR reports does not correlate with the lack of problems for a particular device.

Another significant limitation of MDRs is the presence of insufficient or inadequate information in submitted reports. This lack of data can be caused because the information was not obtainable from the end user by the reporter, or the reported device was not returned or made available to the manufacturer for their evaluation.

Finally, another important limitation of MDRs is their inability to definitively establish causality on their own, between a device used and a particular clinical outcome.

Now I will discuss the MDR review for this issue. MDR searches were conducted in the MDR database for reports of heater-cooler devices associated with patient infections and/or contamination of a device. The data range of the MDRs included reports entered into the database between January 1st of 2010 through February 29th of 2016.

There have been 180 MDRs submitted to the FDA related to this issue. There may be multiple reports submitted for the same event in cases where both the user facility and manufacturer submitted MDRs.

There are a total of 55 user facilities identified in the MDRs involved with patient infections and/or device contamination. So there are cases where the user facility reported an event, the manufacturer reported an event, and where both the user facility and manufacturer may have reported the same event. There are 16 user facilities and 62 MDRs

from 10 different states across the U.S. Outside of the U.S., there are 39 user facilities and 118 MDRs reported from the countries identified on this slide.

This table categorizes the MDRs by the reported device manufacturer and all related brand names and models and the origin of the report as either U.S. or OUS. There are four device manufacturers identified in the MDRs. There were no MDRs submitted related to the CardioQuip heater-cooler.

The second column categorizes the 180 MDRs by the reported device. The last three columns in the table identify the 55 unique user facility MDRs by reported location and totals for the relevant devices, which involved patient infections and/or device contamination. Of the 55 user facilities involved, there were 3 user facilities reporting 2 different manufacturers of HCDs, as identified by the asterisk.

It is important to note that there are 160 MDRs associated with the LivaNova/Sorin device. LivaNova/Sorin has approximately 60% of the market share in the U.S. and 80% of the market share in Europe.

This graph shows the number of MDRs entered into the MDR database over time by month and year. The MDRs were individually reviewed for adverse events reported as patient infection potentially related to the use of an HCD or device contamination where there was no mention of a patient infection. Each MDR is represented once in this graph. Overall, there were 61 MDRs reporting patient infections and 119 MDRs reporting device contamination without known patient infection. The MDRs were then further stratified by user facilities and their geographic origin of U.S. and OUS. U.S. patient infections are represented in blue and device contamination in red. OUS patient infections are

represented in green and device contamination MDRs in purple.

Each MDR was also reviewed for outcomes such as the total number of infected patients, the number of patient deaths where an infection was reported, and the number of devices reported as being contaminated.

This table identifies the number of involved patients and devices reported in the MDRs by U.S. and OUS events by device manufacturer and brand name. These are not mutually exclusive as one MDR may report patient infections, deaths, and contaminated devices. In some cases, an MDR may include a cluster of patients; therefore, the number of deaths and patient infections include the number of known patients involved and may not match the total number of MDRs. Some MDRs imply more than one patient or one device, which is characterized by the plus sign as likely being more than the number listed. Overall, there were at least 66 patients infected. Of those patients, there were at least 14 deaths, and there were at least 159 reported contaminated devices.

As previously mentioned, there were 61 MDRs submitted related to patient infections. Forty-six of the 61 MDRs identified the type of surgical procedure performed in which an HCD was used; in 15 MDRs, the type of procedure was not identified. This graph represents the type of surgical procedures performed. Note that there may be more than one type of procedure performed during surgical intervention. For example, some patients may have had a valve and CABG procedure during surgery; therefore, each procedure mentioned in the MDRs would be represented in this graph. Eleven MDRs indicate heart valve procedures and 13 MDRs -- 10 MDRs simply state cardiothoracic surgery.

This table identifies the types of patient infections as reported in the MDRs with the

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time to the event occurrence, or TTEO. The TTEO is the time frame from the date of surgery to the date of the patient's infection diagnosis as specified in the narrative text of the MDR. There were 48 MDRs which identified the diagnosis and/or location of the infection. The TTEO was available in 33 of these MDRs. Surgical wound infections were reported in 15 MDRs, ranging from 2.5 to 60 months after the date of surgery. Endocarditis was identified in 12 MDRs between 2.5 and 51 months after surgery. And bloodstream infections were identified in 11 MDRs from postop to 60 months after the procedure. Note that one MDR may include multiple infection diagnoses. Thirteen MDRs did not specify the type of patient infection. It is important to note that there may be duplicate reports in cases where the manufacturer and user facility each submitted an MDR.

Finally, the MDRs were further classified by the type of organism identified in the patient infection and/or contamination of the HCD. This table shows the number of MDRs by the type of organism and is characterized by manufacturer and brand name. For example, there were 53 MDRs reporting unspecified *Mycobacterium* related to the LivaNova/Sorin Stockert 3T, 8 MDRs reporting *Mycobacterium abscessus* related to the Terumo HX2. There were other bacteria identified in a small number of reports, including two OUS reports of device contamination 1 week after it was put into use. Note that the counts do not equal the number of MDRs as there are cases where multiple types of bacteria are identified in one MDR.

This concludes the MDR review. The last area of FDA's multi-pronged investigation process that I will discuss is the information request letters.

During the investigation, FDA sent information request letters at the end of 2015 to

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all manufacturers and spec developers of cardiopulmonary bypass temperature controllers and water-based thermal regulators that were listed in our registration and listing database. The letters focused on questions related to adverse event reporting to FDA, design aspects that might encourage NTM proliferation, biofilm formation, and aerosolization. The letters also requested information regarding the manufacturer's validation of cleaning and disinfection, as well as labeling, including the instructions for use.

We are reviewing these responses and will continue to work with the manufacturers to revise device designs, refine disinfection protocols, and improve the reporting procedures in an effort to mitigate these patient infections.

Thank you. This concludes the FDA presentation.

DR. YUH: Well, thank you very much. I'd like to thank the FDA for a very comprehensive and clear presentation of a very multifaceted problem.

We have the next 30 minutes or so to take clarifying questions from the Panel. I'd like to invite anybody on the Panel to ask questions specifically related to the FDA presentation.

Yes, Dr. Hopkins.

DR. HOPKINS: It's a question for Ms. Bauer. Were you able from the MDRs to stratify the wound infections into deep versus superficial?

MS. BAUER: Kelly Bauer. Can you hear me?

The MDRs did not specifically identify whether there were superficial or deep wound infections. It may have just said wound infection, sternal wound infection.

DR. YUH: Any other questions from the Panel?

Yes, Dr. Givner.

DR. GIVNER: Do the dialysate delivery system disinfection process and dialyzer reprocessing system disinfection require intermediate for both of those? I couldn't tell from the documents and presentation, although I may have missed it.

DR. MAYHALL: For the water purification systems and the dialysate delivery systems, they're generally shown to achieve an intermediate-level disinfection.

DR. GIVNER: Thank you.

DR. YUH: Yes, Dr. Leggett.

DR. LEGGETT: For Dr. Mayhall. What data were used as the basis for determining a 50 CFU/mL actionable limit for hemodialysis things? Was it only on the basis of lipo endotoxin or whatever? I mean, was anything done to say that we need this 50 versus 500?

DR. MAYHALL: I'm not familiar with the whole history of that, but Matt Arduino probably can answer that.

DR. ARDUINO: Well, what happens is, is once you hit the 100, you tend to chase a problem, and it's hard to get back down. There's also some evidence from one of the manufacturers of machines and equipment that basically said once you hit 50, there was formation of biofilm already beginning to develop.

DR. YUH: Yes, Dr. Zenilman.

DR. ZENILMAN: Yes, hi. Good morning. I'm not sure who's the correct person, but certainly Dr. Mayhall or Dr. Schwartz. Actually, this is a follow-up to the dialysis question because it seems, from the epidemiology of this, that there's probably an extremely low inoculum size required to establish infection based on the latency and the time. And I'm

curious if there's any animal data. I was looking, you know, to show what -- determine what the inoculum size is for this because that may drive some of the others. For example, you know, all of the data for dialysate is based on pyogenic infections where you have -- where the inoculum size of the bug is actually substantially higher.

DR. MAYHALL: So it's not going to be just what's in -- what the water is contaminated with. It's multifaceted. It's also whether it can be aerosolized and carried out of the HCD and into the OR environment. So it's not just the one thing that we have to take into consideration. It's multiple mitigation factors.

DR. SCHWARTZ: And as to your question with regard to having any experimental data or animal data, FDA certainly has not been in possession of that. Nor have we seen that with regard to our survey of the literature thus far. So that means a gap area.

DR. ZENILMAN: No, I didn't see anything in the PubMed --

DR. SCHWARTZ: No.

DR. ZENILMAN: -- which I just did.

DR. YUH: Yes, Dr. Gallagher and then Dr. Arduino.

DR. GALLAGHER: So one of my general questions that any of you may be able to answer is what caused the concern in the first place that said now we have to go after this?

DR. SCHWARTZ: I think we're going to be hearing a lot more about that from our invited speakers, in terms of really how this initially was identified and how it was further evaluated and tested. So stay tuned for that. FDA were not the ones who obviously identified it initially, but there has been a lot of work done on the European side with respect to that, and you'll be hearing about it.

DR. YUH: Yes, Dr. Arduino. Did you have a question?

DR. ARDUINO: Yes. I know you're concentrating on -- this is just kind of a comment. I know you're concentrating on aerosolization, but these devices are also typically refilled in the -- they add water to them. And so you can have spillage and possibly contamination of gloved hands by individuals. So there are other things. It is water, and it leaks. The instruments. Actually, there's also condensation that forms and when they're operating. So it's more than just the aerosolization, though aerosolization may be the main route. And it's not always the chest cavity. It could be that the implant that is sitting open to be implanted could be contaminated as well.

DR. SCHWARTZ: Yes. Thank you, Dr. Arduino, for raising those other factors. We think that those are also important to consider in a very holistic way, absolutely.

DR. YUH: Yes, Dr. Christensen.

DR. CHRISTENSEN: Just a quick follow-up. You know, this is another comment. We've seen the inside of a machine and noticed the water marks in the machines. Obviously, it was either through the pressure from the pumps or from the condensation and it looked like it was drying and flaking off. So that could be another way. Once that flakes off, it potentially could be aerosolized with the fan as dispersal mechanism. So it's another consideration just -- not just creating a more liquid bioaerosol, but actually a dried bioaerosol.

DR. YUH: I had a question related to that. How certain are we that the organisms, the NTMs are really originating or being cultivated in the HCDs? In other words, as you -- as this organism is in tap water, soil, etc., I know for a fact that Yale-New Haven Hospital, the

water that we wash our hands in before we operate is not filtered at all. It's just tap water. How do we know that breaches in glove integrity might lead to direct contamination of the chest with nothing to do with the HCD?

DR. SCHWARTZ: I think that that's really why we are convening this Panel, and we recognized and stated many of the challenges that we're faced with, with regard to the environment and the ubiquity of the organism and doing the type of investigations, how comprehensive that they need to be in terms of looking at all of the potential root causes or sources for the organism, and we don't have the answers. Really, that's why we assembled a Panel that brings the expertise, as well as guest speakers who can provide even further information to help guide this discussion.

DR. YUH: Yes, Dr. Leggett.

DR. LEGGETT: A follow-up question to that one. Is the FDA aware of any attempts now by the CDC or anyone else to look for what we may have always thought in the past was just another sternal wound infection with *Pseudomonas aeruginosa* or *E. coli*? I notice with duodenoscopes, the only reason we tumbled up on them was the CRE. And now we recognize that that was just the tip of the iceberg, and I assume that this is the same problem. And do you know of anybody who's trying to attempt to look at other bacteria since our disinfection is going to be aimed at regular bacteria as well as non-TB mycobacteria?

DR. MAYHALL: So I think there were some reports where there were infections with other bacteria, but --

DR. LEGGETT: There were. There were like 26 as opposed to the 118 in your slide.

DR. MAYHALL: Right, but those are more easily treated, I guess. And also there seems to be an increase in NTM infections over the years, and I guess Dr. Falkinham will be talking later about NTM and growing resistance to chlorine-based disinfection, disinfectant products. So they just may be more prevalent.

DR. YUH: Thank you.

Dr. Givner, do you have a question?

DR. GIVNER: Yes. Do you have an idea if there was a recommendation to culture for mycobacteria besides just a routine culture for bacteria, from patients who are suspected to have an infection? Since that process has been requested, has there been an increase in the number of NTM infections that are reported?

DR. SCHWARTZ: I'm wondering if you could repeat the beginning of the question. I didn't follow the entire question.

DR. GIVNER: I would gather at some point there was a recommendation made that when patients develop an infection, that they now would be cultured for routine bacteria but also be cultured for nontuberculous mycobacteria. Since that occurred, and I don't know the time span, has there been an increase in nontuberculous mycobacteria infections identified in these patients?

DR. SCHWARTZ: I'm not aware of that particular recommendation. I don't believe that that was an FDA recommendation. And what I would say is that when we issue a safety communication, as we did in October 2015, that raises awareness around an issue, we will always see an uptick with regard to reports that are filed with the Agency, whether it's with respect to contamination or whether, again, because of the heightened awareness, the

heightened visibility on it, people are looking for it. So that's the normal course of what we see in general with safety communications. But in terms of any particular correlation with regard to patients themselves being evaluated or surveillance and monitoring, that I'm not aware of.

DR. GIVNER: Thank you. It seems without the recommendation, you still might see an increase simply because there is more awareness, but there's currently no information that since that occurred there was an increase in NTM infections, correct?

DR. SCHWARTZ: That's correct.

DR. GIVNER: Thank you. Thanks.

DR. YUH: Dr. Zenilman.

DR. ZENILMAN: Yes, thank you.

So this is also to Dr. Schwartz and the epi team. But also in response to Dr. Yuh's comment about the ambient water that surgeons use to wash their hands, it's curious that we're seeing these infections only with these surgeries and we're not -- they haven't been reported yet with other -- hopefully not yet with, for example, prosthetic joints or other common implant surgeries, which suggests that it's probably specific to this, unless the environment changes.

My question is are there any registry -- you presented numerator data, but are there any cardiovascular surgery registries where you have follow-up or where follow-up is feasible to determine what the actual incidence rates are over time, to get a sense of what the scope of the problem is? I think, as was mentioned -- and even in the passive reports and because of the epidemiology of this, it's probably a profound underreport.

MS. MILLIGAN: So we did look at the registries, but the registries don't capture the heater-cooler data.

DR. SCHWARTZ: The registries we have found to be also somewhat limited in terms of the numbers, the denominator of cases, of various types of cardiovascular cases, if that's what you're asking. We had done a little bit of work in terms of reaching out to different societies and found that those numbers were kind of low compared to what we had heard in terms of speaking with subject matter experts in the field.

So I think, for example -- and we had put this in the Executive Summary. The number of cases involving open cardiac surgery were listed somewhere by one registry as 300,000 per year. We subsequently heard that that number is probably a low number, and the breakdown with regard to different types of potential implants, whether they are prosthetic material or otherwise, also was somewhat debatable in terms of those numbers. So we have not been able to find in the published literature really firm numbers of what the denominator actually is.

DR. ZENILMAN: Just from an administrative side, when the heating-cooling units are used in surgery, are they billed as a separate item on the chargemaster database or is it just a package? Because that may be -- I'm curious if that may be a way to look at those.

DR. SCHWARTZ: I don't know the answer to that. We'd have to look into it.

DR. YUH: Yes, Mr. Stammers.

MR. STAMMERS: Thank you.

Dr. Mayhall, I have a question in regards to the validation and disinfection process. Well, first I have a question for the entire Panel. Was the documentation on how often the

HCDs that were implicated in these infections -- is there documentation on how often those devices were -- or how they were maintained in regards to their disinfection processes? Were they following labeling in regards to disinfection, or was that information not available?

DR. MAYHALL: From what we understand prior to our finding out about these infections, is that they were not necessarily maintained strictly according to the manufacturer's instructions or with frequency or type of water or length of treatment or whatever. But since facilities have been made more aware of the issues and particularly the ones that have the infections reported, they've been more vigilant in trying to apply those manufacturer's instructions and may be a little overzealous. But even with that process, they were still finding contamination of the systems.

MR. STAMMERS: If I can follow up with a question for Dr. Mayhall. Dr. Mayhall, thank you. And that leads into the requirements for the manufacturers, the simulated use testing. And clearly that develops -- especially with inoculating the devices, that really gives a nice laboratory analytic mechanism for identifying these -- the permeation and how much these infections are at least occurring, at least the bacteria are occurring.

But my question specifically is, for those simulated uses, is it done only on label following the disinfection protocols that the manufacturers have on their IFUs or, as you've mentioned and others on the panel, either over- or under-disinfecting these devices results in early component degradation, which may accelerate the rate of which these contaminations present? Are manufacturers also required to ultimately stress their systems to the highest magnitude, such as daily disinfecting, so that perhaps they damage the

systems, making them more likely to show these --

DR. MAYHALL: Right. So the --

DR. YUH: If I could just ask you to state your name before you speak, just for the transcriptionist, that would be great.

DR. MAYHALL: Elaine Mayhall.

So, in general, testing is done under worst-case conditions. So if a device is being prepared for testing, it should be exposed under the highest concentrations and worst-case concentrations of the solutions that are used. It doesn't necessarily have to be over the top, but at least be representative of -- if they did over the top, that would help kind of support the position a little bit more. But it's not required to go over the top, but at least worst-case conditions per the instructions and worst-case concentrations.

MR. STAMMERS: Does that worst case include the length of the machine's utilization in hours per use? Because clearly some of these devices may have thousands and thousands of hours of use as opposed to one that is just newly developed.

DR. MAYHALL: Right. So ideally it would be best to have it exposed to the process that would be more representative of the many hours of use. But, you know, it has to be somewhat reasonable to be able to accomplish what that's going to be. But if it's used for 2 years, it's not necessarily -- or 5 years, 10 years, it's not necessarily feasible to expose it to that many cycles.

MS. MILLIGAN: Nicole Milligan.

I'd like to add that the devices also have service life in their labeling, of how long that testing has been out to. And then we're also asking for component degradation at the

worst-case solutions to look at when those inside the heating coils or the pumps or whatever may degrade at the worst-case solutions, you know, concentration and frequency, to give a better estimate. But at the end of the day, a lot of the testing is in the labeling of what we recommend at the best case. And we're also looking at human factors, assessing to ensure that the end user can adequately follow that procedure.

DR. YUH: Dr. Leggett, please.

DR. LEGGETT: A follow-up question to both of those. Currently, when the FDA looks at this, does it just require the manufacturer to provide a disinfectant? Say if chlorine was used, that's the only thing that's looked at? Or given the slide that you showed, is it requested of each manufacturer that they provide whether peracetic acid or other disinfectants can be used? In other words, are separate things looked at with each device?

MS. MILLIGAN: So previously before last year, it was just looked to see if they had a disinfecting protocol in their labeling. However, now that we have identified this issue, we are looking at the validation, which would determine what chemicals they're using. And it was required that they had that validation in their files at the manufacturer.

DR. YUH: Yes, Mr. McGlamery. Then Mr. Thuramalla.

MR. McGLAMERY: Raymond McGlamery.

Maybe one of the doctors could answer this. Is there nothing in the OR during these surgeries that's actually doing an air analysis where you could look at and see what's in the air either in the surgical field or outside the surgical field? I'm just sort of thinking about some of these other possible contamination methods. Is anything being done like that?

DR. ZENILMAN: Do you mean in real time as the operation is ongoing?

MR. McGLAMERY: Not necessarily in real time, but something that could analyze postoperative procedure just to see if there is contaminants in the air and what they are and what the percentages are.

DR. YUH: Yes, Mr. Riley.

MR. RILEY: I'll comment. No, but we do have humidity and temperature monitors that are ongoing all the time.

DR. YUH: Yes, Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

My question is do we have any data where we know that the user facilities were unable to follow the manufacturer's instructions? And do we have any data where the user facilities were using a different protocol or a different disinfectant from what the manufacturer was recommending?

Thank you.

MS. BAUER: Kelly Bauer.

So the MDR data is somewhat limited into what they are telling us. We did have some MDRs that stated that the IFU might be difficult to follow or they were perhaps using a previous iteration of the IFU, but I don't have specific numbers to that.

DR. SCHWARTZ: And I would like to add to that, that --

DR. YUH: If you would turn the mike on, please.

DR. SCHWARTZ: Suzanne Schwartz.

Just adding further clarification that information regarding ability to undertake the cleaning or disinfection instructions and maintenance instructions, as well as whether there

were problems associated with it, were really more gleaned through the types of discussions that FDA had with different facilities as part of our MedSun outreach. They are not necessarily captured, as Kelly pointed out, in terms of the actual MDR reporting data, but rather more anecdotal and qualitative information. And you really have a spectrum there in terms of ability to be able to follow versus where there may have been some breaches.

DR. YUH: Thank you.

Dr. Leggett and then Mr. Stammers.

Oh, Mr. Stammers. Go ahead.

MR. STAMMERS: Thank you again.

Just out of curiosity, in labeling and in the IFUs, is it possible for medical devices Class II or III to have black box warnings? And is this significant enough to go ahead and consider that, or has the FDA considered that?

DR. SCHWARTZ: Medical devices can have black box warnings, absolutely. I think we are interested in hearing, anyway, the type of discussion and deliberation that the Panel will have with respect to what kinds of mitigations are necessary. And, you know, really that's where we are right now.

MR. STAMMERS: Thank you.

DR. SCHWARTZ: Um-hum.

DR. YUH: Dr. Roselle.

DR. ROSELLE: I'm Gary Roselle.

Many hospitals are adding oxidants to their water system all over the country, like

chlorine infusions, and the clinicians won't even know that's occurring. But when it does, you should probably expect the density of NTMs to go up in all the water in the whole hospital because it's chlorine. It's reasonably chlorine resistant, where the other bacteria is not, and the amoebae in the pipes are resistant. So you may have much higher density than you think you have before they started adding chlorine to the water.

The second thing is leaving water in a reservoir is very interesting, because you know water has a lifespan. It ages. So the longer it sits somewhere, if it's coming from the tap, the oxidant would disappear entirely, probably within a day. Any slime layer that's in there has lots of time as it sits. So it's just an oddity that you would let water age. It's like having a dead-end stagnant pipe and hope nothing will be in it. So I think there are some things that maybe have changed over the last couple of years. NTMs, in general, are going up all over the country in clinical cases not just related to this, but in general. So this is probably just a component of other problems.

DR. YUH: Thank you.

Yes, Mr. Stammers.

MR. STAMMERS: Yes, thank you.

A follow-up question to one of the comments. And I apologize, I don't remember specifically who made it. But the comment was that the end user using the HCD should be responsible for disinfecting and cleaning it. And I just wonder, you know, as a perfusionist, some of our institutions throughout the United States don't have the perfusionists who are actually cleaning these devices. There are other individuals who are assigned to do that. Is that something that needs to be further pursued? Because that probably is the standard

the majority of the time, but there is a relatively large percentage of institutions where there are other individuals who are cleaning these devices who would not be applying them in the operating room.

MS. MILLIGAN: So we take that under consideration in our human factors testing, and we would recommend that a wide variety of users be simulated. So whether that is perfusionists or the biomed engineers or nurses or someone else, that would be our recommendation to kind of cover all of those areas.

MR. STAMMERS: So it's not the end user. It could be individuals who are appropriately trained. Okay.

MS. MILLIGAN: Yes.

MR. STAMMERS: Thank you.

DR. YUH: Yes, Mr. Riley.

MR. RILEY: Thank you.

I wanted to follow up on the incidence question. We think in terms of defects per million opportunities, have you made an estimate of how big this problem is, in that terminology? Infections per million operations.

DR. SCHWARTZ: We don't have that information right now, and part of the reason for that is because of the concern regarding a lot of undetected, under-the-radar potentially exposed or infected patients, and simply even getting to what a case definition really is here has been an evolving process.

DR. YUH: Yes, Dr. Arduino.

DR. ARDUINO: Matt Arduino.

The other thing with the heater-cooler issue is, it's part of a circuit. So when you're going to disinfect something, you almost have to do like in the dialysis setting: you disinfect the circuit. So if you're starting -- if you're doing your water supply, you're doing the machines. So -- because otherwise, if you just do the one unit and then you go hook it up to one of the other pieces, why did you even bother disinfecting if you didn't disinfect the auxiliary pieces that connect to it? You end up with recontaminating the whole system.

DR. YUH: I'd like to thank the Panel for some excellent questions.

At this point, I'd like to take a 15-minute break. Unless there are any objections, we'll reconvene here at about 10:17 or so.

Thank you.

(Off the record at 10:02 a.m.)

(On the record at 10:17 a.m.)

DR. LANGE: Obviously, during the 15-minute break, Dr. Lange did not age and become less attractive.

(Laughter.)

DR. LANGE: My name is Rick Lange. I'm the Chairperson and traveled halfway across the country even to be here, so I'm sorry I'm a little late, and I appreciate Dr. David Yuh -- please have a seat, Matt.

(Laughter.)

DR. LANGE: Matthew. Matthew. Matthew, come on, join us. Great.

And I appreciate Dr. Yuh covering for me, as he has since we were colleagues at Hopkins. So thank you very much.

We're at the part where we're going to actually have the industry -- we have three companies who have requested to speak: LivaNova, Cincinnati Sub-Zero, and CardioQuip. The first company is LivaNova. And at the conclusion of all three presentations, we'll have time for clarifying questions from the Panel members. We'll remind the companies, we're pleased that you're here for your presentations. Each of you will have 20 minutes, and I will, in the interest of making sure we stay on time, adhere to that very quickly.

So having said that, LivaNova, please address us.

DR. DUNCAN: Good morning. Thank you, Dr. Lange. I want to thank you and all the Panel members. I certainly want to thank Dr. Schwartz and the FDA for the opportunity to participate in this important session today.

I'm Brian Duncan. I'm the Vice President for Medical Affairs for the Cardiac Surgery Business Unit for LivaNova. I'm also a former practicing cardiac surgeon. I was a pediatric heart surgeon and worked for most of my career at the Cleveland Clinic.

I have with me today three of my colleagues from LivaNova -- Thierry Dupoux, who's the Vice President of Quality and Regulatory Affairs; Christian Peis, Quality Director; and Paul Talbot, Quality Laboratory Services Manager -- all with the Cardiac Surgery Business Unit.

As far as how we'll organize our presentation, I'm going to take you through an introduction, provide some background, and then I'm going to turn over the podium to Thierry Dupoux, who leads the team for quality management at LivaNova, who will take you through the details, the technical details of our approach.

So beginning with our commitment in this area. So as you heard this morning, we

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are the global market leader in the heater-cooler space, and although this problem does present issues for every manufacturer in the room, we are -- we take that position as market leader very seriously, 60% market share in the U.S. and about 80% market share in Europe, as you heard.

So we are absolutely, as with all of our products, committed to patient safety. As you heard this morning, a lot of the findings in this space, as Dr. Schwartz put it, are newly described and unappreciated previously. During this period, we have been in continuous dialogue and collaboration with the FDA previously, and look forward to that ongoing. And I think you'll see from our presentation that we are proactively engaged.

So the issue, again, very well summarized in the presentations this morning, this unusual and unexpected public health challenge which has been posed by nontuberculous mycobacteria. And again, a lot of new knowledge has been developed, particularly over the last many months, to understand the potential risk to public health. Many of the people in the room have contributed substantially to that new knowledge. And then, of course, the public health imperative is to apply that understanding to develop those practices.

Heater-cooler overview. Again, you've seen this, this morning. As described then, it is a critical component of cardiac surgery procedures because it is essential to achieve precise control of patient temperatures during these procedures. Also, as described, the device is not -- it's in the cardiac surgery operating room, but not in the sterile surgical field. We'll talk more about that in just a moment. And it is an indispensable component of cardiac surgery.

