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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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June 3, 2016
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

RICHARD LANGE, M.D.	Temporary Panel Chair
DAVID YUH, M.D.	Voting Member
KEITH ALLEN, M.D.	Temporary Non-Voting Member
RICHARD HOPKINS, M.D.	Temporary Non-Voting Member
GARY ROSELLE, M.D., FACP	Temporary Non-Voting Member
LAURENCE GIVNER, M.D.	Temporary Non-Voting Member
JAMES LEGGETT, JR., M.D.	Temporary Non-Voting Member
BRYAN CHRISTENSEN, Ph.D., MEPC	Temporary Non-Voting Member
MATTHEW ARDUINO, M.D.	Temporary Non-Voting Member
SCOTT EVANS, Ph.D.	Temporary Non-Voting Member
JONATHAN ZENILMAN, M.D.	Temporary Non-Voting Member
COLLEEN GALLAGHER, M.D.	Temporary Non-Voting Member
ALFRED STAMMERS	Temporary Non-Voting Member
JEFFREY RILEY	Temporary Non-Voting Member
NAVEEN THURAMALLA, M.S., CCRP	Industry Representative
RAYMOND McGLAMERY	Patient Representative
MILDRED DUBOIS FENNAL, M.S.N., Ph.D.	Consumer Representative
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M E E T I N G

(8:01 a.m.)

DR. LANGE: Good morning. I'd like to call this meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee to order.

I am Dr. Richard Lange. I'm the Acting Chair of the Panel. I'm President of the Texas Tech University Health Science Center in El Paso, the Dean of the Paul L. Foster School of Medicine, and am a reformed interventional cardiologist. Partially reformed.

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

And for today's agenda, the Panel will continue its discussion of recent reports and epidemiologic investigations of nontuberculous mycobacteria, or NTM, infections associated with the use of heater-cooler devices during cardiac surgical procedures.

Now, before we begin, I'd like to ask our distinguished Panel members and the FDA staff seated at this table to introduce themselves. I'll ask you to state your name, your area of expertise, your position, and your affiliation. And we'll start with Dr. Schwartz.

DR. SCHWARTZ: Good morning. I'm Suzanne Schwartz, the Associate Director for Science and Strategic Partnerships at the Center for Devices and Radiological Health at FDA, and the Acting Director of Emergency Preparedness/Operations and Medical Countermeasures Program. I happen to be a burn surgeon by training as well.

MR. AGUEL: Fernando Aguel. I am a biomedical engineer by training.

DR. LANGE: Fernando, I'm sorry, we need to get you just a little bit closer.

MR. AGUEL: All right. Fernando Aguel, biomedical engineer. I am Branch Chief of the Circulatory Support Devices Branch in the Division of Cardiovascular Devices, FDA.

MR. RILEY: Good morning. Jeff Riley. I am a perfusionist, Director of Perfusion at Mayo Clinic in Rochester, and past president of AmSECT, a professional organization that represents perfusionists.

MR. STAMMERS: Good morning. Al Stammers. I'm the cardiovascular perfusionist and Director of Quality and Research at SpecialtyCare in Nashville, Tennessee.

DR. GALLAGHER: Colleen Gallagher. I am an ethicist, and I am professor and Executive Director of Integrated Ethics at the University of Texas MD Anderson Cancer Center in Houston.

DR. ZENILMAN: Good morning. Jonathan Zenilman. I am an infectious disease physician and Chief of Infectious Diseases at Johns Hopkins Bayview and Professor of Medicine in the schools of medicine and public health.

DR. ARDUINO: I'm Matt Arduino. I am a senior advisor for environmental hygiene and infection prevention in the Division of Healthcare Quality Promotion. I'm originally a public health microbiologist.

DR. CHRISTENSEN: I'm Bryan Christensen, also of CDC's Division of Healthcare Quality Promotion. I am an industrial hygienist and epidemiologist with experience with bioaerosols.

DR. GIVNER: I'm Larry Givner, Professor of Pediatric Infectious Diseases at Wake Forest School of Medicine in Winston-Salem, North Carolina.

DR. LEGGETT: Jim Leggett, infectious diseases, of Providence Portland Medical

Center and Oregon Health & Science University.

MS. WASHINGTON: Evella Washington, DFO.

DR. ROSELLE: Gary Roselle. I'm National Director for Infectious Diseases for the Department of Veterans Affairs. Recently I've been doing a lot of work with the microbiology of the built environment, particularly water systems. And I also, in the past, have run sterile processing for 150 hospitals.

DR. HOPKINS: Richard Hopkins. I am a congenital cardiac surgeon at Children's Mercy Academic Medical Center in Kansas City. Our university affiliations include the University of Kansas and the University of Missouri. My research interests are in regenerative cardiac surgery and tissue engineering.

DR. EVANS: Good morning. Scott Evans, senior researcher, biostatistics at Harvard University.

DR. ALLEN: Keith Allen. I am a cardiothoracic and vascular surgeon at the Mid America Heart Institute in Kansas City, Missouri. I'm Director of Structural Heart as well as Director of Surgical Research.

DR. YUH: Good morning. I'm David Yuh. I'm the Chief of Cardiac Surgery at Yale University.

DR. FENNAL: Good morning. I'm Mildred Fennal. I am a retired nursing professor from Florida A&M University in Tallahassee, Florida, currently serving as 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. I was a caregiver for both of my parents, who had multiple bypasses, and

my sister who had a heart transplant.

MR. THURAMALLA: Good morning. I'm Naveen Thuramalla. I'm the Vice President of Regulatory Affairs with ARKRAY, Incorporated. I'm serving as the Industry Representative on this Panel.

DR. LANGE: I want to thank the Panel for serving. Both the depth and breadth of knowledge here is very impressive, and the dedication that you guys have exhibited, knowing all the information and wrestling with this as well. So thank you very much for serving. I appreciate it.

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

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

MS. WASHINGTON: The Food and Drug Administration 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.

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.

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 discussions 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 purpose 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 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 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 in 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 made 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 3rd, 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 Oncologic Drugs Advisory Committee in the Center for Drug Evaluation and Research, 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 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 3rd, 2016, Dr. Richard Lange will serve as a Temporary Non-Voting Chair.

Before I turn the meeting back over to Dr. Lange, I would 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 and handouts for today's presentations are available at the registration 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 and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with AnnMarie Williams at the registration desk.

In order to help the transcriptionist 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.

Dr. Lange.

DR. LANGE: As Evella said, go ahead and turn your cell phones off. We have

everybody's cell phone number, and we're going to be calling everybody during the meeting, and we'll find you otherwise.

(Laughter.)

DR. LANGE: We'll now hear a recap of Day 1 from Dr. Suzanne Schwartz of the FDA. And I would like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Dr. Schwartz, please begin with your opening remarks.

DR. SCHWARTZ: Thank you, Dr. Lange.

I want to start off by thanking all of our speakers from yesterday and acknowledging how important their insights are. The expertise and the knowledge that has already been shared with us at this meeting is absolutely vital to all of our collective understanding of this complex issue. And it further enables a robust analysis of the challenges so that implementable recommendations can be developed. FDA also appreciates the active exchange of the Panel with the speakers that we observed yesterday, and we encourage you to continue asking clarifying questions as you listen to the presentations that are going to follow this morning.

It has been FDA's goal to put in front of you a most comprehensive package of what's known today so that you're better poised to address the questions that we are asking of the Panel, and that has included the written materials that you've already received in the Executive Summary as well as the opportunity to hear from and interact directly with these world-class subject matter experts who have been present over the past 2 days.

Now, as is true for many emerging public health concerns, public health agencies such as the FDA are often faced with informational gaps, and this might come as a harsh reality to some, but this is the world that we operate in. And while we assiduously seek to close those gaps, we must also take more immediate steps to mitigate risks to patients in the short term. It's incumbent upon FDA to do so, often in the face of uncertainty. And, of course, as more information comes to light, we recognize that recommendations will be continuously updated. This is not static by any means. We're committed to a dynamic and evolving process here.

Parenthetically, Dr. Perz from CDC stressed yesterday the importance of focusing on short-term and longer-term objectives. We wholeheartedly agree. That has been FDA's approach, and that's why we are assembled here today with a set of Panel questions that speak to both.

- What do we need to be doing right now?
- Or, said differently, is what has been put forward thus far adequate to mitigate patient risk?
- Or do other measures need to be added?
- And then how best do we address these issues moving forward?

As we go through today's presentations and then transition into the Panel deliberations, I'd like to ask the Panel to be particularly mindful of the need for all of us here to shift gears from what some would coin "admiring the problem" stage to actionable recommendations, and therefore to focus clarifying questions on what it's going to take to make that adjustment towards the actionable recommendations.

From yesterday, several key overarching principles that I'd like to share in order to contextualize today's discussions. Number one, the potential for transmission of infection of these NTM organisms for this non-patient-contacting device was not recognized during device design, and therefore it was not accounted for in validation of cleaning and disinfection procedures and consequently in certainly early versions of instructions for use.

That being said, NTM infections associated with heater-cooler devices, to the best of our knowledge, are relatively rare. FDA believes that the benefits of HCDs outweigh the risks, including the risk of acquiring an NTM infection.

We're here to discuss the device class and not a single product or a single manufacturer. We're looking for recommendations that can be applied universally.

Once biofilm is present in a device, its eradication and sufficient cleaning and disinfection by a healthcare facility is nearly, if not entirely, impossible. I think we heard a lot about that yesterday.

And now let's talk about some of the key messages or the discussions coming out of the different groups that presented yesterday.

From FDA, our challenges associated with NTM infections include:

- The environment of use
- The difficulties with respect to cleaning or washing and disinfection
- Determining what are the appropriate acceptable levels of contamination in the context of a lack of standards that have been directly applied to this particular device

The limitations of MDR analyses is something that we all have to recognize. We

don't have a denominator that we can point to, and we really don't know what the numerator is either.

Cleaning and disinfection instructions. In some cases they may be difficult to follow or they may be confusing. And even when followed, contamination may not be entirely eliminated.

- Have they been adequately validated to address risks that were previously not anticipated?
- What does worst-case testing look like?
- What does aerosolization testing look like?
- What types of measures for aerosolization testing exist and should be implemented?

We are working with manufacturers, at present, to go through the process of establishing protocols for testing for cleaning and disinfection. But we need guidance here with regard to what standards should be utilized or what test methods should be utilized.

From the manufacturers, we heard, first of all, about the manufacturers working very proactively with the FDA to validate protocols and to address the questions that we have put to the manufacturers through the information request process. Generally, manufacturers believe that if the instructions for use are followed, that the risk of NTM infection can be mitigated. And if there is anything additional that manufacturers can be doing to reduce the potential for user errors, then manufacturers would like to be able to do so.

From our various experts, we heard yesterday about NTM infections being serious,

that they are certainly increasing within the population. Awareness around NTM infection is also getting greater visibility. We heard that the infection, the vector for infection, it may not be direct to the patient in the operating room, but perhaps put forward was through an indirect, more of a staggered contact within the OR environment. Nevertheless, generation of a bioaerosol by a contaminated heater-cooler device is still at the root of concern that needs to be addressed by this Panel, so I would ask that we pay close attention to that. A key variable may include the direction of fan exhaust.

We heard from the Pennsylvania Department of Health regarding the extensive, very elegant, comprehensive research and investigation that has been done on this issue, and that exposure time to the heater-cooler device, as well as time on pump, has a correlation or a relationship, a potential relationship to the risk of NTM infection, and the state of Pennsylvania's representation that 3,700 patients were notified.

So as we go forward in terms of key issues for discussion on Day 2, here are some of the considerations. We know that we can't bring the contamination risk down to zero. That's simply not practicable, and whether that is even appropriate is a question.

- So what is an appropriate acceptable level of contamination?
- And what does worst-case testing actually look like here?
- Given the design of these devices with components that can lead to aerosol generation, should testing for aerosolization risk be performed on all of these devices?
- Should testing distinguish between aerosol generation within the device and aerosol dispersion outside the device?