So again, this is a schematic of the layout in the cardiac surgery operating room. The

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heater-cooler occupies the same area generally that other large non-sterile equipment occupies. That includes the anesthesia machine, heart-lung machine. The sterile field, of course, is where the patient incision is, and also other implants, surgical instruments, and sterile bypass equipment and disposables all reside there.

Again, you saw this, this morning. The fundamental design of the heater-cooler system is the same for, again, all the manufacturers. There are water-circulating circuits which are not in direct contact with the patients, but provide heating and cooling, as appropriate, to multiple circuits for this precise control, temperature control, during the procedures: the oxygenator, cardioplegia, and a heating-cooling blanket.

This is our device in this space, the 3T heater-cooler system with indications for use as -- just as worded in the 510(k) clearance document.

So again, background. You've heard a lot about this already this morning, but just general concepts for nontuberculous mycobacteria. It is a very common waterborne environmental contaminant. And again, I think a lot of the new knowledge that's come out of the past many months has focused on how this ubiquitous organism that isn't generally thought to be terribly pathogenic could get from a device that sits potentially outside of the sterile field, can get to the patient and cause clinical disease. And we'll hear quite a bit about, and already have heard, some information about the key role of aerosolization in this process.

The other, I think, key takeaway -- and again, just as FDA has described, these are fortunately rare infections, and I think it's important because of the context both for patients and as a clinician in how we counsel these patients, and there are issues

undoubtedly related to under-diagnosis and potential underreporting. But they still, I think, are far less common than a lot of the other infectious organisms that are more commonly a problem after cardiac surgery.

And then, finally, to finish up this introduction, again, the clinical need for heater-coolers, I think the case has been, again, well made during the previous presentations from this morning. And it is again, I think, just important to provide context for patient considerations and the clinicians that take care of those patients.

From a recent FDA notice, I think they say it well. For most patients, the benefit of undergoing a surgical procedure recommended by their doctor outweighs the risk of infection, certainly from nontuberculous -- from the NTM organisms.

So with that background and overall context established, I'm going to call upon Thierry Dupoux. And Thierry, again, is our Vice President for Quality Management at LivaNova, and over the past many months, working with the FDA and others, the group's been very busy and I think very productive in this area, and Thierry can provide the information of those details.

I want to thank the Panel again for the opportunity to present.

MR. DUPOUX: Thank you, Brian.

Good morning. I'm Thierry Dupoux from LivaNova.

So we have been made aware of this issue in January 2014 from a report we received from the Swiss competent authority, reporting a problem occurring at the Zurich Hospital. But at that time, this report was making a description of a very incredible scenario by which patients had been infected by NTM which would have been airborne. And considering that

this is a waterborne organism, we had difficulty to believe that it could be true. And at that time there was no firm evidence of implication of the device, that that isn't contributing to the patient's infection. However, we took action quickly and invested time and effort in order to understand this issue and determine how, if confirmed, we could prevent it.

So after some time spent in investigation and consulting with experts, we understood indeed that this waterborne organism can be found in the air surrounding the device. So it has been very well explained this morning by FDA. I'm not going to get back to this. What I would like to just provide, that it is not 3T-specific problem. The fact that water can be agitated is common to all the devices. The agitation might be achieved in a different way, but this is always there. So from our internal testing, evaluation of also all the manufacturers' devices, we have been able to measure aerosolization from -- emitted from all devices. And if this is the water from which you create aerosol also is contaminated with NTM, then you might find NTM in the surrounding of the machine.

One thing which is important to note is that this is a manufacturer problem. So to get the patient's infection starting from an organism into the water, we need to achieve different elements. The first one would be that -- the most important would be that you need to have contamination of your water circuit, and that is very depending on the way you have maintained the device over time. So the level of contamination of the water circuit is absolutely key.

There are also other factors which are important and which were also very well described this morning by FDA, which is the location of the machine into the OR and the direction of the flow. So the machine can -- all machines can emit aerosol, and the

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possibility for the aerosol which is emitted from the machine to reach the surgical field is very depending on the construction of the machine and the creation of the airflow between this machine and the surgical field.

As I was explaining before, even though the scenario was described in this report from the Swissmedic was very incredible, we took action even without having the evidence yet that the machine could be the source of the infection. And in July 2014 we made a worldwide communication to all clinical sites using 3T, to inform them about this newly identified risk, and second, to remind them about the importance of performing cleaning and disinfection of the water circuit of the device according to our IFU.

We reiterated this in the field safety notice that was issued in June 2015, worldwide again, in which on top of reminding again about the importance of this problem and the potential adverse effect of not performing it for the patient, we also indicated how to detect contamination in the machine and, if detected, what you could do with the machine in order to keep operating safely.

We have made some modifications to the manufacturing line. We have introduced, since August 2014, disinfection of the water circuit of the machine before it gets released from production, and this was implemented to supplement the disinfection, which is specified in our device IFU, prior to use of the machine.

We have also made some other changes in manufacturing, implementing some measures in order to control the microbiological load on the device. So all tests with equipment where it's infected, and anytime that we had a water source from which we could fill a device in order to test it functionally, then we implemented filtered water, a

filter.

We also made some changes to the device in order to limit the potential for biofilm to be -- to grow. And we have specifically made changes to the water circuit. All PVC tubing have been changed, and they are now polyethylene, which is certified for drinking water.

We have also made some -- a few adjustments on the water circuit with plugs in order to prevent water to stagnate in some area of the water circuit, and at the moment that's manual.

Recently, there was an article published by a German group, which have made some -- which have reported a potential link between the manufacturing site, our manufacturing site, Sorin in Germany, and some patient infection. So we have tried to get access to the genotyping, patient genotyping, data from which this statement and conclusions were made, but we have been unable to get these data so far.

One thing that I would like to mention is that the reason why this link could be made by the group of researchers which has made -- which has created this article is because we have cooperated with them. The genotyping data from the manufacturing line and from the HCU from which they could make the link between the patient and our manufacturing site came from us. We have provided these data. We are willing to collaborate with anybody in order to investigate and resolve this issue.

However, I would like also to repeat that this article is making a link -- is stating that there might be a link between patient infection and device which has been contaminated from our manufacturing line, but there is nothing that would indicate that this could still be the case after we have implemented the disinfection procedure in the manufacturing line.

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There is also something that I would like to mention because of breaking news for sure in this article is this potential link between the manufacturing site from Sorin/LivaNova and patient infection, which is very unfortunate. However, the article is also making another interesting statement, which is bacteria were also found in other manufacturers of devices. It's not only 3T which is found contaminated with mycobacteria.

The other interesting statement is the fact that although the manufacturing site could have been one possible source of contamination, there was also the possibility that the healthcare site was also the source of contamination. Not all devices were found contaminated by the manufacturing site stream.

And last, other manufacturers' heater-coolers may have been the source of exposure in some cases. So just to balance a bit of the information you have in this article.

There is also potential information which could indicate that 3T is a problem, which are the MDR data that's represented by FDA this morning. So it's indicating a big prevalence of MDR associated with 3T. However, I would like to just mention that there are a few reasons for which comparison might be difficult to make.

First, we discussed about the market share that we have: 80% in Europe, 60% in U.S. Most of the MDRs that are filed have been filed from Europe, where we have this significant market share. On top of the market share, we are also presenting the biggest centers which are performing the most -- the biggest number of cases. And so actually, the number of opportunities to get treated with a 3T heater-cooler is greater than the market share that we have. That's something to consider in evaluating MDR.

Another element to consider, we see in the data, if you look back to them, that we

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have a significant number of MDRs which are manufacturer -- issued by the manufacturer, and we have some which are related to patient infection and some to patient deaths. Our policy for MDR is that we file an MDR for device contamination, whatever are the possible outcomes and potential link to patient infection. Most of the MDRs that we have filed were just about water circuit being contaminated, no relationship with any patient infections. And FDA this morning has emphasized that all heater-cooler devices may be affected by the phenomenon and the issue of potential airborne NTM contamination.

So we believe that patient safety is a partnership with various stakeholders and specifically with the clinical sites. We are providing instructions, detailed instructions for use in which cleaning and disinfection are described. Adherence to the instructions is key in order to achieve the right level of cleanliness of the water circuit. And if this is done, we believe that the risk of growing biofilm or letting microorganisms to grow in the water circuit is absolutely minimal.

Our cleaning and disinfection procedure, I can describe it later. But I would like to say that since the device has been cleared in 2006 in U.S., it has always -- the IFU has always contained cleaning and disinfection instruction. It's not something that we introduced only when we had been aware of the NTM problem. And this instruction required that the device is first disinfected before use. And that has never changed. We have changed the frequency, we have changed the chemical, but this has always been there. This disinfection process has been validated. And I guess that's in your later question and will have more questions regarding the details of this validation.

Our infection procedure calls for the use of some chemicals biweekly, which is

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supplemented by weekly water change and the addition of a preservative, which is hydrogen peroxide, to keep the water clean between -- over the week.

So we are also providing servicing and maintenance to customer which requires this activity in order to help them maintain the device clean over time. Customers can decide to do this themselves, and there are some activities which require company training and certification.

So to finish and summarize. So we are still active in this investigating and resolving this issue. We have already made some changes to the device, changes to the manufacturing line, but we are still investigating other possibilities to further reduce the risk of patient infection. And we are looking forward to cooperating with FDA and other stakeholders to get to a resolution of this issue.

Thank you very much for your attention.

DR. LANGE: Thank you for your presentation.

The next presentation will be from Cincinnati Sub-Zero, and again, you'll have 20 minutes for your presentation. There's a timer up there, and you'll see the yellow flashing 2 minutes before the time is up and the red when the 20 minutes are complete. Thank you.

Oh, by the way, for the record, my apologies. My name is Richard Lange. I'm the President of Texas Tech University Health Science Center in El Paso, and Dean of the Paul L. Foster School of Medicine. In my next life I want to be the chief air traffic controller to get here on time.

(Laughter.)

DR. LANGE: And my previous life was an interventional cardiologist.

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So none of your 20 minutes is taken up by that.

(Laughter.)

MR. BERKE: I notice the timer hasn't switched.

DR. LANGE: Thank you very much. Please proceed.

MR. BERKE: Well thank you, everybody, for allowing me to come and speak. My name is Steven Berke, President of Cincinnati Sub-Zero, a Gentherm company.

So at Cincinnati Sub-Zero, our mission is to deliver world-class temperature management solutions to our customers right the first time. And our vision is to create innovative temperature management solutions to improve life.

So the Hemotherm Model 400 series started distribution in 1981. I was actually product development manager at that time, so I am very familiar with it and have 35 years of experience with this product line and knowledge of this product inside and out.

Hemotherm 400 safety design and preventive of aerosolization. Airflow directed away from the sterile field at a rate of less than 185 CFM, very, very important. The OR room is putting out -- the standard is 2,000 CFM out of the ceiling, and most are designed with two return ducts that have -- will split that to 1,000 CFM pretty much around the table. So if we're putting out 185 going against 1,000 CFM, it's hard to get aerosolization to that OR table, which is the sterile field. But more importantly, our air does not direct towards, as you'll see in a later slide, towards anywhere other than downward.

Water reservoir isolation from operating room environment by two separate barriers. Not one, but two. Closed-loop fluid management system. Excessive capacity available in reservoir to handle overflow. So if they drain the water back to -- after they're

done with the circuit, if they do it in the OR, drain it back to the -- empty their hoses, their tubing, whether it's 3 feet, 6 feet, 8 feet, whatever, it can handle it in the reservoir.

Reservoir lid and covers are accessible and allow for easy cleaning.

Airflow path. Expel through the bottom. And if you look at -- so airflow is in through the front. This is a refrigeration device, no different than your air conditioner at home. And it does need airflow to provide cooling. This is not a water-cooled refrigeration system. So airflow comes in the front, across the condenser, and is directed out the bottom, not towards any sterile field.

Here's just another look. There's the condenser which allows for the cooling of the -- in the refrigerator to provide cooling. The condenser fan motor and the condenser fan. Airflow again from the side view, it's coming in through the front and dispersed out the bottom.

Here's with the grille taken off the front with the condenser, and here's the grille that's removable for cleanability. I know there's been some talk about utilizing filters for air. The problem with that is if they do not clean it, you'll overheat the refrigeration system, and you won't have any cooling effect, which is the whole premise of the device. And here's a look at the bottom of the unit. So the air is dispersed out the bottom.

Hemotherm reservoir. Water is isolated from the OR environment by a reservoir cover and exterior reservoir lid. Excessive capacity we talked about, and reservoir lid. So here is the exterior cover. It does have a single hole in there. But if you notice that -- go to the next slide. So that's the exterior reservoir cover, and you notice the hole does not line up with the two holes so you can add water to the proper level on the individual covers.

Exterior lid and the heat cover and the cold cover reservoir. And the covers are removable so you can get inside to the unit and clean them.

So the other thing you've noticed in some of the articles is you do not want stagnant water. You won't want water sitting in a tube. If you look at the design of the unit and you got your heat reservoir on the right, so the water comes out the bottom. It goes through a solenoid valve, if you're in the heat mode, to the pump, through a filter, out the unit. And if there's nothing attached to the unit, you have an internal bypass in there so you can pre-warm and pre-cool the unit. Water comes back. It can't go this way because this valve is closed. It comes over and back to the heat reservoir. When you switch from the heat to the cool, the same thing happens. It comes out the cool reservoir, through the pump, out and then back, back to the cold reservoir. Now, the only two lines that are stagnant is when you want to drain the unit and allow for draining of the reservoirs for cleaning purposes, and that's been discarded.

Here's the back of the unit taken out. Remove the back, all your components are right there. And the water filter that we do have in there is really -- it's not a 0.22 μ filter because it would be really hard to get flow through there as time goes along. It's really to collect any debris that may get into the system.

Okay, mitigation. So CSZ has been working very closely with a wonderful professor in Virginia Tech in Dr. Falkinham, and we've been very pleased with his ability and his knowledge. We've learned an awful lot in a short period of time. And I know we're all focused on NTM, and who knows what the next superbug will be, but right now our concern and focus is cleaning or disinfecting of the unit. And so he's working on looking at

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evaluating all our systems and not just the heater-cooler, and he's measured aerosolization potential with the Hemotherm heater-cooler and with using the Andersen air stage Cascade sampler. And we'll go into more detail. And a characterization study indicated that Hemotherm does not generate aerosols containing NTM.

So this is the aerosolization testing device that he used, the two-stage Andersen -- two Andersen six-stage Cascade sampler in a room that's 30 cubic meters, and basically, it sucks in air from the environment, so it's a little more severe than, you know, just Petri plates sitting out there and hoping the bacteria falls into the location. You know, it happens to hit four or five sampling plates. This is actually sucking in air from the area and analyzing it.

Okay, so our water system cleaning procedure. We have forever -- actually since we got in the medical field in 1963, we've been recommending distilled water. Change water monthly. Preventive maintenance quarterly. Drain and clean the reservoirs, clean water system, clean filters, refill reservoirs with distilled water, clean condenser and grille.

Could we go one step farther? Yes, we can go to sterile distilled water because you can't guarantee that any distilling system in the hospital, that the tubes exiting after the sterile process -- I mean distilling process -- are clean and are maintained clean.

So adverse event investigation. We've gone through a process reexamining the product risk file and incremental risk associated with the aerosolization and microflora. We've heightened our scrutiny with complaint handling. And still, to date, we do not have any complaints of NTM being aerosolized out of our units or even being found in any of our units. We have had a couple complaints that we talked about that were brought up about

MDRs that were reported, and those were based on a hospital or a state applying a different regulation or a requirement on our units that are something that we haven't required. So it says it has to have drinking water quality. When we sold the units and shipped them and got our 510(k), those requirements were not established at the time.

Establish cross-functional team with our engineering manager, director of quality, regulatory, our regulatory manager, Dr. Falkinham, chemical engineer, and our service team to look at everything and reevaluate everything within the system and scrutinize any questionable areas that we may have. And to date, there has none been found.

Recommend improved communication. We recommended FDA involvement in education initiatives in collaboration with CDC and NIH and user facilities. So we also sent out a communication to all the field to alert them and make sure they're cleaning the units on a regular basis and following our cleaning procedures.

CSZ's conclusion. A characterization study indicated that Hemotherm does not generate any aerosol containing NTM. Checkmark.

CSZ is voluntarily revalidating the current cleaning procedure by a third-party expert as related to NTM. Done.

And none of the existing data suggests that the Hemotherm is a source of nosocomial infection, including NTM. Check.

And I know it was brought up that all units are basically the same. In very general terms, they are. They are not all designed the same; otherwise, we would have all the same units. They are different in their construction and design, whether it's accessibility on the reservoir covers with dual protection, whether it's airflow in through the front, dispersed

out the bottom, not directed. We've gone through great measures to make the condenser fan motor -- condenser larger than normal for a refrigeration system that is in this unit.

This was going back originally for two reasons: to slow down the air speed to make it as quiet for the surgeons and the perfusionists as possible, so the air noise would not sound like a jet airplane taking off, and the other thing is to lower the air velocity so we get the same volume across there and not have a lot of disruption in the air.

This unit has been around for 35 years. In essence, we've made changes to electronics, but the performance of the unit has been virtually the same, other than keeping up with the electrical -- new electrical requirements over the years.

In conclusion, I again thank you for the time. We have a spirit of innovation, and we're here to help and take any suggestions that you may have and make them viable. So thank you. I saved you some time.

DR. LANGE: So noted, well within the 20-minute time frame. Thanks for the excellent presentation. Appreciated.

We'll now hear the presentation from CardioQuip. And again, you'll have 20 minutes for your presentation as well.

MR. PLATT: My name is Douglas Platt, and I am one of the principal partners at CardioQuip, and I'd like to thank the Panel and the FDA for allowing us the opportunity to be here to discuss this issue. During this presentation we will focus on two critical areas of cooler-heater design. And I realize everyone here has been stating heater-coolers, but we speak of them in the terms of cooler-heaters simply because, in the process of cardiovascular surgery, you cool first, then you heat. And frankly I'm an old dog, and it's

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hard to teach old dogs new tricks, and quite honestly, I just don't want to learn that new trick.

So I am one of the partners. I have 25 years-plus experience in this field. We had Jon Gardner, our R&D engineer, also going to attend, but he had a slight run-in with an F1 tornado in his home; he needed to stay there to handle that.

CardioQuip is in a unique position in that we have been a refurbisher of cardiovascular surgery devices for the last 12 years. I'm sorry, 13. And we have also -- I've been in this field for 20-plus years, 25 years, also refurbishing cardiovascular equipment. That is not insignificant in that every cooler-heater that has been on the market or is now currently on the market, I have been inside that unit. I've actually been inside the guts of every cooler-heater that's actually out there at this time. This experience does give us a unique ability to address the relationship between device design and the current situations.

This is our cooler-heater. It's the MCH-1000, basically the same hardware and software in both units, and they are intentionally designed to be safe and have very simple operation. There are redundancies built into every critical aspect of the unit to allow for safe operation, and the units have a very simple user interface that you can see there. It's a touch-screen interface that also helps assist in safe operation. Lastly, the units are easy to maintain with a straightforward, tried-and-true cleaning protocol.

Now, what do I mean by straightforward cleaning protocol? I'm going to get this thing right yet. Open versus closed water path. The open versus closed water path basically is not the slide that I wanted to look at because I want to look at -- hello -- that slide. This is what I mean by tried and true. I'll assume that everyone in this room has one

of these in their home, that you know it can get dirty and that you know how to clean it. This is the basic flush-and-fill method of cleaning, and it is indeed a tried-and-true cleaning method. It is the basis for our MCH cleaning protocol. For our system, you add disinfectant to the water, circulate it through the machine, scrub out the tank, drain the system, and fill with fresh water. A complete cleaning and disinfection, including full wipe-down of all external circuits and a full wipe-down of the tank, takes about 30 minutes. This includes the time for going to get a cup of coffee if you so wish. I'll admit it, it's more work than cleaning a toilet, but not by much.

So why do I put this up here? Not to trivialize the matter that's at hand, but obviously to get your attention, because I also want you to think about design because design is very important. There may be fancy toilets out there, but the design is tried and it's true, and all toilets have an open water path design. So let's go back to that.

Open versus closed water path. Basically what you have is there are really only two basic designs: the open system that can be fully flooded, and the closed system which cannot. There's actually maybe three because we can sometimes talk about semi-open systems, but that's a discussion for another time.

In an open water system design, internal plumbing is purged of air so components are fully submerged. The water tank lid is removable, allowing access to internal surfaces of the tank or tanks for visual inspection. And you can do the cleaning and disinfecting by scrubbing the surfaces, therefore eliminating biofilm.

Differently, a closed water path design includes inaccessible airspace, shown in red, that cannot be smelled, disinfected, or even scrubbed clean in any way. Surfaces in this

airspace are not submerged, so waterborne disinfectants cannot touch them. As a result, these areas can incubate and harbor microbial concentrations. Flush-and-fill cleaning methods only work properly with an open water path design. Because of this, almost every type of cooler-heater in use today uses an open or a semi-open path design.

No, I keep hitting the wrong button. The CardioQuip MCH series uses an open water path design. There are no inaccessible airspaces to harbor microbes. Waterborne disinfectants contact all the wetted components inside the system. As you can see, basically the water runs from the tank, through the system, back into the tank. So the disinfectants can touch every component inside the water path. The tank is easy to inspect and clean. Basically, it's just like the toilet bowl lid. You lift it and you look inside, you can see what's inside the unit. It's right there, staring you in the face.

So here's a quick look -- here's a quick look at our cleaning protocol validation:

- Fill the device with contaminated water.
- Sample the water for HPC test in pre-cleaning.
- Perform cleaning procedures.
- Sample water for HPC test in post-cleaning.
- Evaluate the cleanability.

So what do we mean by that? Our validation addresses two essential factors: basic effectiveness (i.e., does the procedure get the device clean) and what we call cleanability (is the device easy to clean, and is it easy to inspect). The difficulty of a cleaning procedure is directly proportional to the risk that the end user won't clean the device properly according to the IFU, or he will make mistakes in the cleaning of the device according to the IFU. Also,

the heterotrophic plate count is a 48-hour test that measures the approximate microbial concentration in the water samples. It is nonspecific as to what bacteria it is looking for. So testing for a specific microbe requires a different procedure, but we're only concerned with the overall concentration of the contamination in the water as it is. We are not really concerned about the exact results of the HPC test. We are only trying to prove that once the cleaning procedure is completed, the water in the system is better than drinking water quality. The device doesn't need to be sterile; it just needs to be clean enough.

This is part of our validation results. We use EPA drinking water standards as a baseline; i.e., the post-clean water quality must have less than 500 CFU/mL of microbial content. You'll note the variations in both pre- and post-cleaning microbe counts is expected and for multiple reasons. One, we obtained contaminated water in a worst-case scenario for all of our testing. We actually went to fish ponds, drainage ditches, storm sewers to actually obtain water that we could put in our cooler-heater system so that we can let it sit there over a period of time so that it has the maximum amount of contamination that we could possibly afford it.

You'll also note each disinfectant differs in its effectiveness against the different microbes. Also, slight variations in the cleaning protocol, which I have mentioned before, can also affect the results. But you will note that in all cases the cleaning definitely reduced the microbe count significantly. Again, we need to use the term "clean enough."

The OR is not a clean room. There are multiple bacteria generators within the room from non-sterile surgical methods, materials, heart-lung machines, other devices, materials that are just brought into the room to be stored. There is non-sterile equipment. And even

there are people in the room, and they are big-time bacteria generators inside the room. But let's keep this in mind, and I'll address that again.

So why use water? I think that's a very good question. Why not use some other coolant or no coolant at all? From a practical standpoint, because it's always been done. Regulatory history tells us that all the standard tubing and connectors are designed for water. Any device claiming substantial equivalency to any cleared device would necessarily have to use water.

Water also makes sense from a medical standpoint because it is compatible. The blood heat exchanger is a separate device from the cooler-heater. They're all designed for water. And we have seen recently that when you put other chemicals in, they do cause a problem with those blood heat exchangers.

In addition, some spillage is inevitable anytime you're working with anything that works with water. Water is a relatively benign substance. If you spill it on the floor or you get it on your hands, you probably are not going to be very shocked. However, we do ask our customers to treat water as a biohazard or at least as something that could be dirty.

Alternate coolants, however, would incur similar risk to the patient. You'd still have the same spillage problems, you'd still have the same issues, but those alternate materials, at least the ones that have been looked at, benign is not a term that you would use with them. They normally all have detrimental effects to humans or equipment.

Further, the human body is two-thirds water. Water is an excellent choice for the blood heat exchange. The temperature range compatibility and other factors are near identical. Second or another point, one of the greatest things about water is that it makes

ice. No other material on the planet matches the performance of ice for safely and efficiently cooling the human body. If you're performing a circulatory arrest case, you need a massive amount of cooling, and nothing has been shown to be better than ice for cooling.

So the infection control guys are right. Water in the OR poses certain risks. However, there are multiple risks that must be mitigated in the OR. And again, the whole idea is what is clean enough? ORs are not clean rooms. Even with the current technology, the benefits of water in terms of patient outcomes still outweigh the risks. As much as we might like to get that water out of the OR, the net result would be detrimental to the patient.

So let's mitigate it. With risk comes mitigation. We know that having water in the OR has always concerned infection control. So we've come up with several ways that we see to reduce the risk of water in the OR. A huge problem with previous generation cooler-heaters is their open flow water connectors. They can spray water across the room if you disconnect them at the wrong time, i.e., the pump is running. We use two-way valve connectors on our devices and our hoses and disconnect -- if you disconnect the hose while the device is even on, nothing happens, no spray, no leaks.

The standard connections on every heat exchanger, blood heat exchanger, are not valved. They're wide open. So using our dripless connector technology, we designed a hose kit that also allows us and the operator to disconnect the blood heat exchanger from the cooler-heater hoses without opening up the water path at all. Zero spillage. Leave the short sections connected to the heat exchanger until after the patient is out of the room or the oxygenator is out of the room. These are just things that we think you can do to

mitigate the water.

We also use antimicrobial hose materials wherever they make sense to inhibit biofilm formation and improve water quality. For example, the PVC tubing that we use is impregnated with a silver compound that provides antimicrobial protection to all surfaces of the tubing. Inside and out, it is REACH, RoHS, and ISO 22196 compliant. In our internal testing over a 1-month period, this tubing prevented biofilm formation and had about 20% less microbial growth in the water with standard tubing.

Lastly, we communicate with our customers that they should treat water as a biohazard. After you make all the water connections, change your gloves. If you spill water, treat it as infectious waste. You're wearing all sorts of protective clothing in the OR. We're trying to protect the sterile field. Help your cooler-heater to also do the same.

So what other risks are there? There are other risks. The next risk, big risk, is airflow, and it must be mitigated. What are the basics? Surgical ventilation systems deliver filtered conditioned air into the ceiling at the center of the OR. Roughly, you've already heard, it's about -- hang on -- there we go. Roughly, about 2,000 CFM is coming out of the ceiling; it is HEPA filters, and it controls it. There are two return ducts. They have about 1,000 CFM going to each return duct. In practicality, there is sometimes less than that because they've set something before that return duct.

There are standards in the U.S., standards in Europe, standards -- specific standards in Germany and the UK, and there are CDC guidelines for environmental infection control in healthcare facilities. Basically the standards, though, say that cardiovascular OR should have about 2,000 CFM of air coming in from the ceiling, and it should go to two exhaust

grilles.

Let's consider this from the standpoint of device design. If we're designing a device that generates a draft, then that device has to operate safely within that surgical ventilation system, and it has to be built to the minimum standard. What can we say about the airflow our device can generate? If our device can generate an airflow of more than 1,000 CFM, perhaps less than that, then it can overpower the surgical ventilation system and push air into the sterile field.

That's some of the standards we looked at.