Patient notification and identification is a key area of focus for Panel discussion today. And let's draw upon the example, the illustration that was provided by Dr. Miller yesterday, of what he termed a pseudo-infection, a patient whose explanted valve was seeded with NTM while it was sitting ex vivo, outside the body, on a Mayo stand.

- With this evidence of aerosolized NTM in the sterile field only feet away from the patient, what obligation is there to notify this patient?
- What should monitoring of this patient look like?
- Should all patients who are exposed to contaminated heater-cooler devices at a given institution be identified and notified?
- Should notification be based on a risk stratification such as the type of procedure that was performed; implantation of foreign material upon which biofilm can form; identification of an organism that has demonstrated perhaps more aggressive pathogenicity; identification of prior patients at the same institution with NTM infection of similar etiology over past years and how many years?

So these are really questions that we are putting forward. What are the short-term mitigations and long-term mitigations that we need to consider here?

So with that, I'd like to provide the attention back to the Chair at this time. Thank you.

DR. LANGE: Thank you, Dr. Schwartz, for that excellent recap. With this knowledge gap, we'll do our best as a Panel to help fill in with our opinions. Two things are critical to that. One is obviously the information that's provided by the speakers, and I appreciate all

the speakers yesterday and the speakers we'll have today; and then the deliberations of the Panel, in which we'll wrestle with these questions together as a group and be able to direct questions to any of the speakers.

To that end, I'd remind the speakers that there's a 30-minute time limit, not because we wouldn't want to hear more, but just to make sure that we have plenty of time both for presentations and for the deliberations as well. I'll hold pretty strictly to that time limit. So I'll tell our speakers that if the most important slides are your last two or three slides, you may want to move those to the front in case we don't get to them.

(Laughter.)

DR. LANGE: Our next speaker or the first speaker, guest speaker of the day is Dr. Daniel Diekema. And Dan, if I've mispronounced that, please correct me. Thank you for being here.

DR. DIEKEMA: Thanks. So yes, I'm Dan Diekema. I'm the Director of the Division of Infectious Diseases at the University of Iowa College of Medicine, the Associate Hospital Epidemiologist at the University of Iowa Hospitals and Clinics, and the Associate Clinical Microbiology Lab Director at the University of Iowa Hospitals and Clinics.

DR. LANGE: Could you point up the mike just a little bit more?

DR. DIEKEMA: Yes.

DR. LANGE: It will give a little more audio over there. Thanks.

DR. DIEKEMA: Is this better? Okay. And I appreciate this invitation to talk to you about really practical issues that we experienced around our own institutional response to this multi-state and multi-country outbreak. So I'm going to start with what brought to our

attention the link between an *M. chimaera* infection in our hospital. So this is the index patient, the first patient that we identified, a 59-year-old male who had aortic valve replacement on October of 2012 for a dilated aortic root and symptomatic aortic insufficiency that was performed at our university.

The next several bullets are in a blue box. I'm not sure you can see that on the screen. The reason for that is, I think, pertinent to case finding. This patient's care, all of the care delivery except for the surgery, was at another healthcare system because he lived more than 2 hours away from Iowa City. So he did well until about 15 months after the surgery, when he began to have back/chest pain, shortness of breath, cough, fever, pancytopenia, elevated transaminases, and weight loss. He had a very extensive ID evaluation, including multiple sets of blood cultures that were unrevealing.

In April of 2014, he had a really profoundly positive clinical response to prednisone with near resolution of his symptoms. He was provisionally diagnosed with sarcoidosis. I think we've heard that here before. But when his symptoms began to recur after the prednisone course was completed, further workup for a malignancy with the bone marrow and a BAL for further evaluation for sarcoidosis. In both of those procedures in this healthcare system, AFB cultures are standard. They're just done whenever they receive these samples. They both grew *M. chimaera*. Not knowing exactly what to make of that finding, this patient found his way back to a local infectious disease provider who did blood cultures which also grew *M. chimaera*; was then begun on multi-drug therapy and never was able to really clear his mycobacteremia, had positive, monthly positive blood cultures due to *M. chimaera*.

So how did we learn about the case? Well, January 19th of this year, our infectious disease on-call physician received a call from the local ID provider requesting assistance with a clinical syndrome he'd not seen before: an intractable, invasive, disseminated *M. chimaera* infection. We noted that the patient had had bypass surgery for this aortic valve replacement at our institution. We were aware by the time of the situation and the elegant work of Dr. Sax and his colleagues and the experience in Pennsylvania that you've already heard about. So we felt that since there were no other obvious exposures or risk factors for this patient's infection, we absolutely had to initiate an outbreak investigation. So we assembled our HEIR group, Hospital Emergency Incidence Response group. I think I'm going in the wrong direction here.

So over the next 2 weeks we were busy. We notified the Iowa Department of Public Health, CDC, FDA, the Joint Commission, and the manufacturer of the devices that we use. We did an initial case finding that I'll describe in more detail. We removed existing units from service. We had a couple of units in a warehouse waiting for our children's hospital to open, so we retrieved those. We did water samples. I'll talk about those results later. Elective surgeries were postponed until the new heater-cooler units arrived 4 days later. We developed internal and external communication plans, a process for evaluation and management of all patients who had symptoms within 4 years of a procedure involving a heater-cooler unit, and then patient and provider notification. I underlined that simply because that's how the additional cases were identified, was almost immediately through provider notification, and then we did a media release.

The microbiology look-back, looking at all positive cultures for *Mycobacterium avium*

complex in the prior 5 years, was not particularly revealing. We sent a couple of pulmonary isolates from a lung transplant patient because we knew that patient had been exposed to a heater-cooler. I'm sorry, I'm using heater-cooler unit, HCU. In earlier slide presentations, it's heater-cooler device. And my own view on microbiology laboratory look-backs is that they're going to be extremely low yield, and the reason is simple: sterile site AFB cultures are not routinely obtained unless there's a recognized risk factor present. And we still do not have a wide understanding in the clinical community that exposure to a heater-cooler device is a risk factor for disseminated *Mycobacterium avium* complex.

We used our EMR to generate a best practice alert. We talked a lot about how to do this. We identified all patients again who had been exposed to bypass in the prior 4 years, who had any diagnosis that was consistent with a febrile illness, advising clinicians to consider getting AFB blood cultures or other AFB cultures if there was not another explanation for that febrile syndrome. As of a week or two ago, that had fired for 26 patients. Six of them had AFB blood cultures obtained. All so far are negative.

So we deliberated for a while about how to mitigate or eliminate, because we wanted to be able to tell our patients that we eliminated this risk, and we felt the only way to do that was to remove heater-cooler devices from our operating rooms. So on the left, what that photo is of is after our engineering group had drilled through the wall, they put this Corian door in place, through which the heater-cooler tubing could pass as well as the cord that allowed remote control of the heater-cooler device from inside the operating room by the perfusionist. Our OR air, like in many institutions, I assume, is continuously monitored for positive pressure and air exchanges, and we confirmed that even with a

heater-cooler unit running with this portal open to accommodate the tubing, it did not impact the airflow and the positive pressure in our operating rooms. We have had no complaints from our perfusionists about this. They have been pleased with the solution. We can discuss this later. I readily admit and understand that the OR layout in many institutions does not allow for this to be done as easily as we were able to do it.

So we chose to notify all patients who had been exposed to a running heater-cooler device since January 1st, 2012. We chose that 4-year window after conferring with our CDC colleagues. And I will say that I think we're starting to see, as has been mentioned earlier, that going back 5 years or more may be necessary. Cases have been identified where the operative procedure is 5 years prior.

We used billing codes and operating room logs. We didn't do any risk stratification. I think knowing what we know now even 5 months later, having to do it over again, we may have considered a risk stratification and focused only on those individuals who had implants, valves, grafts, etc.

We did notify some who did not have cardiac procedures. One of our liver transplant surgeons likes to use the heater-cooler units during transplant, and so we notified some of those. And some of transcatheter aortic valve replacement patients we notified as well.

We learned that when the heater-cooler unit -- when bypass is on standby in case a surgery needs to be converted to something open, oftentimes the heater-cooler unit is running while it's on standby.

So we wanted to make sure that we confirmed that all of these patients had been

notified. So we instructed them in the letter that I'll show you in a minute to call a toll-free line. The line was staffed by a registered nurse 24/7, who had a scripted algorithm to use. We then followed up with phone calls and mail contacts to all patients who did not respond to this. And I'll discus that in more detail in a minute. We also established a "NTM clinic" to evaluate those patients who had any symptoms or even just had expressed concerns that they wanted to be evaluated. They were also given the option to take the information that we had provided to them and to their referring provider and be evaluated by their own provider.

So this is an excerpt from a patient letter kind of describing -- we had this reviewed by several people, including trying to review to some extent for plain language. We talked about some of the symptoms that the patient should be alert for and then how important it was for them to call us and let us know that they had received the letter. The letters were translated into the patient's preferred language in our EMR, and translators were available for the patient calls.

We also sent letters to all of our referring providers, explaining the situation with a Q&A attached to it. I want to acknowledge that we were -- fortunate is not the right word, but it was good that this occurred after the experience in Pennsylvania because we really relied heavily on our colleagues from Pennsylvania who had experienced this and had also done patient and provider notification and media releases. A lot of the materials that they had used, we could modify for our use. So I want to thank them publicly for that.

We issued a media release then on February 2nd. We wanted to make sure that we didn't notify the media prior to all of the patients receiving notification letters. We were

somewhat surprised we didn't get a lot of media uptake. There were three or four local stories. We're actually hoping the media would amplify this information to the public so that we would improve our response from the patients who were exposed or concerned that they were exposed, and the media response in general was quite responsible.

We established a website -- you can go there now if you wish -- that really included all of the information that we provided to the patients, to providers, to the media, as well as links to the materials that you've already heard about, the CDC notifications, the FDA notice, and other information about NTM.

Our NTM evaluation clinic was staffed by a physician's assistant but directed by an onsite infectious diseases clinician. We used a checklist that we developed with input from our own ID group and also, again, external experts who had cared for these patients and established sort of triggers for when cultures ought to be obtained. Those triggers were based upon symptoms, signs, lab results like elevated transaminases, pancytopenia, and what the prior workup had been.

And we updated our policy for AFB blood cultures, which are not commonly obtained. And we had to distribute -- because they do use special blood culture bottles, we had to order additional bottles and distribute them to all the clinics where these patients would have been evaluated.

We have an active mycobacteriology laboratory. We do cultures and sort of initial-level identification, much of it using DNA probes. So, for example, we have -- pertinent to this discussion, we have a probe for *Mycobacterium avium* complex. We do not do species-level identification. We send out for that. And we also send out our isolates for

susceptibility testing.

The initial evaluation exceeded the capacity of our blood culture instrument, so we did have to convert to our older manual isolator tube method for AFB blood cultures, you know, part way through -- you know, probably about 4 or 5 weeks in. But most cultures from this initial evaluation are now final and negative.

So we ended up notifying about 1,500 patients or at least identifying about 1,500 patients who were potentially exposed during this 4-year period, and because we required a contact, we're still tracking down about 200 that we were unable to reach. We've actually now employed a vendor to help us track those individuals down to make sure that they received the information.

Over 130 symptomatic patients underwent evaluation in the NTM clinic. We have not identified any additional cases yet via this clinic. We did, however, identify two additional cases via the provider notification. And as I said, this was almost immediately as a result of the many in-services and meetings that we had with our cardiac group, our cardiology group, our transplant group.

So the second case had been referred from a local provider for a systemic granulomatous inflammatory process, liver and bone marrow biopsies showing non-caseating granulomas, but all the micro-stains negative. And our hepatologist heard our presentation on this and immediately recognized that this patient was at risk and ordered AFB blood cultures.