In design, you must look at the surgical ventilation system, its limits and what those limits are in a typical OR. Given the basic parameters of the surgical ventilation system, we can assume that in order to be compatible, a device should generate less than 1,000 CFM. That is an absolute maximum, though not necessarily a safe maximum, and that's not what we were trying to determine.

Analyzing cooler-heater devices provides additional insight. The Swiss performed a study with a specific unit that demonstrated the specific cooler-heater's airflow is able to overwhelm the surgical ventilation system and deliver contaminants into the sterile field. Basic calculations that we have done show that that specific cooler-heater has a fan that is capable of generating 1,000 CFM. Now, notice, I didn't say that 1,000 CFM was coming out of that system. I just said the fan, basic calculations of the fan showed that it was capable of doing at least 1,000 CFM. So that confirms -- or at least confirms our basic assumption that 1,000 CFM could be unsafe in a cardiovascular OR. Our research indicates that devices with the next highest airflow have a fan capable of generating approximately 500 CFM.

Again, the fan is capable of that. As you heard from the Hemotherm representative, their unit only did 185, although the fan is capable of more. One of those units or that specific unit has been in the field for 30-plus years, the other of those 500 CFM-capable fans has been in the field for 13 years, and neither of them have any reported issues that would indicate that they are capable of contaminating the sterile field.

So what did we do? Our standard unit has a 500 CFM fan that exhausts out the bottom. It intakes out the bottom. It has an optional refrigeration model that has a front and rear intake, which has the fan -- the fans are capable of doing 300 CFM, which would roughly make it about 150 CFM per side. Again, that's only what the fan is capable of. That system does have a dense steel mesh that is going to reduce the airflow and reduce turbulence out of it, also mitigating whether or not it can actually disrupt air, the sterile field, which our testing shows that it can't.

The compact unit also has a 50 CFM fan. Basically, you can look at that as a PC-type fan. It also has exhausts that are baffled to disrupt airflow and the baffle flow is more -- because baffle flow is more easily absorbed and redirected and does not interfere with the field.

So, in summary, we at CardioQuip believe that the issues facing manufacturers and regulatory bodies surrounding cooler-heater devices can be broken down into four categories.

Water quality and airflow. Maintaining water quality best practices to meet minimum drinking water standards as well as separating airflow from any water source is essential to cooler-heater design and device safety. While the water is very important,

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having the water and the bacteria that's incubated within that water to get to the sterile field is the true issue.

Cleanability and effectiveness. The device must be able to be cleaned effectively and with a certain amount of ease. If the device is not easily cleaned, people don't want to clean it, or they're not going to clean it as well as it says in the IFU. Hospitals run the risk, when the cleaning system is too complicated, that it just won't get done right.

We have risks and mitigation. In this industry, we constantly are having to mitigate risks in just about everything we do. Newer is not necessarily better or practically safer. Let's not throw out the baby because of the bath water, or in this case the cooler-heater water. We have been performing cardiovascular surgery for 50-plus years, and a lot of progress has been made. But we've also had setbacks, and when we do, we need to analyze the problem, determine the facts, and then work together to fix the problem and mitigate the risk to the future patients.

Lastly, communication and education. Finally, we believe that strong communication with healthcare professionals and other peers in the industry will help improve patient outcomes. This is the driving factor we must all understand. We need to help end users and also regulators to understand the risk inherent to our cooler-heater devices and how best they are mitigated. Education is the key to understanding.

And I'll wait for questions.

DR. LANGE: Thank you very much. Another excellent presentation. I'd like to thank all three companies for providing excellent information and within the allotted time frame. I'll ask that a representative from each company come and sit at the table. I think that will

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facilitate the next part of the program, which will be the opportunity for the Panel to ask clarifying questions. And again, we'll have 30 minutes to do that, and I'll remind the Panel that these are meant again to be clarifying questions. We'll have other opportunities during the afternoon session to ask the company or industry representatives additional questions as well.

And the other thing I'll remind you of is when you speak, to identify yourself, turn on your microphone and then turn it off, because our audio experts realize when there are more than one on, it's difficult to regulate the sound.

So with that, let me open the next part of the program for clarifying questions.

Dr. Allen.

DR. ALLEN: Probably a general question for all of you. Keith Allen.

What is your sense of how well facilities are actually following your IFUs? I ask that because one night before coming to this meeting, I queried my nine perfusionists, and they seemed to assure me that they do a good job of following the IFU, but their next retort was that most or a lot of facilities just simply weren't paying attention to this. Do you think really this is just a situation where we just need to be -- clean our house twice a week instead of once a week?

MR. PLATT: Doug Platt, CardioQuip.

I'd like to answer that question because I think I kind of discussed that in our presentation. The cleaning has to be simple, or it's not going to get done. I know cardiovascular perfusionists. They are all dedicated people, and they really want to do well. But the cleaning of the cooler-heater can be a very difficult process. Do I think that they all

do it well? Well, there's a little bit of a scare going on within that community. They all want to make sure that their cooler-heater is clean. So yes, right now I would say that they're cleaning fairly well. The problem is there's a lot of confusion within the IFU of how -- well, how do I do this? How do I get, you know, so many parts per million? You know, they're perfusionists, they're not pool cleaners, and they really want to understand how best to clean the devices. We would advocate some aren't really that cleanable, and that is a problem.

MR. BERKE: Steve Berke, Cincinnati Sub-Zero.

Just over the years, I will tell you that it's not real consistent. We have one complaint that's out there, and it was with a different device, and we know for a fact that they couldn't tell us the last time they cleaned the device. And there was no patient injury, but they couldn't tell us. And it's become very, very hard to get information when incidents are reported, to get information back from hospitals. You know, I don't know if it's because of a legal scare and what's the potential out there, but it is really difficult to get the information. I will say there is definitely -- I agree with Doug, there is definitely a heightened awareness, and people are responding and making every attempt to do it.

MR. DUPOUX: Thierry Dupoux, LivaNova.

So I would say that in the past it has been incredibly variable from clinical site to clinical site, but this different. There are some, even so, to say that some devices have never seen any cleaning. But I would also say that since we have made this communication, at least to our users in 2014 and 2015, and there is so much now awareness created by the communication from the competent authority, people are extremely careful about doing it

right. So I would say that today there might be a few sites that still do not do it right, but that should be a minority.

DR. LANGE: Dr. Yuh.

DR. YUH: Yes, this question is directed to the representatives from LivaNova and CardioQuip. Maybe I missed it, but can you briefly summarize your efforts to determine how much aerosolization occurs with your respective heater-cooler units with normal simulated use? I appreciate the description by Sub-Zero, but I wanted to get sense since that seems to be the putative mechanism of transmission in this discussion.

MR. DUPOUX: Yes. So Thierry Dupoux, LivaNova.

So over the time we have developed clinical -- setting, which allow us to characterize how bubbles are generated. Then, from these bubbles, how aerosol are created and then how aerosol can be emitted. Those three phases are very different, and what we have learned testing different conditions with our device and also competitive devices is that the emission -- the aerosol creation is almost permanent. For sure, you can have some water conditions which are plummeting or lowering the level of aerosol you are going to create -- the water. But the problem is not so much the creation of the aerosol. It's the emission of the aerosol and the unit to have specific conditions in order to have the aerosol leaving the tank. And we have identified which are these conditions, and what we have also identified is that over the course of a clinical procedure, simulated, the time during which you are going to have the emission of the aerosol is pretty limited. It's not over the complete time of the procedure. So we have developed protocols to characterize aerosol emission, measure it and when -- so when we do this characterization, which is easy to do, you don't

need any incubation. Then in order to fully verify our assumption of design change, we go to the next step, which is measurement of aerosol contaminated with NTM. That means it requires inoculation of the water circuit. And then you do sampling, as my colleague from Cincinnati Sub-Zero was describing. But this is extremely long to do. You cannot perform that in order to validate or evaluate a reassumption or design change you do because every time it requires 8 weeks of incubation. So in order to speed up the evaluation and validation, we have determined this old science regarding aerosol characterization measurement, and I think that we have developed something pretty interesting.

DR. LANGE: Dr. Dubois.

MR. PLATT: Was I supposed to address that?

DR. YUH: Yeah, if you could, that would be great.

DR. LANGE: Is it Du-boys or Du-bwa?

(Off microphone response.)

DR. LANGE: Dr. Du-bwa, please.

MR. PLATT: I think I'm supposed to finish -- I'm supposed to answer a question for Dr. Yuh.

DR. LANGE: Yes, sir. My apologies.

Dr. Dubois, if you'll hold on, please.

I'm sorry, Doug.

MR. PLATT: Doug Platt, CardioQuip.

Our basic testing involved taking and opening up and destroying basically two Sorin 3Ts. What we found in the aerosolization process is that there are really three factors.

Well, four. One is the incubation within the tanks themselves. There is what we call entrained air. In the top of the tanks, there is no disinfectant that can touch the top of the tanks. Therefore, there is a bacteria concentration that can grow there, and that bacteria concentration can and does move from the tanks into the field right above the tanks, and it also moves out through the airflow and into the overflow bottle.

That is of a concern because then the aerosolization process that we observed really comes from that there is a cooling fan that cools, I'm assuming, the pump motors. That cooling fan sits right there in the field where the air is raised up from the tanks, and it literally pulls that air out of the system and puts it right outside of the actual unit. There is air that also comes through the airflow or the overflow bottle. By IFU, per their IFU, that bottle is supposed to be -- have no water in it, and therefore air can readily flow directly from it.

And that's where the real issue comes in because the very small fan and the bottle are actually taking bacteria-laden air and placing it in front of a very large fan which is capable -- and again, I'm going to state -- I'm not going to try to tell you what it actually is putting out. But the fan, by calculation alone, is capable of doing at least 1,000 CFM. So I'm literally taking directly from the top of the tanks with a small fan, and I'm dumping out my bacteria-laden air right in front of that cooling fan. And then I am also using the water overflow and using that water overflow bottle; I'm also putting bacteria-laden air right in front of the large cooling fan. That large cooling fan appears to be, according to the Swiss study, capable of overcoming the laminar flow and putting bacteria at the sterile field.

DR. LANGE: Dr. Dubois, just a moment, please.

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Suzanne.

DR. SCHWARTZ: If I may, I think that the question was specific to the differences with CardioQuip, and if you could address that.

MR. PLATT: I'm confused.

DR. YUH: So just to clarify, in terms of what your studies have in terms of investigating the aerosolization potential of your devices, as Sub-Zero had described in their presentation.

MR. PLATT: Very low. Basically, the fans, what we've done is we've mitigated and baffled all of the airflow coming from the fans. The fans are very small to start with, less than 50 CFM in the stated unit and less than 50 CFM in the smaller unit. They almost don't disrupt the flow at all in a smoke test because they're basically PC-sized fans. The larger fan that's in our refrigeration unit, in smoke tests, doing a smoke test, basically it did not incur into the sterile field, and it didn't disrupt the air nearly as much because basically, again, there's 300 CFM -- the fan is capable of pumping 300 CFM into the unit, and it's dispersed out through -- 150 CFM coming out the sides. And then that is again baffled so that all of that air cannot come out, and it's disrupted, and as you disrupt the airflow and make it more turbulent, it doesn't affect the laminar flow nearly as much.

DR. LANGE: Thank you very much.

Dr. Dubois Fennal. Excuse me.

DR. FENNAL: Thank you.

This question is for LivaNova. I just wanted to know, when you took a look at factors that could potentially impact infection risk, was there anything there that indicated that in

places where there was less use or less procedures performed, that the indication for infection was greater?

MR. DUPOUX: Thierry Dupoux, LivaNova.

So we don't have -- we have not performed this analysis. We don't have -- I cannot answer this question.

DR. FENNAL: Is that a no?

MR. DUPOUX: I don't know.

DR. FENNAL: Thank you.

DR. LANGE: Mr. Stammers.

Colleen, will you loan him yours? Thanks. We've determined that that side of the table can't ask any questions. Okay.

(Laughter.)

MR. STAMMERS: Thank you very much.

Thank you for your presentations. I've got a question. The FDA this morning, Dr. Schwartz's group, did a wonderful job in talking about the disinfection validation processes that are recommended. Can you very briefly, each individual company, describe what the worst-case scenario is, which was discussed this morning, in regards to taxing your devices in regards to their release or their ability not to release the NTM? What was your methodology, worst-case scenario for your devices that you have applied following the FDA guidelines? Very briefly, for each of the companies.

DR. LANGE: If you'll turn your microphone off, please, Alfred.

MR. DUPOUX: So I'm going to call my colleague, which has a better understanding

about this piece.

MR. PEIS: So good morning. My name is Christian Peis from LivaNova. I'm Quality Director of the company and maybe is the person who was most involved in the investigation and doing the validation for these devices.

For the validation, we went to an external lab. No, I will start in a different way. We were looking for a standard or a guidance document which helps us how to validate the heater-cooler 3T. And as mentioned in the Executive Summary, or in the presentations this morning, there is no standard or guidance available for this kind of device because we have no direct patient contact. So we were looking for some other guidance documents or standards which can be applied for this validation, and we have found the guidance from FDA for reprocessing of medical devices, which is describing some methodologies, how to validate those systems. And we have also ISO EN Standard 17663, an intentional standard for reprocessing, re-sterilize a product.

And the lab recommended to apply a very similar approach, like for hemodialysis equipment or endoscopes, to have a control device and to have one device for validation, and the intention was to have three replicates of the validation runs and to have additional screening runs. So the lab called the screening runs with a different type of bacteria. And now, coming back to your initial question, how did we challenge or how did we simulate clinical use? We have set up a protocol which was simulating clinical use. So the device was operated daily, from Monday to Friday, according -- similar to clinical procedure. So the temperatures have been changed from higher temperatures down to lower temperatures and then we have -- at the end of the procedure, we have increased the

temperature. We have used the longest tubing which can be applied to the system. We considered very long tubing our worst-case scenario. So we have applied that. We have taken some samples from the system at different positions. So one worst case is at the end of the 5 m tubing, we had a connector implemented, and we took water samples at that position, but also from the different tanks and from the drain wells. We have challenged the systems with worst case, but here we have our challenge bacteria.

The lab, who is very experienced, and Professor Vana, who's a renowned person in Europe for doing this kind of validation, he recommended to use *Pseudomonas aeruginosa* and *Enterococcus hirae* as the test bacteria. We have inoculated the control device as well as the validation device with this bacteria, and after the inoculation, we have disinfected our system according to the instructions for use. And this test was repeated three times, and after the three times we continued with screening runs. So we have used a different kind of bacteria.

Due to the *Mycobacterium chimaera* topic in Europe, we have selected for our first screening run *Mycobacterium terrae*, which is according to European standard which stands for testing tuberculocidal activity. So this is a challenge bacteria for claiming that. And in our second screening run, we have tested *Mycobacterium avium*, which you're testing according to European standards to claim mycobactericidal activity, and those tests have been done. And at the end, after the 14 weeks running interval, we have demonstrated that all the bacteria which have been inoculated to the system have been killed. So for the mycobacteria, we could demonstrate a 5-log reduction because we inoculated 5-log *Mycobacterium*. For the *Pseudomonas*, it was a little bit different. Professor Vana

inoculated a lower number, 10^3 , to show in the control device some growth, that it is growing. So for those *Pseudomonas* runs, we did demonstrate ours at 14 weeks, that we achieve a 5-log reduction. And the *Enterococcus hirae* did show no growth in the control device. So it was we have inoculated it, but the bacteria was killed or not killed, but the number of bacteria was decreasing. So Professor Vana decided not to continue with this test bacteria.

DR. LANGE: Thank you very much. If the others are going to respond, I'm going to ask that they be brief, only because there's a lot of enthusiasm and other questions. Thank you.

MR. BERKE: Steve Berke, Cincinnati Sub-Zero.

So we are experts on building medical temperature controlled devices. We are not experts on how to go about that. So we actually consulted with Dr. Falkinham, and we worked with him to create a procedure. He actually inoculated the device with two different things, *Pseudomonas* and also NTM, and ran it in all three modes, one being with nothing on so the unit just being in the room, one in the heating mode, and one in the cooling mode. And in all cases, no aerosolization was proven.

DR. LANGE: Thank you.

Doug.

MR. PLATT: Can you repeat the question one more time, just so that I make sure that I answer the right question?

MR. STAMMERS: Yeah. I'm sorry it wasn't clear. I said worst clear scenario, because this has come up a lot so far, and really I think the problem is -- and correct me if I'm wrong,

all of your devices are only approved for 6 hours of use, correct?

MR. PLATT: Correct.

MR. STAMMERS: Basically, everybody who's using them are using them off label because unless you have extremely fast surgeries being performed, it's rare that we are using them less than 6 hours clinically, especially in ECMO where we're running them for days on end. So I just throw that out because worst-case scenario to me would be, as you mentioned, the gentleman before from LivaNova, 14 weeks I believe he said was that time period.

MR. DUPOUX: No. Thierry Dupoux. That was a mistake. It's 14 days. He was talking about the interim interval between two consecutive disinfections. So it's not 14 weeks.

MR. STAMMERS: Of course, these heater-coolers are turned on. They're not the length of the operation for cardiopulmonary bypass. But most time they're turned on way before the bypass run begins. So we may use them --

MR. PLATT: That's correct.

MR. STAMMERS: -- 8 to 10 hours on a regular basis, depending upon the length of the surgery.

MR. PLATT: Worst-case scenario. Basically, we work with one of the local labs there that also works with Texas A&M University, and our worst-case scenario, we literally went to a pond and got pond water because it seemed to be the most contaminated thing that we could get at the time. We put pond water in the unit and let it sit for a week, and then we took a bacteria count, and then we cleaned it, took a bacteria count. We used a college

intern to actually do the cleaning procedure because we thought it very important that we have somebody that was inexperienced. We also used engineers to do the cleaning procedure because they're the ones that came up with it, and can they follow it? We also used perfusionists to clean the system as well.

And we tested a variety of different chemicals for actual -- you know, how well they work. Quite honestly, the CDC recommends Pine-Sol in some instances. It's actually on their list. And we actually found Pine-Sol ended up being one of the better cleaners that we could actually run through our system, and it reduced the bacteria count more effectively than anything else.

DR. LANGE: Thank you. We're going to move on to the next question, please.

Dr. Givner.

DR. GIVNER: Thank you. And I may need your help, Mr. Chairman, with asking this question. Please let me know if I do.

It appears, and correct me if I'm wrong, that all three of you believe that your device is not associated with NTM contamination or patient infection when used and disinfected per your IFU in the usual OR environment without contamination in that OR environment from healthcare workers, from devices, etc. So that would lead me to believe that perhaps we're focused on the wrong area and should focus more on the hospital environment and making sure that the hospital is following your IFU. So my question for you is if not, if what I just said is not the case, then I'd like to know why you believe it's not the case. Can you follow that?

DR. LANGE: Each of you will have 60 seconds to answer that question.

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(Laughter.)

DR. LANGE: Collectively. No.

MR. BERKE: I'll give it a stab. Steve Berke, Cincinnati Sub-Zero.

Basically, we believe, first of all, if the unit is brand new and it comes to the hospital and they only use distilled water or sterile distilled water and they use it to maintain the cleaning procedure, how does the NTM ever get in there in the first place? It's got to come from somewhere, whether the sink -- it comes from two sources, tap water and soil. And that's proven, and that's documented in many studies. And so it's either from washing hands or reaching in the reservoirs or something else or using tap water in the system, if somebody gets in a hurry and they decide to use tap water because they don't have sterile distilled water handy and they introduced it to there. If you have a clean system, it should always stay clean and should never get contaminated.

DR. GIVNER: My question is -- I get the sense that all three of you believe that it is the case, if you follow the IFU as directed, that there should not be contamination associated with your device. So what I'd like to know is if we're focused on the wrong area here and, as you say, we should look at the hospital environment, what should we look at? And I just want to be sure. You don't have to reiterate how your device should be used. I just want to be sure that you feel when your device is used appropriately, it's not associated with NTM and we should look elsewhere. And if not, if we should be doing that, we're looking in the right place, why are we looking in the right place? Why should we not look elsewhere?

MR. PLATT: Doug Platt, CardioQuip.

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One, we do believe that our device is safe; that if used appropriately, that it is completely safe and that there won't be an issue with NTM infection. I do not believe that you need to look towards the hospital environment. And I really can't add to that. But you're looking in the right place. You just need to look very specifically.

DR. GIVNER: Go ahead. I'm sorry.

MR. DUPOUX: Thierry Dupoux, LivaNova.

So I cannot say that our device has not been linked or contributed to any patient's infection because there are publications which are making this statement. So I'm not going to say that it's not our case. However, these situations are reflecting a period during which -- over which the level of awareness regarding the importance of keeping the device clean was not as big as it is today. And as I mentioned before, we have evidence from a device that we had returned -- we had serviced and that were returned from the field that the infection [sic] was not performed.

So I think that this reflects a period of time during which there was no level of awareness regarding this problem. But now that people are aware of the importance of doing it right, the possibility for this device to be found as contaminated as they used to be and generate aerosol in big quantity that could be loaded with NTM is very remote now.

DR. GIVNER: So to just quickly summarize, I guess what you're saying is that your device is not associated with NTM when used appropriately?

MR. DUPOUX: Yes.

DR. GIVNER: Okay, thank you.

DR. LANGE: Yes, Jeffrey.

MR. RILEY: Thank you.

I have a question you can answer in 30 seconds each. For the record, would you state what your current frequency recommendation in your instructions for use is for disinfection, changing the water, and answer, do you see those as stable, your instructions? Do you see them changing in the near future?

MR. DUPOUX: Thierry Dupoux, LivaNova.

So we have biweekly disinfection, complete disinfection of the device with chemicals. Then we have weekly water change, and the water needs to be -- in the water, you need to add -- which is hydrogen peroxide. That's the procedure.

MR. RILEY: Do you see those changing?

MR. DUPOUX: We might have to change it if we learn a new element as we all progress in the investigation and understanding of this issue. There is nothing that we can foresee yet, but we are not excluding that we might have to adjust it in the future. I hope I answered your question.

MR. BERKE: Steve Berke, Cincinnati Sub-Zero.

Currently, our frequency is change the water monthly and disinfect quarterly. And currently based on that, it is about \$4,000 worth of sterile distilled water per year. If you go to weekly and monthly on this decontamination, it goes up to about \$12,000 just on the material of the water, not the labor. And we have not changed anything. We are still evaluating that, and to anticipate the one thing for sure is going from distilled water to sterile distilled water instead of just straight distilled system, because you can't guarantee that it's sterile in the tubing coming out of a distilling system in the pipes.

MR. PLATT: Our cleaning procedure currently is based on the flush-and-fill method. Based on the fact that our system is -- our standard system is an ice-only unit, the water is interchanged very regularly as the ice is changed. We recommend with the refrigeration system that the water be changed monthly and that the unit go through a quarterly cleaning process on a quarterly basis. We do not anticipate that changing at this time, per our testing. That testing seems to be adequate.

DR. LANGE: If you'll turn your microphone off, please.

I have a question to follow up on Dr. Givner's question. Is there routine surveillance done, that is, at clinical sites using the IFU recommendations? Is there routine surveillance done looking for bacterial infection and NTM infection?

MR. PLATT: Doug Platt, CardioQuip.

The hospitals that we are currently working with, while we do not require that, most of the hospitals that are currently out there are routinely checking for bacterial count with all of the cooler-heaters. I think it has something to do with the current situation at hand. I don't know if that will continue. Basically, our issue with that is, because of the long growth time, basically if you do an HPC test, basic HPC test, it's a 48-hour turnaround. So if you're using our ice-based system, you've already changed the water possibly two, three times before you ever even got the results back for one test. So I do see that the hospitals -- some hospitals are doing it and -- but I question the effectiveness of HPC testing overall, due to the length of time that it takes to return that result.

MR. BERKE: Steve Berke, Cincinnati Sub-Zero.

We do not require it, and up until recently, we've never heard of people doing it up

until last year. I know of three hospitals that are doing it on a regular basis. I only know of one that is actually testing for NTM.

DR. LANGE: Thank you.

MR. DUPOUX: Thierry Dupoux, LivaNova.

So we recommend to have monthly water monitoring, and in some circumstances, it can go to biweekly. And also air sampling. That's what we have in our field notice issued last year, June 2015, which is not yet included in our IFU because this is under discussion with FDA.

DR. LANGE: Great, thank you.

Raymond, go ahead.

MR. McGLAMERY: So besides the cost that you spoke of about the water interchange, what are -- are there material costs? So if you were more frequently cleaning, I mean, what materials are affected the most and what kind of degradation would be in those materials where you would have to actually replace portions of the machine, which would obviously run into higher costs?

And then my second question. I know Mr. Platt spoke about water being the best solution. Is there nothing that you could possibly treat the water with that would also be non-damaging if aerosolized that could possibly help keep it clean as well?

MR. BERKE: Steve Berke, Cincinnati Sub-Zero.

Let me start in just saying that the more frequently you do it, the more at risk you put the copper coil that has the refrigerant in there. And copper is a very soft alloy, so it will degrade over time and quicker, if you do it more frequently. And we've seen it from

one of the hospitals that has increased theirs to every 2 days, every 2 to 3 days, and it looks like it's been out there for 15 years compared to other units that have been out there that long. Our product life cycle is 12 years on ours. So it does affect it and there is -- we're still looking at other chemicals that will address the NTM, but also you have the biofilm as well. And so once NTM gets in a sac of biofilm, it's really you got to break that down first before you can actually attack the NTM.

MR. PLATT: Doug Platt, CardioQuip.

The short answer to your question is yes, the cleaning procedures, especially with -- let's just say overzealous cleaners have a tendency to break down the machine. There are certain plastics, certain things inside the system that can be broken down. We actually had an overzealous perfusionist put a bunch of chlorine in his heater-cooler, and it literally burnt the stainless steel heaters completely out of it. It didn't have any bacteria, but it didn't work either.

DR. LANGE: Thank you.

Dr. Allen.

DR. ALLEN: Thank you.

You know, part of the process of being here is to help the FDA synthesize some suggestions and being able to uniformly apply these to all manufacturers. So without getting into the specifics between different manufacturers, it's clear to me that things like not having -- doing appropriate aerosol testing, whether it's an open or a closed system, there are a lot of things that I think we're going to be able to make recommendations on. But one of the things that I am concerned about is the biofilm. And one, for example, I look

on my phone at the IFU for cleaning, for example, Sorin's product; the two, being it's only recommended that it be changed once a year. Once again, I talked to my perfusionists, and that's what we do. Apparently, they have protective tubing that doesn't allow light to get in it and reduces biofilm formation. But to me, you could clean your system every day, but if you don't clean the tubing or get rid of the tubing on a frequent basis, unless that tubing has zero ability to form a biofilm, you're going to always have an issue. So my question to each of you very briefly is what are you doing with your recommendations with regard to the tubing? Is that changing, and does it need to change?

MR. DUPOUX: So Thierry Dupoux, LivaNova.

So the water circuit disinfection is not only the tank disinfection. During the disinfection process, the water is circulated, and the water mixed with a chemical is circulated in all the circuits, including the tubing. So this tubing should not be the place where you are going to have more chance to grow biofilm, specifically since we have implemented this change where now the PVC tubing has been replaced with a polyethylene tube, which is certified for drinking water quality. So the chance that you can grow biofilm in this tube, I mean, a higher chance to grow it in this tube rather than the rest of the system is very minimal.

DR. ALLEN: I'm going to interrupt you and just -- I'm going to be a little more pointed because each of you, when you're answering your questions, are trying to sell your product. I mean each of you are doing that, and that's not the purpose of this. It's not to condemn one manufacturer over the other, but that's the sense that I get when I'm listening to your responses, is my product doesn't have a problem. It may be somebody else's. So what

testing specifically have each of you done on your tubing? So, for example, water flushes through it, but that flushing process doesn't fix the biofilm that might upgrade over a 6-month period. Have any of you actually taken your tubing that's been in place for 6 months or 8 months or a year, cut it, scrape the insides off it, and put it on a tuberculin-type product that can grown NTM? And what are your results?