Case 3 was being followed at our institution for a very complicated course after -- before and after cardiac transplant, had just not been doing well on a number of fronts, and

the transplant cardiology and transplant ID coordinated AFB blood cultures.

So this is sort of a summary of the three cases at our institution that we have identified to date. Just some common features that you've already heard. All had some kind of prosthetic material in place: Case 1, an aortic valve; Case 2, an aortic arch graft; Case 3 had had three VAD procedures and a heart transplant and during the process also had an aortic arch repair performed and graft material in place. The procedure dates are listed there. All have invasive disease, positive blood cultures. The time to symptom onset was over a year in all cases. It's a little unclear in Case 3 because the exposures occurred over the course of 11 -- 13 months. The time to diagnosis, over 3 years or close to 3 years in all cases. The first case unfortunately died in May of this year as a direct result of this infection. The other two are under treatment in an extremely complicated clinical scenario.

So I mentioned that we had done microbiological surveillance cultures on our units. So as you can see, on the left are the samples that were obtained, tap water, and then the six heater-cooler devices. Devices 5 and 6 were the ones that were just put in service, as you can see, at the time that we had linked a case to our institution. The others had been put in service years prior.

Our initial set of cultures. Only one unit grew *M. chimaera*. The second set of cultures done -- and I should mention that our perfusionists had been adhering to instructions for use for these devices, the changing instructions for use, the updates that had occurred about 6, 7 months prior, and they had actually been going beyond that by doing more frequent tubing changes and obviously continue to do that assiduously after January 28th. Nonetheless, in April, four of the water cultures grew *M. chimaera*.

I am a clinical microbiologist and an infectious disease physician as well, and I think that the idea that doing routine environmental cultures for NTM is going to be helpful in this situation. Other than as an investigative measure during an outbreak setting, I think, is ill-founded. I don't think these cultures have good performance characteristics. Only a few labs know how to do them well. I think the negative predictive value is likely to be very low. I think you've already probably heard this from Dr. Perz yesterday, and I agree completely with him.

So in my two decades as a hospital epidemiologist, I think this is one of, if not the most challenging situations that we've been confronted with. There are many challenges. Case finding is an extreme problem, which is why I think we don't know the scope of this problem yet. Many patients who receive cardiac procedures, including complicated procedures involving grafts or valves, receive their follow-up care locally, not at the hospital where their surgery is performed. Moreover, the symptoms are extremely nonspecific, as you've heard, and can present months to years after the exposure.

And clinician awareness of this problem -- and this isn't just general clinicians, but I can tell you ID community as well, the awareness is still not high. So mycobacteriology cultures or mycobacterial cultures are not, you know, considered to be performed simply because of a prior exposure to a heater-cooler device. It's not yet widely recognized as a risk factor. I think risk mitigation is obviously problematic as well. I think these units are at very high risk of being colonized, as you've heard.

I do not believe any disinfection method has proven reliable. I've seen one published report that you've already heard about and has been referenced of a peracetic

acid approach that involves changing of all the internal tubing. But I'm just not convinced that whatever you do to these units, once they're colonized they can -- that the organism can be eradicated.

As I said, water cultures, I think, have poor negative predictive value. The safest approach, obviously what we felt was the safest approach, was complete separation of the exhaust air from the operating room air.

So this is my opinion where we need to go from here. I think we have challenges in case finding, case management, and prevention. In terms of case finding, we need to improve clinician awareness of this problem. I believe that there ought to be at least increased efforts for national provider notifications, if not patient notifications.

And we need to be creative. And you've heard some creative ideas about additional case finding. We're looking at crossing our sarcoid diagnoses with our heater-cooler unit exposure list and starting to run down that list as a potential source of cases. You could also say the same about fever of unknown origin, doing text searches in your pathology reports for granuloma and cross that with your heater-cooler device exposure list. So there are some ways we could potentially improve our case finding.

As someone who's been involved in the management of three of these cases, I can tell you that it's an extremely challenging management problem, largely because we have such limited information about this clinical syndrome. It really is a novel clinical syndrome, and issues around weighing risk and benefit of removal or replacement of prosthetic material in these patients, whether that is going to be a curative approach, and in the absence of which, at least to this point, it appears the organism is nearly ineradicable from

the patient.

And then for prevention, I believe removing units that have been implicated in transmission events from the operating room is necessary. I think figuring out how to separate, as I said, exhaust air from OR air is essential. And then in the long term, I think we need engineering solutions.

We know now that we have a bioaerosol generator that's in a critical area of the hospital. It's unacceptable, and you know, we have to figure out an engineering solution for that, whether it involves filtration, whether it involves UV, whether it involves a careful evaluation of the differences in design, the differences between a unit that moves 20 feet per minute and one that moves 750 feet per minute. I think all of these things need to be considered as a more permanent engineering solution is designed.

So I believe that's all I have. Yeah. Thank you.

DR. LANGE: Thank you, Dr. Diekema.

We'll have the opportunity to ask clarifying questions after all three of our speakers have given a talk, so Dan will be around.

We will proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

For the record, the FDA has received one written comment, which is provided in your folder, and it's addressed such, so you'll find that in your folder. However, the FDA has not received any requests to speak for this meeting prior to the established deadline, which was found in *Federal Register* Volume 81, No. 73, dated Friday, April 15th.

Does anyone else wish to address the Panel at this time? If so, please come forward to the podium and state your name, affiliation, and indicate your financial interests.

(No response.)

DR. LANGE: Seeing no speakers, the Public Hearing -- Open Public Hearing is officially closed. I will proceed with today's agenda. But before doing so, I want to just take 2 or 3 minutes to give everybody an opportunity to read the submitted presentation. So there will be 3 minutes of silence unless you need to read out loud. So spend just a couple moments, and I'll allow you to read this.

(Pause.)

DR. LANGE: Thank you for your indulgence. Since it was entered as part of the Open Public Hearing, I wanted to make sure it got due diligence. So thank you all very much.

We'll now continue with our remaining guest speakers. Our next speaker is Dr. Charles Daley. Our next two speakers will have 15 minutes. And again, the timer will show -- will be yellow when there are 2 minutes remaining.

Thank you, Dr. Daley.

DR. DALEY: Thank you, Chair. Yes, my name is Chuck Daley. I'm from National Jewish where I am Chief of the Division of Mycobacterial and Respiratory Infections. This is the division that focuses on all things mycobacteria, and I have been doing that for a long time. As you heard, we'll be sharing the next 30 minutes, Dr. Strong and I, but it will probably be more like 20 minutes/10 minutes in terms of the break. I would like to thank the FDA for the opportunity to present to you all today some things more on the clinical side. This keeps coming up in some of the previous discussions, some of the clinical issues

that need to be addressed.

So this is my outline. In the next few minutes, we're going to look at why is it important to be able to name this organism, or really to speciate this organism, *chimaera*? The clinical presentation is very important and particularly when we think about disseminated disease, because this is not something clinicians in the U.S. are used to. And then I'm really going to, at the end, focus more on the diagnosis and treatment because very important issues come up related to how we care for these patients.

Conflict of interest. You'll see three items here. I don't think any of these are necessarily relevant to today, but I think it's important to disclose anything related to NTM, and these are just three areas of investigation that I'm involved in.

So we heard from Dr. Falkinham that there are a lot of species, and you can see here over time how fast we're identifying new mycobacterial species. And *Mycobacterium chimaera* is actually a relative newcomer to this list. It was reported as a new species in 2004, but it really just sits within this group called the MAC complex, *Mycobacterium avium* complex.

And I suspect that most clinicians could not name over three of these, and most clinicians don't even know what *chimaera* is, and the reason they don't is because their laboratories can't identify it. So it will be called *intracellulare*. That's the report the clinician is going to get, and it will never be identified as *chimaera*. And also, because this is a new -- relatively newcomer to the list and because the labs don't identify it, we don't really know how much is out there, how much *chimaera* is out among the MAC complex.

Well, it's interesting that these initial reports came from Switzerland and Germany

because it looks like they have a lot of *chimaera* compared to other regions. This is an early report, 2008, looking at two sources in Germany, one from the National Reference Lab in Borstel and the other from a hospital. They had 166 isolates that were identified using more typical procedures like 16S RNA sequencing methods, and they were called *intracellulare*. But if you use a more appropriate sequencing method to be able to figure out is this *chimaera* or not, you can see that almost 90% of theirs were not *intracellulare;* they were in fact *chimaera*. So there's a lot of *chimaera* in this region.

We looked at our data just kind of back at the envelope. Max Salfinger gave me this. He's the director of our reference lab at National Jewish. And looking at almost 9,000 isolates that were sequenced using rpoB gene sequencing, about 80% of all the isolates that we get at our lab, which is from all over the U.S., were among the seven isolates, and 42% were MAC. But of those MAC, only 6% were *chimaera*. So at least what's coming through our lab, which is sampling all over the United States, we're not seeing nearly as many isolates of *chimaera* as was reported in Germany. So I think this is still a question: How much *chimaera* is out there?

So what's in a name? Well, there are four general ways we could look at *chimaera* and compare it to its cousins, *intracellulare* and *avium*. Where does it come from? So *avium* and *chimaera* are found in water, and as Dr. Falkinham noted yesterday, *intracellulare* we're not sure, probably soil. I think, very importantly, the few data that exist on pulmonary disease suggests that *chimaera* is the least pathogenic of the three. So this is one of the surprises to us, as clinicians, when we started hearing about *chimaera* causing such severe disseminated disease.

The clinical presentation, at least in terms of pulmonary disease, varies, and it looks like *intracellulare* usually presents with more advanced disease, more cavitary pulmonary disease. But treatment outcomes seem to be worse for *chimaera* and *avium*. So we believe that it is important for laboratories to start speciating these organisms, not only for surveillance purposes but for the clinician, because we're learning that there are differences in how they behave in humans, at least in pulmonary disease. So the name is important.

Now, we've heard a bit about the clinical presentation, but again, if you go to ID and pulmonary docs in the U.S., what they know is pulmonary disease, and they're expecting someone who grows *chimaera*, they're expecting it to grow from a respiratory specimen, and the patient is going to present with cough and fatigue. They may be the tall, thin phenotype that we heard about yesterday, and the laboratory parameters usually suggest some inflammation, like elevated CRP. But generally, even very deep dives into their immune response or immune system shows that they're normal in pulmonary disease.

Now, in disseminated disease, this is quite different, and looking at some of the data presented yesterday by Dr. Sax, the symptom complex, there's certainly overlap, but usually the cough is missing. The signs of disease, such as splenomegaly, hepatomegaly, chorioretinitis, are distinctly absent in the typical pulmonary presentation. But one of the most notable features here are the laboratory parameters. Almost every patient that I know about in the U.S. has had pancytopenia or significant cytopenia. This is not something we see in the typical presentation as well as the elevated transaminases and sometimes elevated creatinine. So the clinical presentations are quite distinct, and this delay that we keep hearing about is remarkable, with a time to presentation being a median of 21

months. This is not something that clinicians know about. We have to educate them and make them understand that this syndrome actually exists.

The other thing that they're not expected to see are infections of the prosthetic valves due to a mycobacteria or vascular graft infections. These various manifestations are often embolic phenomena. These are not something that most clinicians in the U.S., they're not going to tie this presentation to a mycobacterial infection, which means they may not be getting the appropriate culture or samples.

What that means is delays in diagnosis. And there have been a number of reasons that we see, in these patients, as to why there are delays in diagnosis. One is this long period from the surgery to clinical presentation. There have been various clinical manifestations, as I showed and Dr. Sax showed yesterday. Unfortunately, appropriate cultures are often not done initially because of this lack of suspicion. We can't do anything about the slow growth of the mycobacteria right now, but that does add to this delay in diagnosis.