DR. LANGE: So I'm going to just narrow it. Do you test the tubing? Yes or no?

Doug.

MR. PLATT: Doug Platt, CardioQuip.

No, we have not tested the tubing.

DR. LANGE: Okay, thank you. Stop right there.

DR. ALLEN: That's all I need to know.

DR. LANGE: And that's fine. We're just wondering.

MR. BERKE: Steve Berke, Cincinnati Sub-Zero.

We are not -- we have not, but we are in the process.

DR. LANGE: Thank you.

And for LivaNova?

MR. PEIS: Christian Peis, LivaNova.

We have not done the special tests for the tubing, but I would like to explain our concept of preventing biofilm growth. That's very important.

DR. LANGE: I'm going to stop right there. And that's fine. We'll have other opportunities to do that. That's fine. But just in the interest of asking other questions, we just want to know whether it's tested or not. And so all three companies would say, in the

past, not, but it's something you would consider.

MR. PEIS: For our concept, it was not necessary to make this test.

DR. LANGE: Okay, thank you.

Dr. Leggett.

DR. LEGGETT: For Thierry Dupoux. In your explanation about the initial report and your response, I got the impression that you had changed some things in 2014 and altered your machines. Those alterations, are you able to retrofit the machines from before 2014? I was unclear about that.

MR. DUPOUX: So Thierry Dupoux, LivaNova.

Thank you for the question. So what we have changed in 2014 was the manufacturing line. We have implemented disinfection of the units before release. And then we have also implemented some control measures in the manufacturing environment in order to prevent contamination with NTM. The changes that we made to the design of the device were introduced in 2015, between June and November 2015. And so these changes are retrofitted to the devices in the field as we perform maintenance. So whenever we go on site and perform maintenance, the devices are upgraded to the latest standard.

DR. LEGGETT: Thank you.

DR. LANGE: Thank you very much.

Dr. Christensen.

DR. CHRISTENSEN: Yeah, we discussed earlier the aerosolization coming off of these units, and I have a question, a quick question, across all three of you. Have you actually

done a true aerosol characterization looking at particle size, number, and distribution? Not just using, for example, an old-school Andersen six-stage impactor, like actually done a true characterization to see if it even produces any aerosol, not if it just contains NTM or any other bacteria.

MR. PLATT: Doug Platt, CardioQuip.

No.

MR. BERKE: Steve Berke, Cincinnati Sub-Zero.

We have not.

MR. DUPOUX: So Thierry Dupoux, LivaNova.

We have. We have made a full characterization of the aerosolization formation, particle size, weight, time of emission over the simulated clinical procedures. We have all of this.

DR. LANGE: So they have that. Would you like to see that at some point?

DR. CHRISTENSEN: Yes, at some point.

DR. LANGE: Thank you very much for each of you being responsive.

Dr. Hopkins.

DR. HOPKINS: Richard Hopkins.

Kind of a down-in-the-weeds question for CardioQuip and then a larger question for all three of you. I was fascinated by your disinfection, various results with the different chemicals. A couple of quick questions. Pine-Sol actually has two formulations out in the marketplace. One has the original pine oil, and one has replaced it with glycolic acid. Which one was tested here?

MR. PLATT: The glycolic acid.

DR. HOPKINS: Okay. And then the second question is the chlorine bleach is listed as 5%. Five percent chlorine bleach is directly out of the bottle. When the researchers refer to 10% chlorine in the lab to clean bio-hoods, etc., what they're actually talking about is a 10:1 dilution of 5%. So that's actually a 0.5% bleach solution. Which one did you use?

MR. PLATT: The diluted.

DR. HOPKINS: The diluted one, okay. Then the other question for all of you. One of you referred to the lack of feasibility of microbial filtration of the effluent gases from the system as being not an easy design feature. However, if these machines are being cleaned once a year or twice a year or four times a year, and at some point contamination by bacteria per se and ultimately by NTM is almost inevitable, then why is that not a design feature that could be entertained?

MR. PLATT: Doug Platt, CardioQuip.

The first part, I would say, is that when it comes to aerosolization, the biggest factor is to not open your water to where it can actually get to the fans, which can cause aerosolization. If the fans can't -- don't have access to the water, then you don't get aerosolization basically from the fan. You would get aerosolization from the room air, but not from the water. This is really a two-part thing.

DR. LANGE: And I think it's a great question. Many of us don't understand the engineering behind it. What are the impediments to putting in a filter? You had briefly mentioned. So if you could explain to the Panel how that would affect either the device --

MR. PLATT: Putting in a filter that has the capability of trapping the bacteria that

you're looking for is prohibitive in that you have to get air through the filter. And so it really comes down to at what level can we possibly get the filter down to. And then it begs the question, are we going to start making hospitals clean rooms? And if we need to make the ORs clean rooms, well, that's a whole different subject. What's clean enough? And basically what we are advocating, and what we continue to advocate, is that if you have very small fans with very little throughput in the way of air, and those fans do not have access to the water itself, then there is no aerosolization of bacteria. And it doesn't matter whether we put filters on it or not. What really matters is whether or not we allow bacteria to come in contact with the air filter.

DR. LANGE: So let me rephrase the question, and I want a short answer so that the Panel can understand because I think it's an important issue. Regardless of everything else circulating, in less than 30 seconds, the impediments to putting a filter either on the intake or exhaust.

MR. PLATT: Gaining a filter that would allow you to -- to be porous enough that you could actually get air through it, and then you would have to increase the fan capability tremendously in order to be able push the air through that filter.

DR. LANGE: And last question before we break for lunch. And again, there will be other opportunities to interact. This isn't the final question, but go ahead.

DR. GALLAGHER: Sure. This may seem a little different because I'm not an engineer and I have no clue, but I think about the fact that you're heating something and you're cooling something or you're cooling it and then you're heating it, and if I have a glass like this or something and it has water in it and I'm heating it and I'm cooling it, it's likely to get

condensation. So my question has to do with is there condensation that happens either inside the machine or external to the machine that also needs to be considered in this conversation?

Thank you.

MR. BERKE: Steve Berke, Cincinnati Sub-Zero.

Yes, it all depends on the relative humidity and the temperature differential between the water temperature and the air it's in, and the colder you are, the more condensation you will have. So typically, when you get below about 50 degrees, 45-50 degrees in a typical OR, you start condensation. Again, condensation is just in the room. It's not in the reservoir, or it's not being aerosolized. But if the room has NTM or any other bacteria, you are spreading it if it is in the path of the airflow. But on the tubing and stuff like that, that's when you would have to wipe it down. But any refrigeration system will create condensation below a certain temperature.

DR. GALLAGHER: Okay. So if that's on the outside of things, that's one thing. Does any of this condensation happen inside the machines that you manufacture and it would have to be controlled for?

MR. PLATT: Doug Platt, CardioQuip.

I just asked Steve if I could answer that. I do know both of our units use the internal insulation to keep the condensation at a very minimum level. I don't know that we could possibly ever stop condensation, but the environmental standards for the OR do require that, you know, humidity levels be at a certain area as well. So inside the room, they usually don't have condensation problems. They do have it on the hoses, but the hoses are

actually just running across the floor in the room. And we do use antimicrobial hoses, and they have antimicrobial properties on the inside and outside of the hoses. The hoses are good for 5 years. We say replace them every year. I had to get that in.

Thanks.

DR. LANGE: Thank you.

Are there any other burning questions right now?

(No response.)

DR. LANGE: I'd like to thank our industry representatives and leaders. These are areas outside of our expertise for many of us, and so we're trying to look at the entire picture. And so it's not limited to any particular device, but we're looking at it in toto. So we really appreciate it. And there will be opportunities again for the Panel to engage you all as well.

We're going to break for lunch. We're going to reassemble here promptly at 1:00. I'm going to start at 1:00, and I'd like as many of you as possible to be here as well. Have a great lunch. And again, thank you very much.

(Whereupon, at 12:04 p.m., a lunch recess was taken.)

AFTERNOON SESSION

(1:01 p.m.)

DR. LANGE: Good afternoon. It is now 1:01 p.m., and I would like to resume this Panel meeting. We will proceed with the Open Public Hearing portion of the meeting. And public attendees are given an opportunity to address the Panel to present data, information, or views that are relevant to the meeting agenda.

At this time, Ms. Washington will read the Open Public Hearing disclosure process statement.

MS. WASHINGTON: 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 Advisory Committee meeting, 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 relationship 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.

FDA has received a request to speak prior to the final date published in the *Federal*

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Register. The speaker will be given 30 minutes to speak.

DR. LANGE: Thank you, Ms. Washington.

By the way, this room is not a part of the cooler-heater unit.

(Laughter.)

DR. LANGE: So for those of you that were freezing in the first session, we've asked that they increase the temperature. So my apologies for that.

We will have Mr. Brian Orwat from Stryker Medical. Please come forward to the microphone, Mr. Orwat, and during this time we ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of the meetings. And there will be a timer available for your use as well.

Thank you, sir.

MR. ORWAT: Good afternoon, everybody. My name is Brian Orwat from regulatory affairs from Stryker's medical division in Kalamazoo. I want to thank the Panel for the opportunity to present from our perspective as a specification developer and manufacturer of thermal-regulating systems, which would be code DWJ, understanding that most of the proceedings today are discussions around the cardiopulmonary bypass devices, but again our device might be affected on the activities and discussions that are going on today. So we thought we'd like to present some information, and we're also here basically as an information grab. We used to have -- used to manufacture devices that were placed on the market. We do have devices currently on the market, but we have been out of production for a couple years, and we're currently in development of a replacement device for that. So again, we're here to listen to the subject matter experts and ensure that we have current

information to ensure that we will have a safe device when we reenter the market.

So it will be a brief agenda today. I'll talk briefly about the Stryker water heater-cooler background; disinfection effectiveness, which we believe would be necessary and just for this type of device; disinfection methodology validation; some of the risk mitigations that could be put into device design and device labeling; and then a brief summary.

Again, our device is a thermal-regulating system, product code DWJ. It circulates temperature-controlled warm or cold water via patient contact thermal transfer devices for the application of regulating human body temperature.

The system elements are composed of a controller, hose sets, patient thermal-contacting devices, transfer devices, cable, and probes that measure patient temperature. The thermal transfer devices are single-patient use. They're not intended to be reprocessed.

So the device does have a water reservoir. The device does keep separation between the system's refrigeration fan and venting areas within the confines of the main body of the device. However, the device is open to atmosphere through the water fill location, and this is necessary, again, so we don't have a vacuum within the system so we can continue to have flow of water through the system and through the thermal transfer devices.

The device that was on the market was initially cleared in, as you can see, 1980. And only the mechanicals have remained the same. There were some updates to the controller analog to a digital controller and such. But the main, again, guts, if you will, of the device

has remained the same since 1980.

As mentioned earlier today, we understand the limitations of the MDR system and also medical device companies' internal complaint systems. But with that being said, we don't have records of adverse events relating to patient injury or aerosolization of microbes with our devices that are currently in the marketplace.

So as far as disinfection effectiveness is concerned, we believe this is a non-critical device. As mentioned earlier today, it doesn't contact the patients. It's not intended to have any contact whatsoever. Therefore, we believe that an intermediate level of disinfection would be appropriate. We believe that a 3-log reduction of appropriate *Mycobacterium* is right, and so is a 6-log reduction of vegetative species.

Also, along with the effectiveness, we've ensured that we would use clinically relevant waterborne microorganisms for the validation. I know we've talked a lot about the aerosolization, but that is a key piece to make sure that the device is not aerosolized or have a propensity to aerosolize microbes. We would develop test parameters accordingly to make sure that is a valid aerosolization study. And again, for effectiveness with a disinfection process, we believe that human factors studies are necessary on the device reprocessing instructions for use.

Regarding the disinfection methodology, again, as discussed earlier -- and we'll go into much greater detail -- as far as the NTM waterborne, clinically relevant, known-to-form biofilms, we believe that *Mycobacterium mucogenicum* would be a relevant species for the NTM. And also for the vegetative group, a 6-log reduction would be appropriate, as previously mentioned. Waterborne, commonly found in fresh and stagnant water. The

species should survive in prolonged periods of moist environments. Versatile, resistant to antibiotics. Significant survival rates on surfaces. Also capable of colonizing with food and without food. And interactions with biofilms that continue to make these microorganisms grow and persist in aquatic environments. We believe that *Burkholderia cepacia*, *Pseudomonas aeruginosa*, and *E. coli* would be appropriate groups or vegetative microbes to use for disinfection methodology.

Frequency between reprocesses. I know there's been discussion on that. Some say daily, once a week, once a month, quarterly. I think it really depends on the growth, and make sure it stays below a demonstrated log reduction at the disinfection cycle. So, in other words, we understand that being a water-based system, there will be microbes growing in the system. As long as we can reduce it to an effective level, we believe that it is a safe mechanism. And also make sure that the growth stays below the population that correlates to aerosolization. Again, if the device were to aerosolize, you want to make sure that if there is a level of microorganisms in the system which are above that and it would be aerosolized, we want to make sure that the population would stay below that.

Worst-case test articles, again, another hot topic this morning. As we're developing, you know, testing for a device that, again, we have currently under development, we are making sure that we're testing worst-case samples and conditions, worst-case to expected life, things that we're doing as we're accelerating the cleaning agents through the system at an accelerated rate to the expected end of life, plus a safety factor margin. We're ensuring that we have appropriate sit times. We're finding that these types of devices can be used daily. They can be used twice a week. They can be used sometimes twice a month. So

we're making sure that we have appropriate sit times during our worst-case test article preparation to allow growth of biofilm.

And again a human factors study, we believe, is part of the disinfection methodology to make sure that the instructions for use can be followed by the groups that would be using them.

Related to device design and some risk mitigators for heater-cooler devices. Again, there's plenty of things that can be done to ensure the devices are as safe as possible upon release, obviously, the prevention of aerosolization, separation of the water system from any fans and venting water circuits. It's also possible to remove -- I know there's discussion about agitation of the water creating bubbles and the bubbles help to create aerosolization. There's a method that's possible to use a water reservoir just to fill up the system with as much water as possible to circulate throughout the system, fill up the pads or the blankets that are being used, and then remove that effectively from the circuit. So you would have it sit dormant during device use, but you wouldn't have that agitation within the reservoir. We think that would be a design feature that could be implemented into some device in the future.

Also protective wraps could be used on the hose sets to prevent the condensation. We have some of our wraps -- or excuse me, some of our hose sets do have insulation on them, so it reduces the likelihood of the water droplets due to the condensation effect when you're using the device in a cooling mode.

Water circuit materials could be used from materials that prohibit microbial growth. So they have antibiotic properties in them. Venting. That could be again placed on the

bottom of the units so that it doesn't push out the sides and disturb the laminar flow. Also, use of diffusers could be done in the venting systems.

Instructions for use. You want to make sure that, again, the disinfectant that's been validated is included in the instructions for use, the detailed disinfection steps are very clearly written out. Again, through some of our investigations, we found that the end user may not, again, be a perfusionist or an M.D., but it's going to be at the user facility. It could be anywhere from the people from housekeeping, environmental, through OR nurses and OR techs and scrub techs. And those are the ones that at times are responsible for equipment within the OR as part of their job duties. So during the usability study, we're making sure that we are including the user groups into the usability study.

And also, the inclusion of all accessories need to be part of the disinfection protocol. Hose sets, again, were mentioned earlier. That is something that is included as a regimen within device disinfection protocol. The hoses are looped together, so every time that the inside of the machine would get disinfected, the hose sets would also get disinfected.

And again, disinfection. Again, make sure that human factors is done on the instructions for use.

So again, in summary, as far as our device is concerned, we believe we have a safe history, again understanding the limitations of the MDR complaint system. But that is the information that is currently readily used to determine when there are safety episodes out in the field.

Intermediate level of disinfection, we believe, is adequate for this level of device and use of the device. And we also want to make sure we understand if the device aerosolizes

and design against any type of aerosolization. And be sure that the device has clear, concise, and validated labeling.

And that's it. Thank you.

DR. LANGE: Thank you

First of all, since it is a public forum, there are no other public speakers that are currently scheduled, but let me ask, is there anyone else that wishes to address the Panel at this time? If so, please come forward to the podium and state your name, affiliation, and indicate your financial interest.

And if not, Brian, I'll ask you to stay there for a second.

MR. ORWAT: No problem.

(No response.)

DR. LANGE: Okay. So I'm going to pronounce -- there is no one else that wants to address the Panel in the public forum, so I will pronounce the Open Public Hearing officially closed and proceed with today's agenda. I'd like to thank Stryker's medical representative for their presentation and ask the Panel if they have any clarifying questions you would like to address to Mr. Orwat.

Yes, Dr. Givner.

DR. GIVNER: Thank you.

You note, of course, that there's a human factors study, perform instructions for live -- sorry, for use validation in accordance with accepted human factor requirements and guidance, and I think you said that the method for that is input from various user groups who will help you work on your IFU. So I just want to be sure. This is not something you're

going out in the field and doing? This is something you're monitoring? I'm just trying to get an understanding for what that implies.

MR. ORWAT: Yeah, what I was stating is during the usability study where you understand who the users are of the instructions for use, they helped develop the instructions for use for the formative side of the usability study. And then when we go and do the summative, which is the final validation of the instructions for use, we make sure we include members of the user groups as part of our summative study.

DR. GIVNER: Thank you.

MR. ORWAT: Um-hum.

DR. LANGE: Other clarifying questions?

Yes, Naveen.

MR. THURAMALLA: Naveen Thuramalla.

A quick question. I saw the frequency for bringing in this infection. You said that could be guided by the growth levels. What is your recommendation of how can the growth levels be assessed on site, at the user facilities?

MR. ORWAT: That's something we're working on right now because we don't currently have a regimen to go out and assess those gross levels. The things that we're doing is learnings that we're doing internally in laboratory conditions. We're trying to simulate real-use conditions and load the device up and use it. Again, use warm water, cool water, let it sit, and then take bacterial readings on that. Um-hum.

DR. LANGE: Yes, Ms. Gallagher.

DR. GALLAGHER: So I'm wondering if you have -- you said your company is currently

planning to put another one on the market, but you have some that are already in use.

MR. ORWAT: Correct.

DR. GALLAGHER: And you haven't made some in a couple years. So for those that are in use right now, have you considered making any changes to the instructions to those persons who have them already?

MR. ORWAT: Again, we looked at the information from our complaint database, and we found that we don't believe we have a severe problem on there. So it's something we're evaluating right now, and we have not made a decision whether we're going to go ahead and modify the instructions for use for the devices previously distributed.

DR. LANGE: Any other clarifying questions at all?

(No response.)

DR. LANGE: If not, we'll proceed with our special speakers. Thank you very much --

MR. ORWAT: Thank you.

DR. LANGE: -- for your presentation and for addressing the questions. Thank you very much.

At this point, we have two presentations from two guest speakers. The first speaker is Dr. Joseph Falkinham, III. And at the conclusion of the presentations -- there will be five presentations -- there will be time for questions from the Panel members. So the guests will have an opportunity to have their presentation, and we'll take a break, come back, and have presentations, and at the final, be able to address any questions.

So is Dr. Falkinham here?

DR. FALKINHAM: Yes, sir.

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DR. LANGE: Thank you.

DR. FALKINHAM: Twenty-five minutes. All right. I'm pleased that there are so many interested individuals and companies represented here today. This is a big problem. It's something that many of us who should have known better didn't anticipate. So I am a mycobacteriologist. I work at Virginia Tech. There's part of the campus right there. And I have consulting agreements with LivaNova --

DR. LANGE: Dr. Falkinham, I'm sorry. This is me, I'm sorry. I'm not sorry it's me, but --

(Laughter.)

DR. FALKINHAM: You're doing a hell of a good job.

DR. LANGE: And just for the recording, I'll have to ask you to speak into the mic.

DR. FALKINHAM: That's fine.

DR. LANGE: I know you want to address everybody, but we won't be able to get it.

DR. FALKINHAM: All right. I teach all the time, so I'm used to talking to crowds.

DR. LANGE: Otherwise, the transcript will get about every fourth word, and it won't make sense.

DR. FALKINHAM: That's fine.

DR. LANGE: Thanks.

DR. FALKINHAM: I've been consulting with LivaNova/Sorin North America and Cincinnati Sub-Zero having to do with this particular topic.

Now, what are the nontuberculous mycobacteria? They are environmental opportunist pathogens. We haven't the faintest idea of the number of organisms required

for infection. We don't have any good animal models because the infection is not rapid. It's slow. It's not lethal. It's chronic. We can measure the number of mycobacteria in livers and spleens, but there haven't been any studies in humans.

We do know there are people that are unusually susceptible. Taller, slender, older women make up a majority of the 85,000 cases of nontuberculous mycobacteria we have here in the United States.

And I might point out that 2.5% of funding from NIH in which the word "mycobacteria" appears is all that is designated for nontuberculous mycobacterial disease investigation. We are an unforgotten -- or we are a forgotten group of organisms. We are also not notifiable.

We would not see an increase in the number of nontuberculous mycobacterial infections in the databases that we currently try to pull out data simply because the number of cases associated with heater-coolers are such a small proportion of those 85,000 cases.

There are now over 200 *Mycobacterium* species. When I started this work in 1975, we probably had about 40. We now have a huge number, most of which have been associated with overt disease normally in immunocompromised individuals.

We have two groups of mycobacteria, the rapidly growing mycobacteria that take 3 days to form a colony, and the slowly growing mycobacteria that take 14 days. I have had to educate many people about the length of time, but I will point out that mycobacteria are not difficult to grow. They grow on the HPC. We heard about that, the heterotrophic plate count medium. They grow on R2a agar, which is the standard for the HPA count. They grow. They grow on blood agar plates. They grow on most every -- on every medium, but

we never see them because we don't incubate them up to 21 to 28 days. But they are there in the heterotrophic plate count.

The slowly growing species include *Mycobacterium avium*, the primary pathogen here in the United States; *Mycobacterium intracellulare*, which just recently Richard Wallace and I figured out is more of a soil organism; and *Mycobacterium chimaera*, its near twin, which is a waterborne *Mycobacterium*.

The salient feature to always remember about the mycobacteria is they are hydrophobic. The cells are like little wax beads. They are surrounded -- the cell is surrounded by a thick outer membrane. So you have the normal cytoplasmic membrane that all cells have. Then you have a microbial cell wall. And then you have a thick -- making up 30% of the cell mass -- a lipid, long chain lipid outer membrane, which makes these organisms very hydrophobic. It is a major determinant of their behavior and why engineered drinking water systems are an ideal habitat for mycobacteria. Likewise, premise plumbing. Houses, condominiums, apartments, hospitals, hotels are preferred habitats. If you had a shower this morning in the hotel, you probably inhaled something on the order of between 10,000 and 100,000 mycobacteria.

When you hear the word MAC, *Mycobacterium avium* complex, it consists of a wide number of microorganisms. *Mycobacterium avium* has four species. *Avium* infects birds, *silvaticum* infects wild animals, *hominissuis* we share with pigs. We are infected by *hominissuis*. *Paratuberculosis* causes a diarrheal disease in cattle, called Johne's disease, which is a major economic problem and has been proposed to cause Crohn's disease in humans. There are other *Mycobacterium* complex species. They're not subspecies of

M. avium. They're a little distant related. You see one, two, three, four, five, six, seven, eight. That number increases on a regular basis, sadly. Down there at the bottom we have *intracellulare* and *chimaera*, which are probably two of the bigger players here in the United States.

The hydrophobic outer membrane of mycobacteria leads to slow growth. First, they take a huge amount of energy to make lipids. For every two carbon atoms in a lipid, you need one ATP. So they are using a huge amount of their energy, not for making more cells like the organism that I originally was trained under, *E. coli*, but rather to make these lipids.

The slow growth is always talked about as a horrible impediment. It is not, at all. You just get used to it and plan experiments. You don't do linear science. As I did as a graduate student, you don't walk into the lab and say oh, I wanted to do this, grow the culture at noontime before you go to lunch. You do the experiment. And then the next morning you look at the results and plan the follow-on experiments. We would not make much progress in my lab if we did it that way because we're talking about a month in between experiments. So we plan sequences of experiments.

Mycobacterial cells are hideously impermeable. Compared to *E. coli*, they are a hundredfold less permeable to compounds to get in. That means nutrients, including cations and anions. Phosphate, calcium can't get in. They get in very slowly. But impermeable cells means that they're resistant to disinfectant. They're resistant to chlorine, chloramine, chlorine dioxide, ozone, and a variety of other compounds, including glutaraldehyde, which is used commonly for sterilizing bronchoscopes.

Rather than float around in the water, if this were a reservoir of one of the heater-

coolers, we would all be stuck to the wall. That's where the mycobacteria are. If you collect a liter of water, you'll find some mycobacteria. But if you swab 1 cm^2 , smaller than a postage stamp, you'll get upwards of 10,000 mycobacteria per square centimeter.

In a heater-cooler, the majority of the mycobacteria are on the surfaces of the pipes and the reservoir. Now, those are not going to be aerosolized because they're fixed there. We worry about aerosolization of those in the water. So we have two problems. One is to disinfect the water to knock the number down that are going to be aerosolized, but then the mycobacteria come back because there are those in the biofilm that now inoculate, so to speak, to use a microbiological term, the water.

So they prefer adherence and biofilm formation. They grow on low concentrations of organic carbon. They don't have sophisticated growth requirements because these are natural organisms that grow in rivers and streams. They grow slowly, and the advantage of adherence is you don't get washed away. You stick to the surface, so they're on rocks. If you want a sample from your local creek, swab a rock in the creek and you'll find mycobacteria, particularly at the air-water interface.

They grow under reduced oxygen concentrations. Air is 21% oxygen. Mycobacteria grow equally well at 12% oxygen and continue to grow at 6% oxygen, albeit at about half the growth rate. That means that stagnation in which oxygen concentrations fall is not a problem. They're perfectly happy. That's in common with many other waterborne pathogens, of which nontuberculous mycobacteria are one. *Pseudomonas* is an example of another. *Acinetobacter* is another example. *Stenotrophomonas maltophilia* is another example. Those are the emerging pathogens because we've created a wonderful

environment, drinking water systems, that select for those disinfectant-resistant organisms, and they're all disinfectant resistant.

The hydrophobic outer membrane -- and I'll show a figure later on -- are concentrated in aerosols, and that is, I think, one of the key factors that's influencing our discussions today.

Where do we find nontuberculous mycobacteria? Natural soils and waters. Peat, p-e-a-t, the stuff that you get at the Home Depot and Lowe's and other places. That's sphagnum vegetation. You can see it in New England. You see it throughout Finland. When I was in Finland, we got a water sample from a sauna. Unlike here, after the meeting, you go to the sauna. Well, we didn't go to the sauna here, but that had a million mycobacteria per mil in the water that we were pouring on the hot rocks to make a nice steamy aerosol. The northern tier of states, the piney forests in Europe and the United States, are rich sources of mycobacteria, particularly in the drain water and the water that is used for drinking water.

They're found in commercial potting soil. They're in drinking water distribution systems. In fact, mycobacterial numbers increase during traverse in the drinking water system. The disinfectant kills off all competition. So now they have all the organic matter they need to grow on in that system.

They get the premise plumbing. They love premise plumbing. And if you think about it, and I've thought about this a lot, premise plumbing and heater-coolers are the same: closed systems, pipes, heated water, circulating water. So what we know about premise plumbing we can apply to heater-coolers and vice versa. Showerheads are proven sources

of mycobacterial infection. But it's not just showerheads; it's a lot of other things in households.

Water heaters, where you heat the water, are sources for amplification of mycobacterial numbers, *Legionella* numbers, *Pseudomonas aeruginosa* numbers. We are guided to reduce the temperature of our water heaters. That will save energy; we want to save energy. That's good. If your water heater temperature is 125 degrees Fahrenheit, your water heater is a mycobacteria, *Legionella*, *Pseudomonas* culture factory. The organisms are growing in that. If your hot water heater is at 130 degrees Fahrenheit and above, that's 55 degrees centigrade, you'll have fewer mycobacteria.

In a trial that we're conducting right now in Philadelphia with a group of slender, older, taller women who are all infected with the same clone of *Mycobacterium avium* that is in their drinking water supply -- they're in the city, the town of Wynnewood in Montgomery County -- a number of our collaborating women have turned up their hot water heater, and slowly but surely we are getting rid of the mycobacteria in their homes.

Our patients, particularly this group of women, are innately susceptible. That means that they can be infected over and over again, and they worry about that. They worry about mycobacterial exposure. So one of the things that we've been able to do is to say these are the things that you can do to reduce exposure. Now we run the risk of scalding, but in terms of being exposed to mycobacteria, it's an easy decision for these individuals to make.

We had a couple in Florida -- and my technician who does mostly all of our primary isolation, Myra Williams, came down the hall and she said Joe, take a look at this plate. And

I looked at this plate, and it had a confluent growth of more than 10,000 -- and this is a Petri dish which is 100 mm in diameter, 10 cm. It's a pure culture of the mycobacteria, and I'm pretty sure it's the one infecting this couple. A husband and wife are both infected.

So I have been contacted by their son, who is being a wonderful son and said mom and dad have this and I'm wondering about what's going on. I called him, and I said where did you get this particular sample? And he said it was from the water tap in the refrigerator. You know, you have a little tap. You can get ice there, too. Don't. Do what this young engineer did. He pulled the back of the refrigerator off and sent us the entire water unit. It had 100,000 mycobacteria per square centimeter in the big storage tank. It's a wonderful place. It's heated, the water is heated before it's cooled because it's in there with all the big machines that make the box cold, but they generate heat. If you've ever put your foot or, as we do in my house, we put our wet tennis shoes there, and they dry right off.

Hot tubs. Oh, hot tubs. Think about it. A big thing of water that isn't well chlorinated, that puts air bubbles into the air as droplets and a wonderful mist. Get rid of every one. Hospitals should get rid of every therapy pool. I'm being a little adamant and dramatic here, but quite frankly, we are surrounded by aerosols.

Humidifiers. How many of you have a humidifier at home that you move from room to room and you may have used with your children, as I did, because they ended up with a croupy cough? They are wonderful generators of mycobacterial aerosols. We've done some measurements from 1,000 mycobacteria per mil of water, which is pretty typical. Twenty thousand mycobacteria per cubic meter were aerosolized in 10 minutes in a room

that's 30 cubic meters.

Premise plumbing, as I've said over and over again and I'll keep repeating it, but I can say premise plumbing and heater-coolers. Disinfectant kills off competitors. The mycobacteria are relatively heat resistant. We get 100% survival at 60 degrees centigrade. We're measuring that right now.

They grow on the available organic matter. There's a large surface area in households for mycobacteria to adhere. There's a large surface area in heater-coolers for the mycobacteria to adhere. In homes and in heater-coolers, there's regular warming of water. They grow in stagnant water. They also grow in amoeba. Our drinking water has amoebae. All of these opportunistic premise plumbing organisms are amoebae-resisting microorganisms, ARMs. They grow in the amoebae, which phagocytized them thinking they're getting a meal, but unfortunately the amoebae don't survive basically the infection and what they ate because ultimately the organisms outgrow them and the amoebae lyse.

Some numbers on biofilms because I want to focus now on heater-coolers and what we can do. There are many more cells, NTM cells, in biofilms than in suspension. We realize this now in infected patients as well. So if I find 100 to 1,000/mL of water, I'll find 10,000 in biofilms. And I can tell you I have sampled heater-coolers, and I find those very high numbers.

Biofilm cells are embedded in a matrix of polysaccharide, lipid, DNA, and protein. Mycobacterial biofilms have a lot of lipid. Cells lyse, and they release DNA. DNA is a long fibrous sticky molecule, and so it helps keep that biofilm together. Adherence, of course, for the mycobacteria prevents their cells from washing out. The matrix is impermeable to

disinfectants. Chlorine does not penetrate. This is work that was done at the Montana State Biofilm Research Institute, now some years ago. Oxygen doesn't penetrate, but as I said, mycobacteria and a variety of others of these opportunistic plumbing pathogens -- that's fine, they grow on other things. *Pseudomonas aeruginosa*, for example, uses nitrate as a terminal electron acceptor. Because they're in biofilms, no matter what you do to disinfect, the nontuberculous mycobacteria always come back.

Just to give you an idea of the magnitude of the chlorine resistance of the mycobacteria, here I'm comparing *Escherichia coli*, which is the standard in the drinking water industry. The product of the concentration in parts per million, up there at the top, times the duration of exposure in minutes required to kill 99.9% of the cells, 3-log's killing, is the CT₉₉ value. The CT₉₉ value for *E. coli* is 0.05. A standard concentration for water, drinking water disinfection may be one part per million. So that means 99.9% of the *E. coli* cells are killed in 3 seconds. That's why you can have enormous drinking water treatment facilities and run millions of gallons through because the residence time for the chlorine doesn't have to be that long.

If, in contrast, you chose *Mycobacterium avium* as your standard, its CT₉₉ value is 100 to 200. You would have a drinking water treatment system that would be the size of Virginia because the residence time in order to kill the mycobacteria is so much longer. You can use a higher concentration, which you can use in the heater-coolers. That's fine. But in drinking water we have a limit. So high concentration and a long enough dose will kill the mycobacteria.

Now, aerosolization, the mycobacteria are quite hydrophobic and are concentrated

in droplets that are spontaneously generated in water. Small droplets that you almost don't see rise in the water column. The mycobacteria do not want to be in the water, and so they essentially are scrubbed out of the water and adhere to the droplets. The droplets reach the surface and form a crater. When the crater closes, there's one force vector that's not met, and that's the one at the bottom, so we get an ejection of a droplet. It's the major mechanism for transfer from ocean water to atmosphere of various metals and others, and that's where this was first discovered and described by the late Duncan Blanchard at SUNY Albany. He taught it to my colleague Bruce Parker. Bruce taught it to me, and we measured the mycobacteria.

The mycobacteria in the droplets, which you can trap by inverting a Petri dish over the water at about 10 cm -- that's high, that's relatively high -- the concentration in the droplet is about 10,000 -- 1,000 to 10,000 times higher than in the water. So this is a preferential aerosolization of mycobacteria. It goes to an industrial technique as well, of flotation separation where you separate things by bubbling air through something and you get separation. Small droplets, and these are small droplets, are transferred then by airflow.

Here's a figure that was actually from our work. One of my colleagues at National Jewish put this together. Down here at the bottom we have an air droplet, air bubble in the water, and it's being coated with the little mycobacterial cells. The cells reach the surface, the bubble bursts, we get some droplets, but we also get droplets that are ejected relatively highly, and since these droplets are made up of the water at the air-water interface in the bubble, they're enriched for the mycobacteria. The lid of any reservoir with water in it will

have a terrific mycobacterial biofilm because that lid would exist right here where I have inhalation into alveoli. Well, they're on the inside of that lid. If there are holes in that lid and there's airflow above that, I remember my physics professor teaching me a principle where those would get aerosolized.

So how can we disinfect things? We have to think in terms of two steps. Disrupting the biofilm, because that's where the majority of cells are, and that actually determines how soon you have to disinfect. Then you can disinfect the water. Biofilm disruption requires detergent to break the hydrophobic bonds that are in the biofilms, salts to break ionic bonds that hold the biofilm together, and enzymes breaking down polysaccharides, DNA, lipids, and proteins. We've done some experiments, and it seems to work. We're killing cells in biofilms with that combination. Now, the only problems we have, of course, is the tolerance of the instrument for these different conditions.

Thank you very much.

DR. LANGE: Thank you very much for your presentation. Again, at the end of all the guest speakers, we'll have an opportunity to ask questions, so please stick around, Dr. Falkinham. Thank you very much.

Our second presentation will be Dr. Sylvia Munoz-Price. And, Dr. Price, again there will be a timer up there, and it will flash with 2 minutes left, yellow, and then at red we'll conclude your talk. Thank you.

DR. MUNOZ-PRICE: Well, thank you. And thank you for inviting me to speak today on this topic. I have to say that after the previous speaker, I am successfully freaked out about this issue.

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(Laughter.)

DR. MUNOZ-PRICE: So two things. First of all, actually, here are my disclosures. I'm a speaker for Xenex and Ecolab, and I consulted for Xenex and Clorox.

Number one, I rearranged my slides, so there might be some slide differences in between this slide presentation and what you have in the paper. And number two, based -- yeah, go ahead.

(Off microphone comment.)

DR. MUNOZ-PRICE: I will, certainly.

So, number two, after hearing all the discussion that occurred today, I realized that my assumption during my conversations, previous conversations with the FDA and during the preparation of my slides was wrong. And the assumption that I had prior to coming here and listening to you guys discuss was that the machine was aerosolizing organisms, and these organisms were falling into the sterile field and potentially into the open chest. That was my premise before coming here. But now after listening to you, I wonder if there are other pathways of transmission, and let me share these potential pathways with you.

So one of them could be, what if this machine is aerosolizing organisms and they are actually not falling into the sterile field but rather into other areas of the operating room, contaminating surfaces such as the anesthesia machine, the medications that will be infused into the IV hobs of the patient, etc.? Therefore, it's not a direct contamination of the wound from the air, but rather air-environmental surfaces-patient. So that's one potential pathway. And the other one that one of the previous speakers made me wonder is what if the outside surfaces of these machines are contaminated with the NTM during

surgery and then these organisms are transmitted through the hands of operating room personnel into other surfaces or devices that might be in direct contact with the patient?

So based on these additional pathways, I realized that I should share with you the other area of research that I have that doesn't have to do directly with air contamination, but rather it has to do with behaviors of OR personnel, outside of surgeons, during surgery, number one, and the degree of environmental cleaning and disinfection of the operating room.

So I'm going to share that experience with you. However, I apologize that none of the slides you have printed have this information. So you're going to need to look at me and just follow my -- what I'm going to tell you.

So, first of all, the environment in the operating room is not sterile. And actually, even though the policies of cleaning and disinfection of the environment in the operating room state that the OR shall be cleaned and disinfected in between cases and terminally, we know that that does not happen. That happens in less than 50% of instances within a 24-hour period.

How do we know that? We have used ultraviolet or fluorescent markers on surfaces of the operating room. We have placed them before the beginning of the first case and then we have looked for these markers after 24 hours. If the marker is there, that means that nobody cleaned that surface. If the marker is gone, that means that at least once during that 24-hour period there was cleaning done. And what we found is that in less than 50% of objects in the operating room, that one-time cleaning happens. So let me rephrase that. In more than 50% of cases, the objects in the operating room are not cleaned or

disinfected within a 24-hour period, despite of what the policy says.

Number two, hand hygiene in the operating room by a staff that are not surgical providers, it's almost nonexistent. And that includes anesthesia providers. What is worrisome about anesthesia providers is that they have multiple contacts during a surgical case in between anesthesia machine, the surfaces of the patient, including the intravenous hobs, and they actually inject medications into these IV hobs. And we know that in addition to hand hygiene not being present, the hobs are not disinfected throughout almost the entire surgical procedure in most cases.

The other piece of information that I wanted to share with you before I go into the slides is that there is data published that shows that contamination of the anesthesia machine and surfaces of the operating room is associated with contamination of the intravenous hobs. So if the patient goes into an operating room that has a contaminated anesthesia machine with bacteria X, that bacteria X has a high probability of ending up contaminating that hob, the intravenous port of that patient, coming into the operating room.

So those are the points that I wanted to make before starting my slides. I hope they are clear and argue that the potential for going through those pathways that are not necessarily related, directly related with air contamination falling into the sterile field is fully necessary. But you might be contaminating the air, then the environment, and then the patient. Not necessarily through the wound.

Okay. So what I came prepared to tell you about is my personal experience with air contamination, which is not necessarily -- it did not happen in the operating room, but

outside the operating room with *Acinetobacter*. So I'm going to give a brief review of the literature. Then I'm going to go into my personal experience and some insights on why these experiences might have happened.

Okay. You've kind of heard this already. There are two methods to measure air contamination. One is by leaving an open Petri dish on surfaces within a room. You wait an X amount of time after leaving that Petri dish open, and then you go ahead and swab it and culture it. The other which you measure air contamination is through active measures that we did not use at my particular hospital.

All right. So let's go into the review of the literature. Actually, the first paper that shows contamination of the air via *Acinetobacter* is from the University of Iowa, which is the hospital of one of the speakers tomorrow. So in the University of Iowa, they detected 24 patients that acquired a type of *Acinetobacter* within a 4-month period. So there was a small cluster of patients, an outbreak with this organism, and they performed a retrospective review of these cases that showed that most of these patients were using a room humidifier. They actually cultured the water of the humidifier, and they found *Acinetobacter*, the same *Acinetobacter* present in that water.

They also did cultures at different distances, different distances of the humidifier, and during different times of exposure, and they found that the closer the plate was from the humidifier, the higher the growth you were going to find of mycobacteria -- of *Acinetobacter*. I'm sorry, I'm saying mycobacteria, but it's *Acinetobacter*. And the durations of exposure also matter. It's interesting that from this paper in 1977, they were already recommending that hospitals must be aware of the potential dangers of cold air humidifiers

in an inpatient setting and serious considerations should be given to the abandonment of these devices.

So this is another experience from a decade later, published in the *Journal of Hospital Infections* (1987). And basically, they had several cases of *Acinetobacter*, and what they decided to do was culture the air with, again, open Petri dishes looking for *Acinetobacter* contamination within 3 m of the colonized patients. And, of course, they found that 20% of these plates were positive for *Acinetobacter*.

A similar experience in Hong Kong, published in 2001, in which they found that air contamination was present in the surrounding air of patients infected or colonized with *Acinetobacter*.

I found a paper that was published, and it had to do with MRSA, not *Acinetobacter*. But what I find interesting about this paper is that actually there is a temporal association with something that happens in the room of the patient. And as you see here, higher concentrations of MRSA are found after bed-making and not just associated with bed-making, but also with the presence of infection versus colonization. So after bed-making, the amount of MRSA in the air goes up, and it goes up predominantly in patients that are infected and less so in patients that are colonized.

A similar experience in a burn unit in which they found that 16 isolates over a 6-month period, 16 isolates of air isolates were positive and clinically related also for *Acinetobacter*.

Okay. So that's a brief review of the literature in regards to air contamination with *Acinetobacter*. So now let me tell you about my personal experience.

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When I arrived to this large county hospital in Florida, in South Florida, there was a problem with carbapenem-resistant *Acinetobacter* in our inpatients. We had hundreds of cases per year. So in infection control, there are three main pathways for transmission of these organisms from one patient that is infected or colonized to patients that are negative. See, here's the positive patients, here's the negative patients. There are three pathways that are well proven. One is the healthcare worker's hands, the other one is the shared equipment, and the other one is the healthcare environment.

But what if there is a fourth one? What if the air is also involved on this horizontal transmission of organisms from patients that are positive to patients that are negative? So we went ahead and started culturing the air, and we published our findings in *Critical Care Medicine* in 2013.

This is the layout of our trauma ICU, and this ICU is an open unit. It doesn't have physical boundaries in between patients. The other interesting thing is that during these air cultures during this project, the HVAC system of this unit was down. So what they started doing, the facility, was they put big fans on the units in order to provide some comfort to the patients.

So what we did is we did the passive method of culturing. So there you go. One is our infection preventionist with the open Petri dish, and you see that location of the dish is right next to the ceiling tiles and within a couple of feet from where the patient's head should be located. We also cultured the grilles of the vents, and we left plates open to the area where the air was circulating into the rooms. This was to make sure that the air that was coming in -- well, the HVAC system wasn't working for much of the time with this

project, anyway, but we wanted to make sure that the air coming in potentially was not contaminated.

So this is what we found. So of patients that were positive for *Acinetobacter* -- so the rooms had *Acinetobacter*-positive occupants, 21. We found that 52% of these samples had positive air for *Acinetobacter*. Now, out of the patients that -- the rooms that were occupied by *Acinetobacter*-negative patients, we found that 0% of these air samples were positive. Interestingly, we even found *Acinetobacter* in one out of the seven air samples obtained from rooms that were not occupied by anybody, which makes you wonder how far these organisms travel, right, in an open unit. All the isolates were clonally related in between patient's isolates and air isolates.

The second question that we had is was, well, are these just transient contaminations of the air within a room, or does this actually happen over consecutive days? Furthermore, is there a role of the source of colonization of the patient with the degree of contamination of the air?

So we were comparing patients that were colonized in the rectum with *Acinetobacter* versus the respiratory tract versus other sources. And we looked at the behavior of this contamination of the air over time, up to 10 days, and what we found is that, overall, 21% of these days had air positive with the same *Acinetobacter* than the patient's isolates. If you look at the source, rectal contamination with *Acinetobacter* had 26% of days that were positive compared to 11% in the respiratory tract, which was against what we were expecting, right? We were expecting that the air contamination from an airway was going to be higher than the contamination in the stool. But we found the

opposite. And this has been questioned several times by different colleagues. Probably what's happening is that the respiratory contamination of these patients is occurring in patients that are mechanically ventilated, because these were the only ones that were tested for colonization in the respiratory tract.

So it is not that having contaminated stools will aerosolize more than from the respiratory tracts, but rather we have a closed circuit in mechanically ventilated patients, and therefore we're seeing less air contamination when they're mechanically ventilated.

I guess a point that is relevant to the discussion of today is that what we found is when we looked at concomitant contamination of the air and environmental samples, we see that the more contamination of the air, the more contamination of the environment; the less contamination of the air, the less contamination of the environment. So they seem to go together. They are not isolated events, at least outside the operating room. And here, what we were basically comparing is the degree of concomitant contamination of air and environment among rectal colonization versus respiratory colonization. The behavior of air and environment goes together.

So one more point that I would like to make: When we look at the same degree of contamination of the air and the environment with other enterics, like carbapenem-resistant Enterobacteriaceae and KPC producers, what we found is that there is a difference compared to *Acinetobacter*. The degree of contamination of the air was only 4% with enterics. The degree of air contamination if the organism was present in the respiratory tract was also 4%. And if you look at the environment, it was minimal (1% from the respiratory tract and 4% in the rectum), which compared to the other organism

Acinetobacter is much less. So this is telling you something; this is telling you that it's not only the source of colonization, but also the type of organism that you're talking about.

The group at the University of Maryland, after I did these initial studies with contamination of the air, went ahead and did the same studies in their ICU. They actually used an impactor, so they used an active method for detecting contamination of the air, and what they found was something that I was not expecting. They found almost no contamination of the air among their *Acinetobacter*-positive patients. And actually, I wrote an editorial on the topic because it made no sense to me that there was such a marked difference between my findings and their findings. Why was it that they were not finding the same degree of contamination of the air? What could it be?

So I discussed these findings with a person in the industry that does a lot of HVAC maintenance, and his insight was very telling for me, especially in my situation back then in that county hospital without major economic resources. So what he was telling me that the degree -- the amount of money that it takes for a hospital to keep up with their ventilation and cooling, it's markedly high. And you see there the pieces of the pie that have to do with cooling and ventilation, and that has to do with the amount of money that goes into keeping up with the systems.

So here are his comments, which I thought were very interesting. "Most facility directors do not make the connection between poor HVAC operation/maintenance and the higher risk of HAI." And the rest, in summary, is that there is no upkeep of these HVAC systems in the way that the policies might indicate.

Lastly, I wanted to comment on this poster that was recently presented by the VA in

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Pittsburgh that basically looked at the amount of viable particles in the air after shutting the HVAC system in an ICU. They were actually able to measure it before and after the shutting of the system, and they were able to determine that the amount of viable particle counts goes up markedly after the HVAC system is shut down.

See, the problem with the HVAC system is that it's something that we can't see, right? We are assuming that it's happening as per policy. It is not like the environmental cleaning and disinfection or hand hygiene that we can actually measure ourselves in infection control. The functioning of the HVAC system is something that we assume that the facilities do because they have to. But let me tell you, it's not necessarily the case. We should not assume that that really happens.

So the take-home messages from my presentation. I think the environment in the operating room and the behavior of operating room personnel should be considered in the pathway for transmission of *Mycobacterium chimaera*. The ambient air contamination with pathogenic organisms occurs, but differs based on the organism. And as the previous speaker mentioned, *Acinetobacter* and mycobacteria might differ from other organisms.

And I ask you to please consider that the ambient air contamination might be associated with the functionality of the HVAC systems, and do not assume that the laminar flow or the HVAC system in hospitals is always functioning as per policy.

I think those are the main messages that I wanted to share and convey with you today. That concludes my presentation.

DR. LANGE: Thank you very much. And again, if you'll make the presentation available to the FDA for distribution.

We have a unique opportunity as being a little bit ahead of time. And so that will allow us the opportunity to ask the last two speakers -- I'll ask them both to come to the table. Dr. Falkinham and Dr. Munoz-Price, if you'll come here. And let me open the Panel up for some clarifying questions again.

Dr. Yuh.

DR. YUH: Thank you.

This question is for Dr. Falkinham. A wonderful presentation. Can you give us an idea of the antibiotic susceptibility of NTM versus other common pathogens that we see?

DR. FALKINHAM: Okay, thank you. Because of the thick outer membrane, mycobacteria, for the most part, are resistant to most commonly used antibiotics. They are susceptible to a number of antibiotics. Leading the charge is clarithromycin, azithromycin. Rifampicin and its relatives are fairly effective. Ethambutol, which is not a strong antimicrobial, antimycobacterial drug, inhibits the formation of the outer thick layer. So it's used in conjunction with other antimicrobials, such as clarithromycin, because it makes cells more permeable. So most of the patients are getting a cocktail of three or more antibiotics.

DR. YUH: So where this is going is that if we identified a patient subset that was at high susceptibility for incurring an NTM infection via cardiac surgery, is it practical to give them a short course of any of these antibiotic regimens, or is it reasonable from an antimicrobial perspective?

DR. FALKINHAM: I don't know what the cardiac surgeons feel about this, but we certainly -- when a patient goes into surgery and we have a positive nasal culture for *Staph*, they're treated with mupirocin or an anti-*Staph* antibiotic. When we did a study of HIV-

infected patients, we discovered that the gay men's health network had published information on effective antimycobacterial drugs, and many HIV-infected patients were taking effective antimycobacterial drugs prophylactically, even though they didn't have *M. avium* infections, but felt that they would -- because the organisms are everywhere -- get exposed and come down with *M. avium* infection. So I would ask the surgeons first, but my inkling would be that that preventative therapy might be worthwhile.

DR. LANGE: Dr. Allen.

DR. ALLEN: Yeah, it's petrifying to listen to your talk.

(Laughter.)

DR. FALKINHAM: Sir, I only get invited to places once.

DR. ALLEN: Yeah.

(Laughter.)

DR. ALLEN: So I guess my question is to maybe perhaps bring us back down to earth, because when I listened to your talk, it's the world is ending and I'm going to be devoured by *Mycobacterium*. I'm afraid to go take a shower tonight.

(Laughter.)

DR. ALLEN: But let's be realistic about what we're dealing with and how actually big of a problem -- I understand there are 80,000 NTM infections, but in the scope of things, how big of a problem is it? That's what I'm having a hard time wrapping my head around. So if we're going to ask companies to fix a problem or we're going to try to fix a problem, do we spend a trillion dollars to fix a very, very tiny problem? Or, you know, what is it worth to us to do that? I have to get a handle on that, and I'm not sure I still have that yet.

DR. FALKINHAM: This is an emerging problem that wasn't anticipated, and I don't think we know the full spectrum. We don't know how many cases there are. I'm aware of a number of hospitals who are going back 5 years now, because we have a case that in between surgery and the appearance of the mycobacterial infection was 4 years. So I don't know how many we have out there. I did quickly look, after I saw the paper in October '15, of how many transplants we perform in the United States annually. It's about 2,000, and we have a few infections.

So the judgment of whether we need to go spend lots and lots of money to change machines so they have no water in them, or to move machines out of the OR with the attendant problems that that creates in terms of heat transfer of something that warms and cools, I don't know whether that's going to be justified or not.

DR. LANGE: Dr. Givner.

DR. GIVNER: Dr. Falkinham, let me ask you two questions. One is I'd like to know about the older, slender, taller women in terms of why are they at higher risk for NTM infection? That's very curious.

DR. FALKINHAM: I think Chuck Daley can answer that question better than I can. But some of them are carriers of a cystic fibrosis mutation. They've been healthy all their lives, but that may be 10%, 15%. Some may have alpha-1 antitrypsin deficiency. That's a small percent. But for the most part, they lack risk factors and were discovered in Philadelphia and described initially because they lacked all of the classic risk factors for mycobacterial disease.

DR. GIVNER: Thank you. And my second question is in follow-up to Dr. Allen's

question, but I guess even more basic is can/do the healthcare devices with the IFU being followed prevent NTM colonization?

DR. FALKINHAM: I'm sorry, could you repeat?

DR. GIVNER: Can or do the healthcare devices being used with the IFU being followed prevent NTM colonization of the heater-cooler devices?

DR. FALKINHAM: They will not prevent colonization because that could happen in a variety of different ways. But if you disinfect monthly and empty and refill the heater-cooler weekly without a disinfection cycle, every time you empty a heater-cooler you essentially remove 10% of the suspended bacteria. So you reduce their numbers when you refill it with sterile distilled water. So you do have a way of controlling and keeping the numbers way down to the 100 or less colony forming units of mycobacteria per milliliter.

DR. GIVNER: So do the current IFUs that are recommended by the companies do what you're saying these other things can do?

DR. FALKINHAM: I haven't looked at every one of the protocols for disinfection, nor have I measured them. The ones that I have looked at appear to meet my standard of at least keeping -- getting rid of the majority, 99.9%, after disinfection, and then that number stays low for about a month.

DR. GIVNER: Thank you very much.

DR. FALKINHAM: You're welcome.

DR. LANGE: Dr. Zenilman.

DR. ZENILMAN: Yes, I have a question for Dr. Munoz and also for Dr. Falkinham, but also let's actually step back for a second and recognize that I absolutely agree with the

speakers that NTM infection is an understudied and under-resourced area. But my belief, and I believe it's shared by most clinicians in this, is that the vast majority of these infections are coming from people who are coming from environmental exposures outside the operating room, despite what -- and I think we're focused here on a specific topic.

So for Dr. Munoz. You presented, you know -- and a lot of the data you're showing basically is looking at the issues of contamination in the OR by a variety of organisms. The studies that you showed are pretty much more standard pyogenic bugs. But I think you raised an interesting issue, which is the number -- the area of contamination, that the potential for contamination by the aerosols in the NTM setting would be, you know, to other parts of the OR: anesthesia machines, potentially the lights, and so forth.

However, as far as we know, recognizing the potential of underreport, are there any other NTM infections acquired in surgery, in surgical situations outside of the ones that we're seeing here? So, for example, are there any cases that you're aware of where an OR is used for a cardiac surgery case and then another case afterwards has an NTM infection probably because of some type of cross-contamination?

DR. MUNOZ-PRICE: So that's an interesting question. Let me tell you my personal experience. We had a cluster of over 10 patients in South Florida due to an atypical mycobacteria in plastic surgery cases. Why did that happen? We never found out what the source of that was. But I think that the OR is an under-explored --

DR. ZENILMAN: But were those hospital -- actually, we just had a case of -- we published a series of cases in *M. abscessus* due to surgery in the Dominican Republic. We had the index case. But I think there's a series of things which happened in those cases,

usually taking fat pads or other things. Here, are we talking about hospital high-end, you know, hospital-based -- were those hospital-based cases or a surgeon center?

DR. MUNOZ-PRICE: They were in the hospital.

DR. ZENILMAN: Okay.