And very importantly, when it is not speciated and it has to be sent to another laboratory, that adds another element. And then, believe it or not, there's disbelief of some of the providers. They didn't believe the results, and there were some delays in initiation of therapy because of that. If we have delays in diagnosis, that means delays in therapy. Delays in therapy mean worse treatment outcomes.

So this is kind of the schema of, from start to finish, how long it takes to make a diagnosis of a mycobacterial infection in most circumstances, generally about 8 weeks to get to the point of drug susceptibility. But again, if it's moving between laboratories, this

could be 12 weeks or more. What I circled here is identification, and I think that's what has come up in discussions over the previous days. It is very important that this goes to a laboratory that can identify which species it is. Otherwise we're not going to even think about *chimaera* because you're going to be told it's *intracellulare* when it is, in fact, not *intracellulare*. So how we speciate is a critical component.

So there are molecular methods available, including in-solution hybridization probes, but unfortunately they cannot identify *Mycobacterium chimaera*. There are line probes available. Not in the U.S. But even if they were, they do not identify *chimaera*. So we're left with sequencing, and there are different ways to do sequencing. We use rpoB sometimes with heat-shock protein 65 backup if the rpoB cannot distinguish it. But without a sequencing approach, we cannot tell the clinician that this is *chimaera*, and most laboratories in the United States cannot identify *chimaera*.

So sequencing. So, many laboratories cannot do it, and they can't even tell you the species, but they can't tell you the next step, which is important with *abscessus*, and that's the subspecies. So that requires sequencing. And rpoB we use at National Jewish, but there are other ways to do this. But importantly, these are all validated by CLIA standards.

One of the things that I keep hearing about and wanted to add here was how long does it take to get your results back? Again, it depends on the lab and the methods. For example, our turnaround time would be about 3 to 5 days for identification once we have a positive culture for *chimaera*. So it's a little faster than what I've been hearing about, if it gets in the right place.

The other thing that's important for the clinician is that it also goes to a laboratory

that can provide drug susceptibility testing. These are panels we offer, but the two drugs that are most important are the macrolides and amikacin, and the clinician needs that information to be able to develop an appropriate treatment regimen for the patient.

And here's what I mean. The most important determination is does the organism have susceptibility to the macrolides? This is an approach that we use to treat pulmonary disease. The duration of therapy is 12 months, culture negativity. So does the organism -- is the organism susceptible to the macrolides? If the answer to that is yes, we then ask, do they have cavitation on their chest X-ray? If they do not, we can treat a patient with MAC with three drugs three times a week, with a very high rate of culture conversion. If they have cavitation present, we use daily therapy, and we usually use intravenous amikacin. And this will come up in a moment when we talk about disseminated disease. Very importantly, if it is a macrolide-resistant isolate, we only treat with daily therapy. But the macrolides don't work, so then we have to find additional drugs. These are some of the additional drugs we may go to and we have used in some of these patients with disseminated disease. And we may also add intravenous amikacin.

So we do have some fairly good data on how patients do with this approach to treatment with pulmonary disease. And so let's start with that, and then we'll compare to disseminated disease.

So if someone has pulmonary disease that is macrolide susceptible without cavitation, we expect culture conversion in about 80% of the patients. If they have cavitary disease, it drops. It's probably 50 or less percent. So that's an important predictor of their outcome. If they have macrolide-resistant disease and you don't resect that part of the

lung and give them a prolonged course of an aminoglycoside, it drops to 5% culture conversion. It is not curable. So when I hear discussion about prophylactic regimens and giving macrolides, well, if you do that and it fails and the patient has now macrolide resistance, you have doomed the patient. So I'm very concerned about this idea of preventive therapy. If you do surgery plus an aminoglycoside, you can actually get it back up close to 80% culture conversion.

So this is what clinicians in the U.S. and most of the world are used to in terms of treatment response, and it's based on whether there's cavitation present and whether there's macrolide resistance or not.

Now, this is the general approach, very similar. But here we don't have to worry about cavitation. So we still need to know is there macrolide resistance or not? So the laboratory must be able to provide this as quickly as they can. We would use daily therapy if there was macrolide susceptibility or resistance. And the issue comes in, do you use IV amikacin? So most of these cases that I'm aware of and have consulted on, we did use intravenous amikacin. Intravenous amikacin will often convert cultures while it's on, I mean, while the patient's receiving it, but we can't give it for very long because of drug toxicity.

What some of the papers coming from Europe have suggested, perhaps a 3-month initial course of intravenous amikacin, but in all honesty, we don't know how long we should give it, nor do we know how long we can treat. Part of the reason for this is because people, despite four, five drugs with these disseminated *chimaera*, have not converted their cultures. Some have converted their cultures and then recur with positive. So the best

drugs that we have, giving even more drugs than we do for pulmonary disease, has been a very difficult case to try to convert their cultures.

So this is kind of a busy slide from Kohler's paper that Dr. Sax presented yesterday and the point of this is outcomes. I showed you the outcomes for pulmonary disease for which we have a number of studies that can give us those data. But we have very few data to date, at least what's been published on outcomes in these patients.

But what I want to point out in these 10 patients in the Kohler paper -- these are the patients from Europe -- each of those boxes is a patient who died. Half of the patients died, and they were on multiple antibiotics that in a pulmonary case should have been effective but were not effective. Each of the little triangles up there was a surgical intervention. So you can see some had repeated surgeries, and they still died. So this is an extremely difficult-to-treat patient population that has been -- and one patient that I have been involved in recently died, despite five-drug therapy for over -- much of it over a year.

So this leads, of course, to this question: Why is it so difficult to treat? One is that delay in diagnosis leads to further dissemination and tissue invasion, obviously endovascular infection of foreign material. And unfortunately, these are largely bacteriostatic drugs. And for the infectious disease doctors here, you know, they know trying to treat an endovascular infection with a bacteriostatic drug is an uphill battle. We also know from some of the papers from Europe that many of these patients had low serum drug concentrations, and I don't know if that contributed to their poor response or not, but also the presence of comorbidities. So this has been a very frustrating issue, and that is, how to cure these patients.