DR. MUNOZ-PRICE: Yes. But we never found out the source. But the point that I wanted to make is that I think that, overall, not just for mycobacteria but for other infections as well, that we don't know where they're coming from. The OR is an under-explored source of infection and transmission, and there are multiple reasons for why that might be happening. One of them is our misconception that the OR is sterile. That's one. And the other one is the fact that we cannot clearly tie -- except for these *Mycobacterium chimaera* that is exotic enough that it allows you to beam-point the source, but we cannot tie the exposure with the outcome as clearly in other type of infections that are more common in other areas of the hospital, such as *Staph aureus* or *Pseudomonas*.

DR. ZENILMAN: Right. No, I -- yeah. Well, actually --

DR. FALKINHAM: I do have a case that fulfills your criteria, Doctor. It's in a hospital in South Carolina.

Thank you, Matt.

DR. ZENILMAN: Oh, is that -- I think I'm -- is that the --

DR. FALKINHAM: It's a case in neurosurgery. A neurosurgeon operated on a woman who ultimately died, and subsequent to the surgery and her death and treatment was the discovery that the cardiovascular surgeons had a *Mycobacterium abscessus* problem associated with surgery, and she died of *Mycobacterium abscessus* infection.

DR. ZENILMAN: Right. So I'm aware -- I think I'm aware of that situation. But I think, interestingly enough, those do not -- they were clearly not using these -- were they using the devices that we're asked to opine on, in those situations?

DR. FALKINHAM: I think they were.

DR. ZENILMAN: Okay. Another question. I had a group of questions for Dr. Falkinham.

DR. LANGE: Okay, real quick and then go to --

DR. ZENILMAN: The other thing is, I'd be very careful about recommending prophylaxis in this situation because, you know, for everybody -- in answer to Dr. Yuh's question because, first of all, the drugs -- there's a variety of resistance profiles. There's a variety of toxicities. These patients have multiple things going on, and I think we're still dealing, you know, with the situations that you brought up. For example, HIV, transplant, and other things are situations where there's very clear clinical indications for prophylaxis. I don't think this -- I think I would not go there yet.

DR. LANGE: Thank you.

Again, for continuing clarifying questions. Dr. Hopkins.

DR. HOPKINS: Dr. Falkinham, are these NTMs with the thicker cell walls and the layer outside the cell membrane, are they more resistant to UV sterilization than other bacteria?

DR. FALKINHAM: No, they're not.

DR. LANGE: I have a question. Have you all randomly sampled the units, that is, cooler-heater units or heater-cooler units, either one, and determined what percentage of

them have NTM infections? The first question.

The second is -- I want to make sure I understand. Once a unit is contaminated, you had implied that you really can't disinfect it. What you can do is just keep the count down. So if you'll address both of those.

DR. FALKINHAM: I've only sampled a limited number of heater-coolers, and all of them had mycobacteria, all of them had *Pseudomonas aeruginosa* and a variety of other organisms, including *Stenotrophomonas maltophilia* and *Acinetobacter* as well.

With regards to individuals who have sent me heater-coolers for me to do experiments with, I have told them that they have made a donation to the Virginia Tech Foundation because we don't have to buy one to do the experiments, and they will not want one back after I've been inoculating it with 100 million mycobacteria per milliliter, an unrealistic number, but if we're looking for a worst-case scenario, that's the worst-case scenario.

So what I've been thinking of, and it is an ethical responsibility on our part, everything that comes out of my laboratory is autoclaved. Now, I realize now that with these heater-coolers, I'm going to be autoclaving anywhere from 2 L to 22 L of mycobacterial-laden water. We can do that. It will take us some time, but we can do that carefully and safely. And then I was really pleased with the comment about taking the pipes out and cleaning the pipes. We will dismantle those instruments. I think that's our burden, and it's just because I can't leave them sitting around.

DR. LANGE: Yes, sir.

DR. ARDUINO: Joe, can you give them -- this is Matt Arduino -- give them an

explanation? Since we're talking biofilms here, explain regrowth to the members of the Panel.

DR. FALKINHAM: Yes. A good point, Matt.

You can disinfect a hospital by hyperchlorination and super-hot water. You can get rid of all the mycobacteria in the water in a hospital or a heater-cooler, as we've done, and don't find any with some degree of precision, and then within a month they come back. And there's an old story in mycobacterial lore about them coming back. So what you've left is this film that's got a lot of organisms. It's not releasing many.

We, in fact, know more about adherence than we do the release of organisms from a biofilm, but the biofilm does break down to some extent, and those organisms then are entrained in the water, and they grow and the numbers increase over time. And that's what we mean by regrowth. In the drinking water industry, you can take a sample from the treatment plant and show that there are very few mycobacteria, and then you can go to a house at the end of the waterline and take a sample, and you realize now there are more mycobacteria there or more *E. coli* or more Pseudomonads. That's their drinking water's special use of the word "regrowth." It has a unique meaning in the drinking water industry.

DR. LANGE: Thank you very much.

Raymond.

MR. McGLAMERY: So to sort of dumb this down a little bit for myself, it sounds to me like, from your presentation and from your observations in the OR, that as these mycobacteria proliferate and grow and change, we should expect more infections regardless of the heater-cooler devices. Would that be safe to say, I mean, that these will

grow in number as time goes by?

DR. FALKINHAM: That's the troubling picture of the data, that the increase in the number of infections not associated with heater-coolers is increasing in the United States and Canada at about a 10% rate every year. Right now we're looking at a doubling, if not more, of the number of cases in the Toronto, Ontario area that's just appeared over the last 6 months and I became aware of it. So we have those.

And I think it's -- I think we need to look at other organisms as well. You spoke about *Acinetobacter*. I now sort of have an idea of maybe where the *Acinetobacter* infections occurred to our troops in the Middle East. They may have been humidifying the climates that they were in, in that region at the dry, dry times. As I said before, throw out all your humidifiers, throw out all your hot tubs if you're worried about this.

We also face the fact that in 2025, 60% of U.S. citizens are going to be over the age of 60. Now, we worry about that in terms of Social Security and other things. I worry about that in terms of public health. How many more slender, taller, older women?

DR. LANGE: Dr. Sylvia Munoz, if you will turn off your lectern just a second until someone asks.

Dr. Givner.

DR. GIVNER: I know we're going to be hearing from Dr. Sax later about the results of his trial published in *Clinical Infectious Diseases*. But with your expertise, Dr. Falkinham, I'd like to know what you think of their finding that air sampling cultures were positive only when the heater-cooler unit was running, but not when it was turned off. What does that say to you about the pathogenesis or a source of the infections in these patients that he

described?

DR. FALKINHAM: Their approach is the same as mine. I measure aerosols when the machine is not operating. I UV-irradiate the room before and after every collection. I collect for 60 minutes. So I collect a sample when the machine has not been -- when the machine is not operating but is in the room, and then I turn the machine on under its kind of normal working conditions and we collect an aerosol. So I think that's appropriate. It leads us directly to the heater-cooler.

DR. GIVNER: So you had the same findings as Dr. Sax does?

DR. FALKINHAM: No, I do not have the same findings. Our experimental approach is the same.

DR. GIVNER: What I'm asking, I'm sorry, is do you find the NTMs only when the unit is on, not when it's off, when the unit has been in use for a while?

DR. FALKINHAM: No. I, in fact, find mycobacteria in the room without the instrument in there. Because we are a mycobacteriology lab, we have mycobacteria floating around all over the place. So we have a background level of microorganisms, and if anybody wants antibodies against mycobacteria, you're welcome to collect a sample. I probably have the highest titer in the world.

(Laughter.)

DR. LANGE: Mr. Stammers.

MR. STAMMERS: Thank you.

A very quick question and then -- excuse me. A quick comment, then a quick question for Dr. Munoz-Price. These devices are used -- the heater-cooler devices are used

in other procedures in an operating room, and just listening to your ambient air contamination issue, I wonder if it would be worth going to look at patients undergoing liver transplants that have these same devices that are used during their procedures. These are big, vascular, open wound, similar to cardiac surgery. I wonder if we should epidemiologically look at other areas as well.

But the question I have -- you bring up very eloquently the importance of a strict sterile technique and that the anesthesia machine and individuals may be contributing towards certain infections because of their interventions. They are located underneath the laminar flow and that doesn't move them outside. But the laminar flow devices in an operating room do include their devices.

But the heart and lung machine -- and again, if you look geographically at what's happening in the operating room, I'm not sure if individuals are aware that the actual oxygenator itself contains a tank, a reservoir that's 4 L in capacity that literally half of the patient's blood is sitting in at any particular time. That is open to atmosphere. That has anywhere between a 1 cm and a 2.5 cm hole in the top of it for venting. And the majority of procedures that are being performed use normal open heart surgery, and it's outside of the ambient realm of laminar flow that's coming down. Could that be a source or worth looking into as well, since it's just this large hole in all of our devices, the majority of our devices, that is outside of the flow patterns?

DR. MUNOZ-PRICE: Well, more than three questions there. Okay, let's see. The anesthesia machine might be underneath the laminar flow, but I want to remind you that that doesn't mean that the whole anesthesia working area falls underneath the laminar

flow, because the anesthesia working area does not only include the anesthesia machine, but rather it goes all the way to the anesthesia drawers where they keep all the medications, the IV drugs. And the area, if that's the patient's head, here is the anesthesia machine. The IV pumps are going to be over here, and the drawers are going to be over there.

So you're talking about a large area, and it might not all be covered by the laminar flow. And the problem is that anesthesiologists have a very high frequency of touching: contact with the anesthesia machine, the patient, the floor, picking up things from the floor and going back to supposedly clean areas and the drawers, so -- without hand hygiene in between these interactions. And we're trying to change that behavior, but it's quite hard because there is not a link, in their heads, of their actions during surgery and infections down the road. So that's Point Number 1.

Point Number 2. I think that the fact that we do not know of NTM infections or *Mycobacterium chimaera* infections among solid organ transplant patients might not be because they don't exist, but because Hugo Sax did not look at them necessarily in solid organ transplant recipients and therefore nobody has looked into that. Remember that having a negative culture does not mean that patient is negative for mycobacteria, but rather you have to wait 14 days and get that special culture that is probably not being ordered. So yes, the answer to your initial comment is yes, we should look into that.

And the third question?

MR. STAMMERS: The third question. You know, perfusionists are the ones who are handling the heater-cooler, the HCD, then they move, just like the anesthesiologists handle

medications, drugs. They're also above a 4 L reservoir that can contain half the patient's blood volume for hours on end. That's outside of the laminar flow area.

DR. MUNOZ-PRICE: It absolutely can be the source, especially because other than the surgeons, I did not observe hand hygiene in most personnel that are surrounding the sterile field. They go from surface to surface without hand hygiene.

DR. LANGE: Yes, sir.

MR. RILEY: Thank you very much.

DR. LANGE: Alfred, if you'll turn your speaker off, please. Sylvia, if you'll turn yours off. Thank you.

MR. RILEY: Jeff Riley.

I don't know you, Dr. Falkinham, but I feel compelled, as a representative of the perfusionist community, to share with the Panel that we met Dr. Falkinham at our international conference earlier this spring, and he made a great presentation there, and it didn't scare us because we work with cardiac surgeons every day. So we don't get scared very easily.

(Laughter.)

MR. RILEY: We built an educational course around that presentation and the FDA's guidelines. I just wanted the Panel to know that the two professional organizations for perfusionists take this very seriously and have identified it as an educational objective and built a post-graduate course around it. And to Dr. Munoz, 50% compliance with cleaning surfaces within a 24-hour period in the OR, is that what I heard you say?

DR. MUNOZ-PRICE: That is correct. Less than 50%.

MR. RILEY: I think that's high. I don't think the compliance is that high.

DR. MUNOZ-PRICE: Yes, thank you very much. Just so that you have a point of reference, the other day I asked the VP of facilities that is in charge of the operating room, I asked him how often do you think the environmental surfaces in your operating rooms are being cleaned? That's it. This is a very high-functional hospital. And he said, well, the policy says that it should happen in between each case. Therefore, it should be 100%. So we bet on the percentage of cleaning over a 24-hour period of his operating rooms, and the percentage of cleaning was actually 19%. So you are correct, yes.

DR. LANGE: Any final question?

(No response.)

DR. LANGE: If not, a couple things. One is, again, the speakers this morning from industry were terrific. You all were terrific as well.

Dr. Falkinham, after your talk, if nobody shakes your hand afterwards, it's self-inflicted.

(Laughter.)

DR. LANGE: We're going to take a break. We're going to resume at 3 o'clock and have Dr. Sax speak with us.

Thank you all very much.

(Off the record at 2:40 p.m.)

(On the record at 3:00 p.m.)

DR. LANGE: We will now have presentations from our remaining three speakers. The first speaker is Dr. Hugo Sax, who will be telling us where it all started. And I'd like to

remind the Panel that there will be time for questions after the three speakers.

Dr. Sax, thanks. You got here from Zurich before I got here from El Paso. So thank you very much.

(Laughter.)

DR. SAX: Thank you very much for the invitation. And it's exciting for me to be here and see how everyone tries to make sense of this new challenge for patient safety. I would like to say that I have no conflict of interest to declare. And then I would like also to say that I'm grateful to my team and everyone else that was involved in making sense of this.

And one word to the extent of the problem. We have seen that the period that our cases in Zurich, the six patients that got infected with the *Mycobacterium chimaera* in heart surgery were in a period where 3,000 heart surgeries were performed, and all of these 3,000 patients got really helped by this incredible technology of being operated on their heart. And at the same time, and this is what I would like to point out, there were probably 150 patients getting surgical site infections, and you know that this is a great problem we are fighting. And now when we talk about this very specific problem of *Mycobacterium chimaera*, we don't want to forget that there are many other challenges linked to healthcare and infections with bacteria that we have known for a long time with *Staph aureus* or gram-negative germs linked to all kinds of risks that we should mitigate.

So this all started with two cases, and actually, when my colleagues wanted to submit these two cases for publications, this was the first time *Mycobacterium chimaera* was found to infect patients in heart surgery and endocarditis and systemic infections. The peer reviewers asked if there was not a link, and my colleagues didn't have this in mind

because the patients got operated on 2 years apart. So how can you get the same sort of infection 2 years apart and how should that be linked?

But then the microbiologists in Zurich came up with a test that took it from *intracellulare* to genome typing on these two -- on this *Mycobacterium chimaera*, and they found that they have the same patterns. So there we were, two patients infected 2 years apart having the same bacteria, being infected by the same bacteria. And that's where my team came into play in infection control, and we did what we usually do, an outbreak investigation to see what is the bacteria. Where does it usually live? And we found out that it lives in water. So we went to the OR, and we went through the hospital to see if we can find a source where patients are exposed to water during their stay at our hospital.

And I'll quickly tell you these two cases. So one was a mitral annuloplasty ring, the diagnosis of systemic sarcoidosis with unspecific multi-organ granulomatous inflammation, and the patient had been treated for 1 year with immunodepressive medication, with prednisone, and he got worse and worse, and then he came back to the hospital. And that was the first of the two cases. And when he got reoperated, the material showed foamy macrophages and necrotic valve tissue. And then the pathologist actually discovered the problem by seeing acid-fast bacilli that are typical for mycobacteria, and they could be grown then, and the diagnosis was made.

So there was the second case in a 51-year-old man, and he had composite graft for aortal dissection and was readmitted for fever of unknown origin. And there was a whole workup, and in this workup from bone marrow, *Mycobacterium chimaera* was found and he was treated, but he died of splenic rupture.

So I was talking about the fact that our microbiologists found ways to type these two strains, and they were the same strain.

You know, there are -- in the test being alluded to, there are several hospital-acquired infections due to mycobacteria. On the left you see a skin infection linked to ink that was diluted with water from the tap, and you see these small red spots that are the infections, and then plastic surgery on the right and the lung infections in the immunodepressed patients.

You cannot see this slide, what is on here, but these are all infections with mycobacteria in surgery that have been investigated, and the reason has not been found how exactly this comes about.

So from 2013, we got into this outbreak investigation, and we did observations in the OR to find out what actually happened, who walked in with water, who did what, touched what, we even videotaped the whole intervention. We did interviews with people, and we did a workflow analysis. And finally we cultured all the water that we found in the hospital. There was water in heating blankets that were underneath the patients that were warmed by a water circuit. This has been mentioned already. Then the heater-cooler unit, something with this covered infection control. I wasn't aware of this, that there was water in the OR like in a device like this, my bad. And then we also thought that the patients then, when they were better, they were on the units and they showered, so we were swabbing the showerheads and we were culturing water, and we were also culturing drinking water fountains that you will see a picture later on. We saw these devices that are in every corridor, and people can have cold water there or sparkling water. They were in our

hospital installed in the ICU, and nurses used to draw water there to give it to patients because they thought it was cleaner water than just from the tap.

And what we found was actually, to our surprise, that there was *Mycobacterium chimaera* in the heater-cooler unit tanks, in the waters, and in the circuits. But we also found it in the drinking water fountains. Where we never found it, until today, was from water just out of the tap. And we sampled a lot of water. We went into the -- below the sinks. We found other atypical mycobacteria, but never *Mycobacterium chimaera*.

But because we had two different points where we could cultivate *Mycobacterium chimaera* from the drinking water fountains and the heater-coolers, our first hypothesis was that these heater-cooler units got contaminated by the water system of the hospital. We also went down to the community in town, to the water production system for the town, and tried to cultivate it there and did swabs, but we never found anywhere *Mycobacterium chimaera*.

You have seen this design, how the heater-cooler units work.

Here is a picture of the heart-lung machine with all the machinery, and you can see here the heat exchanger on the right for the patient blood circuit, on the left with the cardioplegia solution. So it's there where the water flows against the blood or the cardioplegia solution and cools it on the left and warms it on the right side.

On the right side, here you can see -- and in the middle you can see the heater-cooler unit. We use LivaNova 3T models uniquely in our hospital, and the first hypothesis was that these -- this device, that the setup with this water bottle is the overflow was important in the dispersion of the mycobacteria into the air, but I will come back to that

later on.

Here you see another picture, and you see there are many tubes coming out of the machine. We also thought about the possibility that there was splashing and splashing into the operating field, but this seemed not quite probable.

Here you see another picture of this oxygenator and temperature exchange where the water flows against the blood flow to warm, to keep it warm, and here again the point where the cardioplegia solution gets cooled by the water from the heater-cooler units.

Then we turned the heater-cooler unit upside down. I wasn't there. I don't know exactly how this was done, but we saw that water dripped out. So we learned that this whole system is actually not water tight. And you can see that -- on the upper part you see the tank. On the lower part you see some tubes. And on the left side, that's where there is the fan and the heat exchanger that gets rid of the superfluous heat.

Here is a picture of the inside of this heater-cooler unit. And it was already mentioned that there are signs of water dripping down on the floor, and one of our hypotheses was that the water -- that the water tank leaks and that there are droplets dropping down and into the quite strong airflow that is produced through the machine. You see the vent on the right side. And we dyed the water in the tank with fluorescent dye and tried to find if there was a hole and if there were droplets dropping down, and that wasn't the case with that machine, where we tried it.

Here you can see a picture of where the water is filled into the machine, and you can see that it is quite -- it's not rusty, but it's old. And you can say dirty and not clean in the sense of a surface that is smooth.

Here again, this overflow device. And I had the hypothesis that the water in that bottle gets out in the air and then would hang in the airflow. So we put it to the side, and you can see that it is clamped there, but we still found mycobacteria in the air and this was the case.

Here you see a picture of this drinking water fountain, and you can see that, against many models that are -- by water bottles that you put upside down, big bottles that you put upside down on top, ours is directly hinged to the -- hooked up to the water system of the hospital. So we didn't find mycobacteria in the water that was coming out of the wall behind the machine but only in the machine, telling you something about the need for mycobacteria to grow in stagnant water inside this machine. But actually the machine, that was perceived as being more clean water because it's coming out of a machine, is actually a production site for atypical mycobacteria.

We cultured them, several in the hospitals, and they more or less are all contaminated. And our people from hygiene, from food hygiene, because cold water is considered food, so it is subject to inspection at their authority. They never heard of mycobacteria that should be tested in drinking water, so there are no levels and no standards of how to do that.

We did these air cultures then. That was the invention of someone in my team who inserted -- we have this collector there where that aspirates 250 L of air a minute, and that goes over a culture plate. And usually we culture air if you have a problem somewhere with usual media, and he puts into this device a typical mycobacteria plate. And actually that was when we found, in September 2013 the first time, *Mycobacterium chimaera* in the air

in the operating theater, but as it was said before, only when the heater-cooler units were turned on. The cultures always for *Mycobacterium chimaera* were always negative when they were turned off.

There were, however, many atypical mycobacteria, and you can imagine that we did a lot of culturing up until now, several hundreds of cultures, and we often found other non-typical mycobacteria in the air where we have no idea where they come from. There is no obvious source around. Against these *Mycobacterium chimaera*, it was always linked to these heater-cooler units.

This is sort of an explanatory design of what happened, what were the results. It's very small here, but you can see that the air cultures were only positive when the heater-cooler units ran. We never found it in the water. We didn't find it in the shower but found it in the drinking water fountains.

This, again, in the operating theater. When heater-cooler units were contaminated, so we had positive cultures in the water but they were not running, the air cultures were negative, as they were -- when a heater-cooler that we found not contaminated was running, there were also negative cultures in the air.

We then did, with the same technique of RAPD-PCR, gel electrophoresis. We compared the strains of these six patients because, after the first two patients, we found four other patients. One patient, for example, came in, and I was the IV physician who saw the patient, and he had a bone infection on the right hand. And because they didn't find any bacteria in there, they did a broad-range PCR -- we do that quite often when we don't find germs -- and with that broad-range PCR, a genetic test that would detect any bacteria.

We found *Mycobacterium chimaera* as the reason for this bone infection, this osteomyelitis, which is quite unusual. And then we went back and saw that this patient actually also had heart surgery with an implant. So all of these patients that -- we know they have implants, which is probably also because of the biofilm forming on this artificial material that you put into the body, that this is the sort of weakening spot that makes these patients get infected.

And we saw that two patients we knew already had the same strain, and three other patients had the same strain, and one patient didn't have the same strain. And then we never found the same strains in the water or in the air, but you have to consider that they were years apart between the culturing of the heater-cooler units and the air. That was in 2013-14 and '15 and the patients being operated on much earlier. But what we found was the same type in the water and in the air that we cultured at the same time, which showed us that actually this *Mycobacterium chimaera* came out of the water into the air.

But this was not always the case. So the hypothesis goes that several strains of *Mycobacterium chimaera* can infect or contaminate one single heater-cooler unit. So you get maybe sometimes the same strain in the air as in the water, and sometimes it doesn't match because of that.

I will not go into the diagnostic challenges. Not every lab can identify these germs.

We have then the case definition, which was mainly the patient was operated on in heart surgery with an implant and had *Mycobacterium chimaera*. We found these six cases. And then these cases all had different implants. So it wasn't coming from the factory of the implant production, which is also always a concern that something would be contaminated and then delivered and implanted in the patient. That was the case in the past, but here we

had all different implants and different manufacturers. But all of these patients had implants, all had invasive infections.

And so these are the numbers that I alluded to someone else about the incidence, and it's true, we don't know if we have found every patient, but we really looked very severely in these cases. And I can tell you that we found two new cases in Switzerland meanwhile. But here you can see that there are many operations and not many infections. So it must be that not every patient operated on such a machine gets infected. This is a very rare event.

Then we went into culturing all the heater-cooler units with the help of the public health authority in Switzerland, and there are 16 cardiac surgery units in Switzerland, and only in 8 hospitals they grew *Mycobacterium chimaera*. And I say only, but at the time this was sort of, for us, somehow good news for our hospital because we were not the only ones who had this problem. And I can tell you that on July 14th, we went public with this with the help of the Federal Office of Public Health, and it was a challenge to do this in a way that we don't scare patients away from being operated. So there was a helpline, and we clearly announced that this was a rare event and that we tried to mitigate it in the sense of not infecting any more patients. And I'll tell you something more about this in a minute.

We then went into an international collaboration, because there were cases in Germany and in the Netherlands, and described in more detail in the next paper the challenges of diagnosing these patients. That is difficult. There is no diagnostic test that can, in the latent phase, detect these cases, which is a challenge to find them, and the challenges in treatment, because even when we treated the patient for 1 year with

medication, when the implant was explanted, for the patient, it still grew mycobacteria on them. So, again, the biofilm might be the problem. So these are these cases, and then it went on from there to European and then a worldwide connection and exchange of this information.

In another work that we did in 2014 we looked into how can these mycobacteria go from the machine to the operating site? And in our hospital we have laminar flow. This is not always the case, and you are probably aware that the technique of laminar flow to prevent infections is debated. There have been publications that hospitals who use this laminar flow, they have more infections.

So I would like to quickly show you this video that we made. It's very small here, the projection, but you see on the upper part of the left where the smoke is aspirated by the heater-cooler unit that is turned away with the flow from the operating site. In the front, you see the operating table. And below, you see that the flow is turned against the operating theater, operating table, and you can see how the smoke is blown towards the operating table. On the right, this is another angle. One can see, when one looks at this video, how the smoke, because probably of the heat coming off this machine, goes to the ceiling, and it's there sucked into the laminar flow, and this laminar flow has no protection coming down from the ceiling. So it's aspirated by this flow that creates a vacuum. And then it's rained down directly onto the patient, the sterile field, and also probably all the implants that are unpacked and lying there in the sterile field.

We also measured particles. Not bacteria, but particles. And you see in this graph to the left, the machine is turned off. In the middle, it's turned on and then oriented towards

the operating table, and then to the extreme right, particle counts when the heater-cooler unit is turned away with the airflow from the operating table.

So one element might be why there are sometimes infections and sometimes not. At that moment when the airflow from the heater-cooler unit is turned towards the operating table, then there is a high risk of infection.

Some words on the experience of cases that might be useful. So I have talked to you about the bone infection. There were several cases now notified that had bone infections. Here in the hand it's very unusual, but in the back spine infections was a primary discovery of these cases. Here you see the evolution of this infection in the bone.

Then there is a specific picture in the echo of the heart. You see a very fine adhesion, fine floating material on the valve. And then that is very specific, that in the eye there are these lesions that you can see in these patients.

Something that I have to underline is that we have now seen several cases that were a misdiagnosis of sarcoidosis because it makes the same picture in the tissue of granulomatosis. And usually, then, these patients receive exactly the wrong medication, that it's an immunosuppression by steroids. And the most recent case had also this wrong diagnosis because you don't find a germ because they're difficult to grow. And then the conclusion is that this is a sarcoidosis and it's treated like that. So one of the things we are thinking about now is to look for cases in Switzerland, specific, reevaluate all the cases of sarcoidosis diagnosis for this infection when they have heart surgery before that.

Prevention. Because of my personal experience at my home, that the coffee machine, where the water is in there, gets slimy. If I let the water sit in there for several

days, when I put my finger in, it's sort of slimy in there. I had the idea, when we had the new machine that became positive after 6 months of the treatment that we did according to the protocol, I said we have to change the water every day. So we had first to do this with our physicians from the infection control unit, but then we had to hire someone additionally on the perfusionist team to do these daily water changes in all the machines and we did that until the -- today's date.

We bought new machines from LivaNova in 2014, in the first half, and they remained negative for a long time and became then positive after 6 months. They are now up and positive. And what we did additionally, we built a custom-housed -- a custom-built stainless steel housing around this machine and hooked it onto the exhaust system of the OR. So a third of all the air going through the OR is sort of aspirated through this housing, through the heater-cooler unit, so that all the air coming from these heater-cooler units goes outside the OR and -- because we couldn't position the heater-cooler units outside the OR because there was no space and there is a maximum length of tubing that you can -- that is allowed of 8 m.

So here I come to my conclusions of this whole experience. I've learned a lot on my microbiology, on politics, on how risk is dealt with. And you can imagine, it was a difficult time because every time we found something new, I was responsible, together with all the other important people at the hospital, to decide if we would stop heart surgery and what we would tell the patients and what we would tell the press. And so we always try to figure out a way to make that patient safety is guaranteed.

And so what I learned is when a system can fail, it will fail. So we have to do it with

very complex technology nowadays, and we don't imagine what the next problem will be. And we always have to think about these problems.

So a note on common sense is that probably to have water inside the OR that is not sterile is not a good idea from the start, 1 m away from a sterile field, and that creating airflow in the OR is not a good idea either.

Then I learned that medical devices are not grounded like airplanes. So if there is a problem in one airplane, all the models of the same make are grounded and cannot fly anymore. This was difficult here because we couldn't stop heart surgery, and we heard that there were only a few producers of these machines.

And then the outbreak investigation of an international level is slow. It was amazing how long it took until everyone got into recognizing that there was a problem. But it is a complex system, the whole political and geographical thing.

And to end, we don't know yet how big this is. Maybe there are several patients still harboring these germs on their heart valves and they only come out later. So there is research going on to see if we can test these patients to find out if they're infected or not.

And I would like to end with the idea -- my idea of this problem is that this corresponds to the Swiss cheese model, not because I'm coming from Switzerland, because I think it's a really great model. I think that maybe these mycobacteria, they're introduced at the factory because, as we saw in a publication, this was at the factory there were positive probes, positive cultures. They could have been introduced at the hospital level, as well, because you see that our drinking water fountains were positive and it's not excluded that someone put water that was not filtered into the machine, and then that this machine

creates an airflow and that the machine is turned towards the patient. And so there are several factors that have to align to create a case. And maybe that's why there are not every patient that is, that was operated with a contaminated machine was actually sick in the end.

Thank you.

DR. LANGE: Thank you, Dr. Sax. An excellent presentation.

We'll now hear from Dr. Joseph Perz, who will be giving us the perspective from the CDC.

DR. PERZ: Thank you very much to the Committee for the invitation. I appreciate following Dr. Sax very much in that it was his outreach to us, I believe, in the summer of 2014 that helped put this issue on our minds at CDC, as well as at FDA. Oh, I need to disclose that I have added a couple of slides. After listening to the presenters who preceded me, I realized that a little bit of background might be helpful. So those have been uploaded, and I'm very happy to share those, but I apologize, if you're following along, that a couple of slides won't quite match. Also, I'm realizing that I'm in some ways the filler between, you know, two, I think, very significant investigation summaries. You know, the first description of recognized NTM transmission from heater-cooler units in the EU. Publications and communications around that helped raise awareness that in turn led to identification of a situation in the U.S., which the speaker who follows me will describe in great detail. So I'll be glossing over that.

While it's true that our awareness of the potential for these devices to create a bioaerosol containing NTM, that that's all new to us, the idea of a heater-cooler unit as a

potential source of infection is not quite new. This paper, as you might be able to see, was published in the perfusionist literature in 2002, and one of the -- on the lower left, if you can make it out, you probably can't, but in the fine print it indicates that these -- how did they put it -- disinfecting heater-cooler units is very difficult. That's a bit of an understatement. So the idea that waterborne pathogens might possibly be introduced into the OR environment is actually one that's been with us for some time.

As others have, you know, offered sort of the bigger picture of NTM and healthcare-associated infections, I thought I would just add this slide and offer the CDC perspective based on our experiences conducting investigations with health departments, facilities, following the literature.

So outside of surgical procedures, NTM transmission has been associated with injections, dialysis, inpatient hospitalization. Of note, during the ID week meeting last fall, a presentation from Duke University, talking about a large number of respiratory infections among lung transplant patients, they concluded that they were likely exposed to NTM via ice and tap water, to oral care, gastric tube flushes, consumption, and bathing. And they describe a sterile water protocol for that patient environment. In the OR or surgical setting, we have seen NTM transmission associated with humidifiers, as was described in Sylvia's talk earlier. But also the CDC published just last fall an *MMWR* article summarizing an outbreak of NTM as a result of LASIK surgery and the use of commercial-grade misting humidifiers. And so this might be of interest to the device Committee as well. In the case, the LASIK manufacturers specify a narrow range of humidification, and some practitioners take it upon themselves to meet that specification by having supplemental residential-style

humidifiers in the OR.

You know, we've talked about premise plumbing and showers and spas and the like. And, in fact, we have a small collection of outbreaks from recent years involving OR personnel who used personal hot tubs prior to presenting for their case. And we've also had a number of NTM infections associated with liposuction, skin, and soft tissue infections. And Dr. Sax provided a photo exemplifying that.

But, you know, the issue before us today is, you know, again, it's one of perhaps many pathways for these bacteria to reach patients, but it is a significant one because of the severe infection that results. And so with that, I'll talk a little bit more about specifically our role in the heater-cooler unit NTM investigations.

So we became aware of a cluster of NTM infections that, I believe, at the time -- and Dr. Miller will get into more specifics -- they were presented as just *M. avium* complex. And because of the recent publications, there was an awareness that this possibly -- because these were cardiothoracic patients, that this was possibly related to the heater-cooler device. A very extensive field investigation was performed in concert between the CDC, the state health department, and the affected institution. And you'll hear more about that. Those results were, for us, very significant. By October of that year, we also had lab data connecting the devices that were used at that hospital to the actual infections detected among their patients. And so on the heels of the FDA guidance that had been issued earlier that month, we made this effort -- let's try that again. Aha. To amplify the FDA alert using our own channels to reach a broad swath of the provider community and adding specific guidance on identifying patients with infection. And we structured this in a way that it

would have specific guidance for the hospitals, for clinicians, for health departments, and also for patients.

So issuing guidance is one thing, but it does take a lot of effort to actually make our partners aware. So we had phone calls with literally dozens of professional associations and other partners, including the American Medical Association, the Society for Thoracic Surgery, the American College of Surgeons, the American Hospital Association, and others representing infectious disease, internal medicine, and so on.

We believe that that has been helpful as far as raising awareness. I think that there are still some gaps. And before talking about those and ongoing efforts to address the gaps and awareness, I should also, you know, sort of help reference this Committee, this Advisory Committee for FDA to some of the discussions that took place with CDC's Healthcare Infection Control Practices Advisory Committee. The heater-cooler unit issue specifically was addressed at the November and March HICPAC meetings, and Dr. Schwartz summarized some of that for you earlier. I would perhaps like to share that there was active discussion at both of these meetings around the need for both short- versus long-term solutions, you know, recognizing that some of the issues perhaps around the cleanability of the device or the potential for generating bioaerosol, you know, might take some time to address in a lasting manner if they might require any kind of redesign. But emphasis on the need for practical short-term solutions was discussed, and one of the concerns raised repeatedly was burden on the end users to have increasingly challenging requirements and changing requirements around maintenance of the devices.

I'm having a little trouble with the clicker. So I have to aim at you. Thank you.

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We have ongoing engagement with state and local health departments and facilities. So as the notices from FDA and CDC and scientific publications have accumulated, more and more institutions are reviewing and looking and, in some cases, finding issues with contamination of their devices or potentially infected patients.

CDC's role, my division, is actively engaged in consulting with those institutions and health departments. We tend not to do onsite investigations nearly as often as we're providing consultation. Of course, one of our messages every time we hear from an institution or health department is to ask, you know, whether FDA has been made aware, and emphasizing that in addition to the MDR reports, it's very important to consider engaging directly in conversation with the FDA staff leading the device investigation aspects.

So I will briefly summarize our guidance, which dates back, I'd say, as I mentioned, to last October but was recently expanded. And so what we are continuing to suggest is that healthcare facilities that perform cardiac surgeries using a heater-cooler unit consider taking steps to identify patients at risk. And the first step there we would offer is to consider a laboratory assessment, essentially a review of NTM positive cultures obtained from invasive samples such as blood, tissue biopsy, implanted prosthetic material, and to do that using internal records, for example, the microbiologic database for the hospital laboratory in question.

How far back to go is something of an open question. Many facilities that we've talked with, you know, have chosen to go back about 4 years. But as we've learned from reports now from the EU and elsewhere, not only is the development of symptoms often

delayed by many, many months -- even years -- but there may also be a corresponding delay in diagnosis. So it appears that it is possible for a patient to, you know, be diagnosed with this invasive NTM infection, you know, up to 4 or 5 years after the actual procedure where the exposure occurred.

A second step is to perform a clinical assessment, cross-referencing these NTM positive cultures with medical and surgical records to identify patients who meet at least one of the clinical criteria, which include prosthetic valve endocarditis, prosthetic vascular graft infection, sternotomy wound infection, mediastinitis, bloodstream infection, or disseminated infection, and then to consider tying that together by assessing exposure, in other words, history of surgery requiring cardiopulmonary bypass.

So this is one approach. The order is not as important as including these various components, and I would emphasize the exposure assessment and the laboratory assessment. You know, this is perhaps an example of due diligence on the part of facilities that have been using heater-cooler units. To go back and look retrospectively at what we've learned, you know, is often a hidden risk or issue. It's not going to pick up every case, by any means. Many patients will not have had a specific NTM diagnosis. I'll explain more on the next slide, how to better pursue that.

And we also have to, I think, realize that among the many thousands of patients who've had lifesaving cardiac surgeries, some have died in the interim, and an unknown number, you know, will have been the result of infection that will never be diagnosed. A high index of suspicion again is critical in making this diagnosis. I'm sure that Dr. Chuck Daley will talk more, and from more experience than I can, when he presents tomorrow.

But an important point that's been made already by others, but to emphasize here, is that NTM infection is not generally diagnosed using routine microbiologic testing and instead requires cultures for acid-fast bacteria, or AFB. And so indications for that would include patients with exposure to heater-coolers and any of the clinical criteria presented on the previous slide, as well as recurrent or persistent fever of unknown etiology, night sweats, joint or muscle pains, weight loss, fatigue, etcetera.

And any positive NTM and especially *M. avium* complex positive cultures probably should be sent to an NTM reference laboratory. The number of laboratories that are truly proficient in sorting out the exact species of mycobacteria in question are few in number.

This is just a screenshot showing part of this guidance. The web URL that's indicated there is a pathway to locating this CDC guidance. I will add that we are actively discussing ways of partnering with infectious disease clinicians and other interested partners to help get the word out more effectively, perhaps through a CDC-sponsored webinar later this month.

I'll just close with a few takeaways. I think that, you know, while the questions around intrinsic contamination, in other words, you know, the idea that contamination could have occurred in a factory setting, that's important. But, you know, in some ways, as a proof of concept as much as anything -- because as you've heard, NTM are present in the premise plumbing of many hospitals. So it is perhaps equally likely in any given case that a heater-cooler unit that has NTM actually reflects a local source. And while reducing, eliminating the chance of an intrinsic contamination in terms of the unit being shipped is of paramount importance, that does not, of course, eliminate the chance of extrinsic use on

the user side.

Another point to consider is that infections are uncommon and while -- you know, earlier this morning we talked about how a precise estimate of risk is not possible, and I would put forth, you know, it's not something that we're going to determine in any kind of practical way. What we can do is, I think, learn from some of the outbreak examples. So as Dr. Sax showed you, approximately 6 patients with confirmed infection among 3,000 -- that's about 2 per 1,000 procedures -- it's, you know, I think you would agree, possibly an underestimate because of the shortcomings as far as diagnosis. And in the presentation which follows, you know, you'll have another sort of point estimate which is, as you'll see, a little bit higher.

So I don't know that CDC or any other entity will be able to help the Committee understand precisely what that risk is, whether it was 1 in 1,000/1 in 10,000. But I would, I guess, suggest that we consider, you know, is there a threshold? You know, if the risk was 1 in 10,000, is that okay? Do we approach it differently than if was 1 in 1,000? And that's just a rhetorical question.

Finally, to address the previous risks, assuming that the current risk level is considerably lower, as I hope it is, that will take heightened awareness, as we've talked about. And as our own HICPAC committee made clear, there is a need for both short- and long-term solutions to the identified device risks.

Thank you.

DR. LANGE: Thank you very much, Dr. Perz.

The final guest speaker will be Dr. Jeff Miller. He will tell us about the State of

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Pennsylvania's investigations into these issues.

Thank you, Dr. Miller.

DR. MILLER: Good afternoon. My name is Dr. Jeff Miller. I am a CDC career epidemiology field officer, and I'm also a commander in the United States Public Health Service. I'm here today representing the Pennsylvania Department of Health. I've been embedded in the Pennsylvania Department of Health for the last 5 years.

And so I will be talking about an investigation of nontuberculous mycobacteria in a Pennsylvania hospital and -- excuse me. So I'll be talking about nontuberculous mycobacteria in a Pennsylvania hospital and our experience with it. Sorry, I'm getting distracted by the feedback here.

So I have no conflicts of interest to declare. I will be presenting a number of photographs in this presentation, and I wanted to get entirely clear that you should not assume that the photos were all taken at a single hospital. Our experience in Pennsylvania is actually over the course of multiple hospitals and you should not assume, because of the position of the photo within the presentation, that it is from a particular hospital.

So my objectives are to describe the findings from our investigation. I'll present the public health response to date, including our guidance to facilities and aggregate findings from hospitals in Pennsylvania, and I'll share some ongoing challenges.

So our story in Pennsylvania starts in July 2015 on the heels of the brilliant work that Hugo Sax and company wound up publishing from Europe. So Hospital A reported a cluster of nontuberculous mycobacteria infections among cardiothoracic surgery patients in the context, again, of the recent information coming out of Europe. After identifying this

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cluster of infections and notifying the Pennsylvania Department of Health, Hospital A replaced their heater-cooler units and their attached devices. The Pennsylvania Department of Health and the Centers for Disease Control and Prevention investigated the cluster of infections.

So our objectives were to determine the extent of the outbreak, determine the associated risk factors and exposures, and recommend control measures. To do this, we observed current infection control practices, reviewed policies and procedures, conducted an epidemiologic study, and analyzed environmental and clinical NTM isolates.

So as part of the policy and procedure review, we took a deep dive in the instructions for use and tried to better understand what was the gold standard, and it's difficult to say. So what this table shows is that over the course of 5 years, there were three different instructions for use: 2010 IFU, 2012 IFU, and 2015 IFU. And on the rows we have different domains, including the type of water that should be used, how often it should be changed, the disinfection schedule, whether there should be additives, hydrogen peroxide, propylene glycol, tubing and accessories, and so forth. And what I want to point out here is not only the complexity of these, but also a few specific things. So, for instance, the water change in the 2012 IFU was once every 2 weeks, and in 2015 that was changed to weekly.

I've also bolded some words here. You'll notice that rather soft words like "should" and "recommend" were changed to "must." I'll also point out that an instructional video that was released at approximately the same time as this investigation included 56 distinct steps for disinfection.

Cleaning has been mentioned in the same phrase as disinfection. As somebody who

investigates healthcare-associated infections, I bristle at the word "cleaning." It's used when we talk about the Spaulding classification. I really don't like it because it gives the connotation that if it is clean, it's appropriate for use. That's not true. I really prefer the term "washing," and it is the physical debridement or the enzymatic debridement that we're talking about that needs to occur before disinfection is successful. And that's a central tenet when we're talking about instrument processing, at least. And I understand that, you know, the treatment of heater-cooler units is a little bit different. It's never intended to come into contact with the patient. But that's something that I really wrestle with here because, as was described before, the biofilm issues are really important.

So we wanted to take a step back. You know, we knew what was coming out of Europe, and we wanted to approach this without having blinders on. So we wound up casting a wide net. One of the really important things to note here is that our current surveillance systems, as Dr. Falkinham had mentioned, are not great at picking up this infection. It's not a reportable disease, okay? So in the state of Pennsylvania, hospitals, if they have a cluster of infections, are required to report it. If it meets healthcare-associated infection case definitions, they are also required to report it. However, because of the latency -- we talked about the challenges in diagnosis, but also because of the long latent periods, these infections don't meet CDC's National Healthcare Safety Network case definitions, surveillance case definitions for healthcare-associated infection.

So we had to look someplace else, and we wound up looking at microbiology data. So we went to Hospital A's lab, and we asked them for any isolate that could possibly be nontuberculous mycobacteria or AFB positive.

I'll mention, as an aside, that other hospitals who are doing this currently should also look at their histopathology results because there are a number of cases that may show up on histology but may not actually be cultured initially.

So, you know, in short, of these 144 isolates that were pulled from the microbiology lab, a third of them had a history of surgical procedure. And there were some others. So, you know, three-quarters of the samples were respiratory specimens, perhaps not surprising based on what we've heard and what we'll hear from Dr. Daley tomorrow as well. But there were some that were invasive, and that was interesting as well.

So again, wanting to make sure that we weren't missing here, we wound up taking a look at all of the surgeries that were performed at Hospital A and the three most common surgical types: cardiothoracic surgery, general surgery, and orthopedic. And you'll note that the rate per 10,000 of NTM infections was three to four times the other surgery types, so about 20 per 10,000. And so this wound up sort of giving us confidence that we should perhaps follow in Dr. Sax's footsteps and perform a case-control study to actually look at what risk factors might be contributing to this higher increase.

So in this case-control study, we wanted to evaluate risk factors. Case patients were defined as cardiothoracic surgery -- patients who had cardiothoracic surgery performed between January 2009 and July 2015, and they needed to have an NTM-positive culture between January 2010 and July 2015. That's not a typo; that's correct. And we broke that down into those with probable disease and suspect disease. So probable cases were those with non-respiratory specimens, extra-pulmonary, if you will, and suspect were those with respiratory specimens. It was an unmatched design, 3:1 ratio controls to cases.

Controls were selected from a list of cardiothoracic surgeries. So the surgeries were picked first, and then we wound up defining an exposure period and actually extracting all of the possible exposures within that period of time. And I can explain that more if the Panel is interested.

So with regards to history of surgery, the cases and controls were similar. And they were also similar with regards to their demographics. We looked at typical things: age, sex, race, lung disease, diabetes, and whether or not they were immunocompromised or not. I will point out that only 30% of our probable cases were immunocompromised.

Okay, let me orient you to this table. We're going to spend some time here. So this is basically a line listing, or what we call in epidemiology a line listing. It's a spreadsheet, if you will. So these columns over on this side include exposures: the heater-cooler unit exposure, the time on pump, whether or not they had impaired immune function, and whether or not they had a history of a cardiovascular implant. These are continuous variables, and I've actually ordered it as if they were continuous variables. I've not included the exact on-pump time to protect patient confidentiality.

So let me point out some other parts of this table. So we have the specimen, source, and then the type of organism that was collected from these specimen sources. Let's walk through this. Okay. So down here at the bottom, again ranked according to exposure to heater-coolers and on-pump time, we have two patients, one with an NTM not otherwise specified -- I can't tell you if that's MAC or not, but it was not specified as MAC in the microbiology data. Then we have a second one here with rapid-growing NTM.

So now the patients that have been highlighted in yellow here. These are patients

that either had MAC complex or *M. chimaera* specifically. Of these eight patients, only those in red here, listed as *M. chimaera*, did we actually have specimens to go back and do the subsequent specific typing to look to see if it was *M. chimaera*. So these other ones might have been *M. chimaera*, but we don't know because we were unable to look. All we know is they're MAC complex.

So these now are two patients shaded in red. So this patient, immunocompromised, had an implant, pleural fluid. This patient down here, again immunocompromised, implant, pleural fluid.

These four, again, with heater-cooler exposure greater than 5 hours, on-pump time greater than 2 hours, with implants, had really a remarkable constellation of isolates here. So note that they have blood, they have spleen, they have bone marrow. And for you clinicians in the room, you may be thinking, bone marrow? Well, in fact, these patients early on, as Joe mentioned, may be presenting with very nonspecific findings. And so a number of these had pancytopenias and were worked up for malignancies. And so they had a bone marrow biopsy, and they were found to have granulomatous disease.

Again, sort of moving down this rank of order to maybe exposure, this patient here had a deep abscess that looked like a deep sternal wound, and their exposure, heater-cooler unit, greater than 5 hours, on pump for less than 2 hours, also had an implant.

So this patient here -- I'm sorry, I had that backwards. So this is the one with the deep sternal wound. This patient up here, a deep abscess. It was actually vertebral osteomyelitis with an adjoining psoas abscess. So this patient, you know, may have had vertebral osteomyelitis in an adjoining psoas abscess due to hematogenous spread, again,

sort of this indication of disseminated infection.

DR. GIVNER: Excuse me. Mr. Chairman, is there a reason that the slides aren't showing up here? They're only showing up, up there.

DR. LANGE: The same slides, just colored a little differently. In other words, this slide here is there. It's just the coloring on the -- can you see it, Laurence?

DR. GIVNER: That slide and the last slide. Yeah.

DR. LANGE: Audiovisual, if you'll take a look. Thanks.

DR. GIVNER: That one's been there for a while. But it says 19 on it. So it is moving, but it's not showing the color.

DR. LANGE: It's not showing the colors. Is there anything we can do? Hold on just a second.

DR. MILLER: This is actually the last slide of this series, if it makes a difference.

(Laughter.)

DR. LANGE: Figures.

DR. GIVNER: Just in time.

DR. MILLER: As we're working out the technological issues, the upshot of this whole thing is that there appears to be perhaps the appearance of greater disseminated disease with more on-pump time or more exposure to heater-cooler units.

Okay, time between surgery and NTM culture. This point has been made before. Patients present with disease late. So half of the patients wound up presenting with their disease in 1 year, but it's quite clearly skewed here.

When we looked at surgery type and odds of NTM infection, major cardiac surgery

was -- there was increased odds among patients who had cardiac surgery versus thoracic surgery.

When we compare probable cases and control patients being on pump, having an artificial valve or graft, had an odds of 5.6 and 10.1, respectively.

And when we look at exposure to the heater-cooler unit and on-pump time -- and again, I think it was mentioned earlier today that often these machines will sit on and stand by in the room for long periods of time. And for controls, we did not -- we were not able to extract exact incision time and closure time for every single patient. And so we used entry into the OR and exit out from the OR to capture that exposure to the heater-cooler unit, the data there. And you can see that the probable cases had quite a bit more exposure on average.

I'm having a really hard time with this remote. Okay.

So we wound up trying to take another look. You know, I sort of presented a clinical gestalt for perhaps greater dissemination, and then we tried to look at that epidemiologically. And so those patients who had heater-cooler unit exposure greater than 5 hours, the odds ratio was 12.9 as compared to controls. And the odds were 16.5 times as compared to controls if you were on pump for greater than 2 hours. In stratified analysis, the only statistically significant result -- all right. So the only statistically significant result was this one here, greater than 5 hours. However, again, if we overlay the clinical data, this first strata was the non-MAC NTM and the rapid grower. This was the deep sternal wound infection. This was the patient with a vertebral osteo, again, maybe hematogenous spread. And then greater than 5 hours included six patients pleural and disseminated disease.

Okay. So when we looked at other risk factors, specifically postoperative exposures, perhaps not surprisingly, those patients who had a shower before being discharged also had a statistically significant elevated risk.

The next slide, please.

Okay. So now I'm going to show you an operating room schematic from Hospital A. So this is sort of cartoonized. You've got the ice machine, the door, the scrub sink, the patient table, the cardiopulmonary bypass device, and the heater-cooler unit. What we've learned working with hospitals is there's quite a lot of variability on how this is actually set up, but this is the way it was in this particular hospital. And down on the bottom in the lower right-hand corner there is the OR exhaust.

The next slide, please.

So we collected water samples from the scrub sink, from the ice machine, and we also collected water samples from the heater-cooler unit itself.

Next slide.

We also collected swab samples. As Dr. Falkinham mentioned, that's a great place to look for NTM.

Next slide.

And we collected large-volume air samples. So these are 500 L samples, air samples. And note the position of these arrows next to the heater-cooler unit and the OR exhaust.

Next slide, please.

In total, 56 environmental samples. And as previously mentioned, we had three patient isolates.

Next slide.

So now I'm going to present the results from our air sampling.

Next slide, please.

So in this simulated procedure in this operating room, this was quite literally a perfusionist, and our Pennsylvania Department of Health and CDC team there with the perfusionist doing a mock procedure. You can see that when the machine is off -- I know this was a question earlier. When the machine was off, there were no positive samples. Samples were collected at multiple points in time. It wasn't until about 2 minutes -- 2 hours into this 5-hour procedure, with cardioplegia on, that we recovered *M. chimaera* 18 inches from the HCU exhaust. Notably, there were AFB-positive organisms, but they were not NTM that were recovered next to the room exhaust.

DR. LANGE: Dr. Miller, before you leave the slide, for those that have trouble seeing it, that yellow says AFB positive, not NTM.

DR. MILLER: So *M. chimaera* was also recovered next to the heater-cooler exhaust at 3 hours and 4 hours, and when the machine was then turned off, we did not find any more *M. chimaera*.

Next slide, please.

So this is what the heater-cooler unit internal water pathway looks like. And I apologize if these colors are not showing up, but there is material in this tubing of sort of a blue-gray-green color. This is not visible to normal operators of the machine. This was only upon disassembly that this was seen.

Next slide.

So let's now talk about the water pathway laboratory results. Based on that slide, you may not be surprised to see that we did, in fact, have positive results. But there's a really interesting story here. So there are three heater-cooler units represented on this slide. One was shipped to CDC. Heater-Cooler Unit 2 was actually used in a simulation. Heater-Cooler Unit 3 actually stayed at the facility, and the facility had done some drainage and collection of water, and then we wound up testing that. Not difference in labs, difference in collection. So the water drained by the facility (15 CFU) as opposed to water that was drained after shipping and the machine running (3×10^4 CFU). Agitation matters.

Swab of the biofilm. I'm sorry. So let me talk about Heater-Cooler Unit 2, still talking about water samples. Again, a similar picture: 1.5×10^5 *M. chimaera* from water drained immediately after the simulation.

Okay. Next slide, please.

Now we'll talk about the swabs. The swabs from both the inside of Heater-Cooler Unit 1 and Heater-Cooler Unit 3 were positive for *M. chimaera*. We didn't swab the inside of Heater-Cooler Unit 2. And a swab of the interior of the cardioplegia machine was also positive for *M. chimaera*. So it's been alluded to that we've got these attached devices. Well, it depends on what facility you're talking about in terms of trying to understand what exactly that means. Cardioplegia devices, some of them have a disposable water pathway, and some of them actually have a fixed water pathway. And so you can imagine that if you've got a device that does not have a disposable water pathway, you could have *M. chimaera* hiding in there as biofilm and could potentially reseed your devices, because although the tubing is part of the instructions for use, the attached cardioplegia device does

not -- is not typically connected.

Okay. So continuing on with our laboratory investigation, let me talk about the fingerprinting that we did, the genetic analysis of these isolates.

So we have clinical cultures of *M. chimaera* from three case patients. We've got the environmental isolates we talked about. And in short, all of these are highly related PFG patterns. They were collected at different times, and it was previously mentioned also today, you know, this is not a monoculture. These machines may have multiple organisms in them. And so I'm told by my laboratory colleagues that the PFG patterns, being highly related but not identical, are still strongly suggestive of connections here.

I want to spend a minute talking about the possible pseudo-infection. So sometimes in epidemiology, the outliers are some of the most interesting cases. So I lied. We don't actually have three clinical isolates. We actually have four clinical isolates that were all *M. chimaera*. One of them didn't meet our case definition. The reason that they didn't meet our case definition is because the culture was actually obtained the same day as their procedure.

So let me put this together for you. The Mayo stand I showed you right in front of the heater-cooler unit is likely where the explanted valve -- this patient had a valve replacement surgery for *Enterococcus*, culture-positive *Enterococcus*, had an explanted valve. The culture results on that explanted native valve were not only positive for *Enterococcus*, they were also positive for *M. chimaera*. And that PFG pattern was also highly related. So with that being right in front of the heater-cooler unit exhaust, and our other laboratory findings, I would hypothesize that perhaps it was seeded at the time that

the valve was explanted.

All right, there are some limitations here. Mr. Chairman, I have 3 minutes left?

(Off microphone response.)

DR. MILLER: Okay. So this is an experience in one facility. It's a snapshot in time. A small sample size, only 10 case patients. I, as a non-laboratorian, wonder about the epi and genetic diversity of *M. chimaera*, and I will leave it to others to determine how well that's been established.

Okay. So increasing awareness. So these findings, we discovered this on the heels of Dr. Sax and some of the communications were described. And so if you don't go looking for things, you're not going to find it. And so we went looking.

So turbid water. You can see the paper behind here to try and demonstrate the yellow color.

To orient you here, this is the overflow tube. We've seen pictures like this before. The overflow tube comes back down here into this overflow bottle. There is a secondary overflow tube that is capped. You can see the turbidity here.

This is a drain. There is a substance here in this drain.

Many hard-to-clean connections, and we've made that point before.

Where you fill your water in the operating room suites matters. This was where one facility was filling their machines.

You know, we hypothesized that there may, in fact, be differences between machines, as was alluded to this morning. This is a big fan.

There are other methods that may or may not be as safe. So here, these are

machines that were not actively in use at that particular moment, but they were in a staging area to be used, and you can see the residual water in there.

And if you don't have a machine that has active cooling, how often are you actually changing that filter? I don't know if it shows there well, but that's not a particularly clean filter. And in the back there, there are additional filtration devices for the water itself as opposed to the air.

So based on what we found when we went looking, we felt like we had to do something. And so we issued detailed guidance to facilities through our PA Health Alert Network, and that's available up on our website.

I want to run through our guidance quickly. So basically, the most important message is that these are lifesaving devices and lifesaving procedures, and providers and patients should not delay their procedure.

We didn't have a whole lot of information to assess the adequacy of the instructions for use. And so we really said follow the IFUs in the absence of additional information.

We urged a comprehensive approach: human factors, engineering factors, systems factors. We wound up leading the reader through -- and facilities through a discussion of assessing the situation, then administrative controls that they could implement and elimination processing and engineering controls. And we also recommended bacteriologic surveillance. We felt that we had to have some type of proxy, giving visibly what we are seeing, to try to make some recommendations for facilities. And so we used the EPA drinking water limit.

I need to really hammer home, though, that we're talking, we think, about

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aerosolization. And so we don't know if that's an appropriate threshold or not.

We also made recommendations for patient surveillance, and I talked about the limitations of the National Healthcare Safety Network and really are emphasizing needing to cross-reference microbiology and NTM culture first, to start there.

We also proposed an interim surveillance case definition based heavily on the case definitions coming out of Europe. Our case definition has components including:

- Time frame
- Infection
- Whether it's localized or disseminated
- The specimen and the pathology results

We don't want to hear about specimens that are solely via bronchoscopy. We think that that's a different animal. And then based on the type of pathology result, we'll determine whether or not it's a probable or a suspect case.

So at this time, we can't categorically recommend the elimination or substitution of one heater-cooler unit over another unless there's evidence -- visible, bacterial, or epidemiologic -- to suggest that there is colonization or transmission. However, heater-cooler units with discoloration, visible biofilm, visibly turbid water, or machines with water cultures outside of EPA drinking limits we want to hear about. We recommend and, in fact, insist that facilities contact the FDA through the MedWatch mechanism.

So what's the impact here? So impact on healthcare facilities themselves. So, in total, four hospitals reported possible heater-cooler unit contamination. However, these facilities went back, they did a thorough, deliberate look at their microbiology data, and

they didn't find any clusters of probable cases.

We are aware that five hospitals have actually made, or intend to make, purchasing decisions as a result of these investigations.

And we have anecdotal reports that it's very difficult to achieve the heterotrophic plate count levels that meet EPA drinking water standards in heater-cooler units from a variety of manufacturers.

DR. LANGE: How many more slides do you have?

DR. MILLER: Four.

DR. LANGE: Thirty seconds worth.

(Laughter.)

DR. MILLER: So not to shortchange the patients, but the impact to patients, you know, is really quite profound, not only in terms of mortality among these initial case patients but also in terms of their fear and anxiety.

So two hospitals in total identified 14 probable cases now, and 3,700 patients were notified of possible exposure.

Others have already publicly talked about the challenges related to patient notification.

I should get a couple minutes just for the clicker here.

(Laughter.)

DR. MILLER: So, you know, the FDA has charged this Panel with a number of questions, and I want to just take a moment to frame them from a public health perspective. The recommendations and the questions, I think, need to -- they need to be

operationalized, and they really need to be contextualized with regards to the facilities and the patients.

So we covered a lot of science here, but the real question in my mind that I deal with in my work is does my heater-cooler unit have a problem? Looking backwards, how do I make sure -- and looking forwards, how do I make sure that it still doesn't have a problem?

But I have heater-cooler Unit X. Does it matter? Is the risk the same? Right now, at this point, we don't have that information, and we have a lot of proxy measures to suggest that these biofilm problems exist in all machines.

Are the current IFUs adequate? And from a public health scientific standpoint, are they adequately validated? Can facilities do more? Are there disadvantages to that that we're not entirely sure of? What should I do with my existing machines?

So the question of whether or not the current IFUs are adequate has been asked many times. But at least for one manufacturer, they've changed multiple times. So even if the current IFUs are adequate, what about all of those other machines that are still in service? What do we do with those?

I think I fixed my problem.

How do we put our machines back in service? What do I do with attached devices? And you ask the attached device companies, and they don't know.

DR. LANGE: Thank you. I want to stop right there. And again, not to be rude, but the three talks have really -- will stimulate a lot of questions, and I want to make sure there's adequate time for the panel to answer those. And so I would like our three guest speakers to please have a seat. For the next 30 minutes, we'll have the opportunity to -- for

the Panel to ask clarifying questions. I know I have one or two. And again I want to thank Dr. Sax, Dr. Perz, and Dr. Miller. Excellent presentations.

And my first question will be to Dr. Miller. The issue was raised about not only aerosolization but environmental contamination. And do we know whether the non-cardiac cases, either the general surgery or the orthopedic cases, happen to follow cases in which a heater-cooler unit device is used?

DR. MILLER: These two particular rooms -- so this facility had two rooms in which cardiovascular on-pump procedures were performed and pretty much exclusively.

DR. LANGE: That's very helpful. Thank you.

Dr. Zenilman.

DR. ZENILMAN: Yeah, I have a comment and a question for Dr. Miller and Dr. Perz. First of all, the comment is, as an infectious disease doctor, I'd really like to commend Dr. Sax for discovering this. And I think the individual who discovers these outbreaks is usually really somebody who's very curious and was stuck with something, and we think of Larry Bush, who was the guy in Florida who discovered anthrax, and Michael Gottlieb, who was the first discoverer of HIV back in the early 1980s. And I really want to commend you.

My question for Dr. Perz is you basically mentioned that we should think about NTM cultures in terms of the context of positive cases. You didn't mention anything about molecular diagnostics, and I think -- so my question is, one is if we took sequencing, which Dr. Sax performed to identify some of these cases, we couldn't do that in the United States because they're not CLIA-approved tests. So we can't make decisions based on non-CLIA approved tests.

And second, CDC really has been able to develop molecular testing methodologies for a large number of infections, and including TB, with partners. And is there any -- you know, 12 weeks to get the diagnosis is really a very long time, because you're looking at 6 weeks for the culture to go out and then another 6 weeks to speciate it. And I'll follow up with a question for Dr. Miller.

DR. PERZ: Okay, thank you very much. Ironically, one of the people best equipped to answer the question is one of your fellow Advisory Committee members sitting next to you, Dr. Arduino.

(Laughter.)

DR. PERZ: But also Dr. Sax might have a comment. I guess all I can say is that it is very challenging, and the delays are -- it's already a challenging diagnosis, and then the delays with --

DR. ZENILMAN: Right.

DR. PERZ: -- the culture methods only compound that.

DR. ZENILMAN: My policy question is that there's an enormous amount being spent on diagnostics for infections which are not present in the United States, where we've had very few cases diagnosed in the United States, and here we have an enormous problem. And I understand this is not above your pay grade.

(Laughter.)

DR. PERZ: Yes.

DR. ZENILMAN: But I think, relevant to the --

DR. PERZ: Yeah. No, it's a good point, and we'll take that back to CDC.

DR. ZENILMAN: Okay.

DR. PERZ: And then, you know, where we use, you know, the PCR-based methods, sequencing is in the context of outbreak investigation, but it's a stepwise process to get there.

DR. ZENILMAN: Right. My question to --

DR. LANGE: Let me see if anybody else has one, too. Okay, Jon? So we'll hold -- we're trying to hold it to one or two and then come back. And then as you present your question, after you've done it, if you'll turn your microphone off.

So Dr. Yuh.

DR. YUH: Yes, this question is directed toward Dr. Miller, but perhaps the others could weigh in. So you had mentioned, and towards your conclusions, that the adequacy of the IFUs currently is unclear. So in your opinion, do you think, to get a better handle on that, that more rigorous documentation of maintenance of each individual heater-cooler unit might be helpful in discerning that, understanding that the IFUs have changed and evolved over the years? Because otherwise you're looking at a moving target. With these IFUs changing, you're always going to be uncertain of whether or not there is -- if they're adequate or not, or any one is adequate versus the other.

DR. MILLER: So I think it's actually much more simple from a public health standpoint because we don't have visibility of how the machines have been validated. And so, you know, our message to our facilities has been, well, we don't license these things. We don't test these things. We don't know. And so, you know, we license you, hospitals, but we don't license and regulate the devices, and we rely on our other colleagues to assess

that.

I worry a little bit about the seeding of the water with NTM as the worst-case scenario. I think some of the cardiologists on the Panel may appreciate my concern of sort of an embolic event or a mycotic aneurysm. You know, we've got this biofilm. Yes, we can clear the water. But unless we wash the things, we're not going to clear the biofilm. And what's to say we're sampling at the right time and not capturing the embolic event that is coming off of that biofilm?

And so I do have concerns about the adequacy of the validation, largely because I haven't seen it, but also from sort of a theoretical perspective, learning about these things.

DR. LANGE: Dr. Allen and then Dr. Givner.

DR. ALLEN: So once again, I want to come back to the charge for this Panel is going to be to try to come up with recommendations, and I consistently am struggling again with do we really have a problem with this infection, or do we have a problem with quality control and hospitals and personnel not doing what they need to do to keep these machines clean? Because one is kind of an easier fix than redesigning all these machines and coming up with new problems.

So specifically to Dr. Miller, in the cases that you looked at, I'm sure you asked the hospitals so what were you doing with these machines? Clearly, the pictures you showed up there were not machines that were well maintained and well cared for. Where a person got the water from, I would shudder if that were my hospital. So I'm concerned that yes, we have a problem, but the problem is with we're not following instructions on how to take care of these things.

DR. MILLER: So, you know, I think it's actually more instructive to look at what happened in these facilities after there was detection of a problem. So Dr. Sax already mentioned that with a brand new machine, with all of his scientific curiosity, he still wound up finding *M. chimaera* in the machine.

You know, we have 66 cardiac programs in the state of Pennsylvania, and we have heard from relatively few. However, in a convenient sample among infection preventionists, it's pretty clear that people are not looking for this thing. And the facilities that we've heard from, they are our champions. They are our champions who are sounding the alarm with regards to this specific thing.

So, you know, I think I would look at the experience of Dr. Sax and Dr. Falkinham and not the fear that Dr. Falkinham might have jokingly engendered with regards to the ubiquity of NTM, but rather take that as they are ubiquitous, they are around. We need to figure out how to prevent them from aerosolizing and to find out whether --

DR. ALLEN: You answered my question.

DR. MILLER: -- or not there are differences --

DR. LANGE: So I'm going to stop for a second. So I want to be very specific.

Dr. Allen's question is did you have the opportunity to ask the hospitals whether they were following the IFUs or how closely they were? In other words --

DR. MILLER: Yeah. You know, I think I'm going to comment on the policies and procedures that we saw when we went into the hospitals. I don't think it's appropriate for me to talk about what may or may not have been happening in those hospitals.

DR. ALLEN: No, I think it is absolutely crucial to the discussion that we're going to

have to make decisions on, because if I'm going to make recommendations and vote on huge changes in manufacturing and purchasing and so forth, I need to know whether if somebody had just done their job and it fixed it, then I'm okay.

DR. MILLER: So --

DR. ALLEN: Let me finish. So when you refer and say Dr. Sax says that things are recolonized, I get that. But we also heard earlier that if you do frequent changes and you keep your burden of infection or colonization at a low level, it may not result in clinically significant infection. So this is crucial that we understand. I understand you're reporting them, but I need you to really answer my question, and I'm not sure why you don't want to answer that.

DR. MILLER: So I think Dr. Sax's Swiss cheese model is right on. And in our guidance, we talk about the human factors, the engineering controls and the administrative controls that need to be in place. You know, I would point to the FDA advisory that came out yesterday that identified perhaps additional risk in machines that were manufactured before September 2014. So these IFUs have changed. So even if you were following the IFUs exactly right, what do we do with those other machines?

DR. LANGE: Dr. Sax, would you like to answer as well?

DR. SAX: First, I think that always a design solution is better than a human-based solution because now everyone is aware. And in our hospital, certainly they were not maintained as they should have in the past probably, to the letter. Now, they are because there is this problem. And we have heard that before. Five years from now, maybe some people will start to forget again, and then this human-based rule-following is not so strict

anymore. So a design solution would be better.

Second, I think that -- as I said, now the heater-cooler units got recolonized. Maybe they were already colonized when they came to the hospital. They just grew afterwards. The problem is we don't know for the moment the level that we can accept. We have negative air cultures, for the moment, with positive machines probably indicating that the load in the machine of mycobacteria is quite low. But we don't know if our air culture sensitivity is good enough to detect mycobacteria in the air that would infect patients. So we don't know exactly where the border is where the risk begins. And until we know more about that, I think the only solution is to separate the air of the OR from the heater-cooler units.

DR. LANGE: Dr. Givner, then Dr. Leggett.

DR. GIVNER: Thank you.

We have certainly seen lots of compelling data regarding cultures, including contamination of the HCDs inside the reservoir, as well as air cultures comparing when the machine was on and off when it was facing toward the patient or away from the patient. My question is in view of all of that data and hearing somewhat about the IFUs and how complex they are, I wonder if rather than ask whether the IFUs are followed, which is an important question, should we ask can the IFUs be followed within reason? How complex are they? Can they be followed? If followed, will they be successful? And if we increase the complexity by asking for more things to be done, more steps -- if that's what the Panel recommends -- again, we're increasing the complexity. So that's what I wonder. Rather than are they followed, can they be followed even in the best situation in the best

hospitals?

DR. LANGE: So I'll start with all three panelists with just a yes or a no to that. Can they be followed as currently written? And Dr. Miller, we'll start with -- there's no right or wrong answer, and we're soliciting your opinion. And we'll go left to right. Jeff, what do you think?

DR. MILLER: So there is a whole field of science that looks at processes. I'm not an expert in them. We have not --

DR. LANGE: I'm going to ask for your opinion for just a yes or no. We'll start there. Just yes or no, in your opinion.

DR. MILLER: I need a third choice, which is I don't know.

DR. LANGE: Okay, that's acceptable.

DR. PERZ: The same, I don't know. We don't have enough --

DR. LANGE: Okay.

DR. PERZ: -- firsthand knowledge of the whole current IFUs.

DR. LANGE: We don't either. That's why we're asking you guys.

Dr. Sax?

DR. SAX: Yes, there are current recommendations by LivaNova. The machines that we have can be followed.

DR. LANGE: Okay.

(Off microphone comment.)

DR. GIVNER: Yes, thank you.

DR. LANGE: It does, okay.

Dr. Leggett.

DR. LEGGETT: A follow-up question regarding this whole process. Dr. Miller and Dr. Sax, you had air samples in the OR, and we heard data before about CFMs and the way that could have an effect. Were your machines, Dr. Miller, the same ones that Dr. Sax used? Because he at a certain point -- Dr. Sax, you mentioned that maybe it's the heat and not the sort of airflow, but it's just the fact that there's heat that raises things above. So whether we have a very small PC fan or a huge, you know, airport fan, will the heat from those particles get us to the top of the laminar flow no matter what and that's why it doesn't matter on the device? Or do we have to focus on, if you've got this particular type of device, building that extra unit and exhausting all the flow? Were you talking about the same machines when you did your sampling in the air?

DR. MILLER: In our presentation, we're not identifying hospitals or machines. We are talking about differences between them, but we're not identifying machines or hospitals.

DR. SAX: I only have experience with this one brand, and I think there should be more research on what exactly happens with airflow and these different models, because technology might be important, the technology on the side of the different models of machines, airflow, heat, everything, but also on the level of the OR because our laminar flow system has a certain configuration, and it might be different with other configurations.

DR. LEGGETT: My point to yours was if it's a second device, that clearly is important information for us to have.

DR. LANGE: So Dr. Miller, without giving any information -- again, we're going to do

it at the larger level. We're going to look at these as a single equipment that's necessary and important. In other words, nobody is going to advocate that we shouldn't be using heat exchangers for cardiopulmonary bypass. Nobody. That's not in question. But we will be trying to sort out what sort of things that we need to consider. So Jeff, without any other information, can you tell us, is it -- does the hospital that you're looking at use more than one machine?

DR. MILLER: So the hospitals in which we have identified cases, the immunosurveillance case definition, all use one machine and one specific model. However, they have also used others.

DR. LANGE: Thank you.

Dr. Gallagher.

DR. MILLER: If I just may address that very quickly. So tracking is really an important issue. And so one of our recommendations is, in fact, every procedure needs to have a specific serial number and model documented. And one of the challenges in doing this type of research -- you know, we've looked at the Society for Thoracic Surgery database, which is very comprehensive, but we don't have the exact exposure information that we need.

DR. LANGE: That's very helpful.

Dr. Gallagher.

DR. GALLAGHER: Thank you.

My question is primarily for Dr. Miller, but others, please feel free to answer. I'm going to change gears for a moment away from machines to people who become patients, okay? So one of the things you said was that there were 14 probable cases and that 3,700

patients were notified of possible exposure. So I'm wondering what, if any, response came from those patients once they were told that there might have been exposure? Was there anything they were instructed to do? You know, those kind of questions.

Thank you.

DR. MILLER: So in Pennsylvania -- Pennsylvania, as well as CDC, provided guidance to the facilities on best practices for patient notification. But the facilities themselves executed the patient notifications and have been managing, you know, the follow-up and the monitoring of those patients. So I am, in fact, not the best person to ask about that.

DR. LANGE: Thank you.

Jeffrey, do you have a question?

MR. RILEY: A comment and a question. The instructions for use can be followed. The question is how many people and how much money does it take for us? Dr. Perz, we had a great conversation before the October '15 statement from the CDC. We talked about routine surveillance, culturing of heater-cooler devices, and I noticed your Venn diagram didn't include that. What's the CDC's current stand on culturing these devices?

DR. PERZ: I would say that specific culturing for NTM on a routine basis is fraught with challenges. The testing is not sensitive, and it's not specific. It's not reliable. It's not timely. So we're not actively endorsing that.

DR. LANGE: Other than that, there's no problem?

(Laughter.)

DR. LANGE: Suzanne.

DR. SCHWARTZ: Yes. I wanted to provide a little bit, also, more clarity and more

information to the questions that both Dr. Allen and Dr. Givner had previously asked, from the FDA's perspective in the engagements that we have had with healthcare facilities regarding instructions for use. And you had asked, Dr. Allen, whether their instructions for use are being followed. And I can tell you, of course, with all -- across all issues, that you're always going to have some breaches. It doesn't -- whether it's heater-cooler devices or others. But we have spoken to quite a few facilities that have different types of heater-cooler devices in terms of their adherence, their strict adherence to the instructions for use, and in spite of that adherence, still having contamination subsequent. So that answers that question.

With regard to your question, Dr. Givner, in terms of how feasible is it to undertake the instructions for use and -- well, you heard some of the answers already, but I would say that this is an area that FDA is particularly interested in, and that is why we have engaged with all the manufacturers in terms of also doing the human factors-related studies and pursuing validation testing of the instructions for use to really get at that. Thus far, we have not heard that it's not feasible to carry out. We have heard that it can be quite timely, quite time -- not timely, but in other words, it can take a lot of time and focused attention but that it is doable and it is feasible.

DR. LANGE: Dr. Aguel, did you have your hand up?

(Off microphone response.)

DR. LANGE: No. Yes, Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

This is a question for Dr. Miller. I think in the morning I heard two of the three

companies were not even considering any changes to the IFU, and one of the three was thinking of making some changes. But later in your presentation, I heard that there were already IFU changes happening. So I couldn't understand that. Could you please explain?

DR. MILLER: The IFUs for the particular device that Hospital A was using, we compared the 2010, the 2012, and the 2015 IFUs, and there were differences among all three of those IFUs.

DR. LANGE: Thank you.

Other clarifying -- yes, Dr. Leggett.

DR. LEGGETT: To follow up, Dr. Perz, what kind of surveillance is currently being recommended, since we don't know the correlation between regular bacteria and NTM-type stuff? In other words, if -- so we go back to Dr. Miller's question. Now that I've got a machine that works, how do I know that it keeps working? So to me, that sort of says okay, what kind of surveillance are we going to sort of ask people to do to make sure that the machines are still not dangerous?

DR. PERZ: Dr. Leggett, I think you're referring to culturing or sampling the machine itself, whereas I think, you know, I would be more qualified to talk about surveillance in the sense of, you know, maintaining awareness for possible cases of infection.

DR. LEGGETT: Oh, got you. Okay.

DR. PERZ: Yeah, the device issue, the sampling of the device is not something that --

DR. LEGGETT: So then I guess Dr. Miller and Dr. Sax again. What sort of things should we consider as feasible, not going to break the bank, and then sort of gets at the answer that we need, since NTM cultures are difficult?

DR. SAX: I think that the cultures, when you have a reference center for these mycobacteria, you can do these cultures, and usually we grow these mycobacteria. But I can only say what we do. We do, every month, one culture in every heater-cooler unit, and we also do in those that we have positive cultures, air cultures to go with it.

DR. ROSELLE: Can I add one perspective, which is that if a device is not generating a bioaerosol, if it's not capable of that or if we have a margin of safety somehow engineered in to prevent that bioaerosol from reaching the patient, then the question of NTM-specific surveillance cultures is moot.

DR. LANGE: Thank you.

Dr. Hopkins and then back to Dr. Zenilman.

DR. HOPKINS: I'd like to ask Dr. Perz this, but I think the others can answer this too because you were kind of touching on where I wanted to go. And then just taking a number of the observations that we've heard from multiple presentations, it seems that with however assiduously the IFUs are done, even if you start with a new machine and use only sterile water -- I'm not quite sure why I would use EPA drinking water standards, but using only sterile water, you still inevitably get contamination in the machine. That is going to happen at some point; is that true? So Dr. Perz, your response was to maintain the effluent from the machine, the gas effluent from the machine outside the OR. In other words, if it does get contaminated, that blowback does not occur inside the OR to contaminate the laminar flow field, which can be contaminated by too much traffic in the OR. I mean, there are a lot of things that have been shown to increase the infection rates in cardiac ORs.

Do any of the three of you have a solution that would preclude the inevitable

contamination, no matter how assiduously the IFUs are written, researched, and done, and therefore direct us to a different way of thinking about solving this problem?

DR. PERZ: I will mention that, you know, at least the HICPAC committee was looking for, again, sort of like a secondary, you know, engineered solution along the lines of, you know, filtering the exhaust leaving the machine, and whether that's something that's necessary for every make and model of HCU, we can't say. You know, based on what we heard this morning, it sounds like there's a varying potential in terms of the volume and the concentration of air containing NTM that might leave one of these units.

Another idea that, you know, I've heard from hospital epi colleagues and CDC colleagues is introduction of something like a UV light, some other secondary means of providing a layer of insurance, knowing that humans are humans and errors may occur in terms of strict adherence to the currently recommended IFUs.

DR. MILLER: So building on this idea of what do we do with the effluent, the air, the exhaust, you know, Dr. Sax and others have come up with ideas, recommendations, even from one of the manufacturers, to put the unit outside of the operating room or build a box around it. And on the surface of it, that seems great to me. But as a public health person making a recommendation to a facility, I need to say hold on, wait a minute. I don't know that that's going to work. It sounds good. But I also don't know that we are going to end up recommending something that is going to change the heat transfer capabilities of the device. And so that's where we look to the FDA and the manufacturers to say yes, that's an okay thing to do.

And then, additionally, I would like one additional layer to then look at the human

factors to say, well, if we have it outside of the room, what is that going to do to the perfusionists and their delivery of care? What's that going to do to the bulkheads that might be through the wall? Is it going to be a tripping hazard? Are there more risks of disconnects and splashing in the operating room? I think those things need to be looked at, but I don't think that they're insurmountable.

DR. LANGE: Dr. Zenilman. And if there are any other burning questions after that, please make me aware of them. Otherwise yours will be the last question.

DR. ZENILMAN: Okay, thank you.

This is going to go back to the surveillance as opposed to the IFUs. So, you know, Dr. Sax has the benefit of a reference lab which probably collects nationally. This disease really -- there are multiple labs who do the testing, it's not reportable, and there are case definition problems. Have you thought of any other ways of monitoring this? For example, Dr. Miller, when you did your case-control study, did you look at the -- how were these cases coded? Were they coded accurately? Did they lend themselves to other potential -- other ways of monitoring this?

DR. MILLER: I believe we did look at coding issues just to make sure that we were capturing the exposures correctly, not the outcomes per se.

DR. ZENILMAN: What I'm thinking is administrative databases have the ICD-9 and ICD-10 codes, you know, and basically that's used a lot, and sometimes they're good and sometimes they're not good, and I'm curious of what your sense is on this. Could that be used?

DR. MILLER: So we didn't look at that specifically. My sense is that it would not be

good. We've looked at administrative data for other things, and it's really challenging. The clinical diagnosis is really hard. I would add that the whole issue of sarcoidosis, we had three of our probable case patients that actually had a diagnosis of sarcoidosis. I don't have enough information to say that that was a misdiagnosis, but they did have sarcoidosis diagnosis.

DR. LANGE: The nice thing is this is a 2-day Panel. Many are 1 day dealing with the specific issues. So this doesn't end the discussion obviously. We'll be able to continue it tomorrow and direct questions as well.

Is there anything, any other questions that are burning tonight that you won't sleep if you don't get an answer to?

(No response.)

DR. LANGE: Okay. FDA, any final comments about today's --

DR. SCHWARTZ: We're fine. Thank you.

DR. LANGE: Great. A couple things. One is I was remiss in not thanking the FDA for their excellent presentation this morning that kind of set the stage. Again, our industry representatives, our guest speakers, our public forum, all terrific, very informative. And thanks for allowing us to ask questions as well.

I'll remind the Panel that tomorrow we're going to address this in toto about machines, heating-cooling devices or cooling-heating devices, however you refer to them, in toto, and less so on individual devices to see what we can do to mitigate the issues. I'll remind you that there are some review questions. If you can take a look at those tonight and begin to formulate your thoughts. And then tonight, share a beverage with your fellow

colleagues. Don't share any conversation, however, with your fellow colleagues about this. We're going to start promptly at 8:00 a.m. tomorrow morning. We've heard that both showering and bed-making increases your exposure.

(Laughter.)

DR. LANGE: So if you don't do those, you can be here on time. It won't be any issue.

With that, again, I'd like to thank our Panel, which is obviously engaged and enthusiastic, and our guests. Thank you very much. This will close tonight's session, and we'll resume tomorrow morning at 8:00.

(Whereupon, at 5:00 p.m., the meeting was continued, to resume the next day, Friday, June 3, 2016, at 8:00 a.m.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

June 2, 2016

Gaithersburg, Maryland

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