So I'll end and then hand it over to Dr. Strong. I'll leave these there for you to read. The bottom line is that I think that if we cannot find earlier diagnosis, basically earlier case finding, we do not have much hope in curing many of these patients. If we found them earlier, perhaps we could intervene and do surgery again, remove the infected graft. But at the time that they're being found, they're often so sick it is very difficult to do that.

So let me stop there and let Dr. Strong take the podium.

DR. LANGE: Thank you, Dr. Daley.

Our final guest speaker is Dr. Michael Strong. And at the conclusion of Dr. Strong's presentation, the Panel will be permitted to ask clarifying questions to any of the three speakers.

Thank you, Dr. Strong.

DR. STRONG: Um-hum. My name is Michael Strong. I am an associate professor at National Jewish Health. I also have an affiliation at the University of Colorado at Denver. I run a research group that focuses on genomic and computational approaches to infectious disease pathogens. I'll tell you a little bit about our work in nontuberculous mycobacteria as well as focusing on *Mycobacterium chimaera.*

As Dr. Daley and Dr. Falkinham alluded to, there's been an increase in incidence of nontuberculous mycobacterial infections over the years. This is not thought to be due to better diagnostics but actually because more people are getting these infectious diseases. In the U.S. this has been characterized, and abroad. So it's an increasingly recognized and increasingly important area of disease that sometimes gets shadowed by other global diseases such as tuberculosis.

Our research group focuses on multiple methods to analyze and interrogate infectious disease pathogens. I'll mainly be talking about our genomic approaches, which involve whole genome sequencing and targeted genome sequencing. All bacterial genomes are circular in nature. They encode about 4,000 to 5,000 genes. In that the nucleotide sequence, which is the DNA sequence, encodes about five million to six million base pairs, this is the finest resolution that you can get to understand what genes are encoded in the pathogen as well as to compare pathogen extremes. This can tell us about virulence. It can tell us about drug resistance. It can tell us about similarities in clinical phenotypes matched with genotypic information. So our group has really dived into this area. I've been working in mycobacterial diseases for about 15 years now, starting in tuberculous and then merging into understanding nontuberculous mycobacterial infections.

We're very interested in the triad of interactions between humans, pathogens, and their environment. And this is specifically important for nontuberculous mycobacteria, which the primary mode of infection is thought to include the environmental contact that's transmitted to the human, as opposed to tuberculous disease, which is directly human-to-human contact of the pathogen. There have been some suggestions that there may actually be human-to-human passage of certain species or subspecies of nontuberculous mycobacteria, but the dominant transmission is thought to include environmental components.

We use a variety of sequencing methods in our laboratory. We've used all of these platforms: Pacific Bioscience, Illumina, Life Tech. The common thread among all of these instruments is they can produce large amounts of genomic sequence information very

rapidly and robustly for us to sequence entire genomes of pathogens in a robust manner. For certain types of projects where we want to get a full assembled circular bacterial chromosome, we use technologies such as Pacific Bioscience, which gives us a longer read length. But for our current projects we use Illumina MiSeq, and I'll be presenting some of that data today.

So this is a simplified version of our genomic pipeline. We initially start with the bacterial colonies. So samples are typically sent to National Jewish Health for diagnostic and species classification. We then can take those samples, purify genomic DNA, construct genomic libraries, and then sequence them using various next generation sequencing platforms. An important part of our projects, in addition to doing the research and analysis part, is we always upload our information to NCBI so that others can use it, not only us. And we actually use a tremendous amount of data from NCBI and other sources in our comparisons, because then we can really understand what's the global diversity of some of these pathogens. What are we seeing here? How is it different, and how is it similar?

So this is just one example where we studied an outbreak that had occurred in Brazil. This is not a *chimaera*. This is of the *abscessus* class. But what we wanted to do is understand are there any similarities and differences between other *abscessus* strains that had been coming out in different regions of the world and involved in other outbreaks? And so this is a phylogenomic tree. It's similar to a phylogenetic tree, but it's based on full genome information. And so what this does is we can compare the sequences at the genome level of all of these strains, and it will cluster, bring together strains that are most similar genomically at the DNA level. So this is the finest resolution that you can get to

distinguish whether a strain is similar or different.

We can also look at larger genomic variations and these -- instead of looking at single nucleotide changes, we can look at larger changes, and this could include deletions or insertions in the genomic DNA. And this is just a schematic. Where there are troughs here in the schematic, like this, this means that these strains have a deletion in this area. We're not getting any next-generation sequence reads that map to that region. So we can quickly identify characteristics that might be different, that are much greater changes than single nucleotide polymorphisms. And this comes into play with plasmids. Plasmids can be acquired in some cases, and they can be lost in some cases, and this kind of analysis will help us identify those kind of larger changes.

So we've looked at a lot of different mycobacterial species and subspecies using next-generation sequencing and whole genome sequencing and looked at the diversity. So we've sequenced well over 200 strains to date of different types of mycobacterial strains, and one thing that we've noticed is that *Mycobacterium chimaera*, the species diversity at the genomic level isn't as great as some of the other species that we looked at, like *abscessus*, which emphasizes to us that if you really want to look at relatedness of strains, whole genome sequencing is probably -- it is the most fine resolution method that you can use to really understand, are these related or are they not?

So this just shows a number of *Mycobacterium chimaera* strains that we have sequenced prior to getting involved in this study, and we were looking at the strains from different locations in the U.S., initially Hawaii because it has the highest incidence of nontuberculous mycobacterial infection in the U.S., and they also have a high number of

chimaera strains, both in the environment and in clinical samples.

So we started to look at some samples that were sent to National Jewish Health for characterization using rpoB sequencing, as Dr. Daley alluded to, and using rpoB, you can speciate into *Mycobacterium chimaera* or *intracellulare*. We started to sequence some of the strains that came in, including sequences from heater-cooler units as well as patient isolates. And so this is a schematic of a number of samples from different areas, regions of the world. We have strains from Texas, from Ireland, Oxford, Hawaii, and we have three that are related to this discussion, one from a heater-cooler unit and two from patients.

And so this schematic here doesn't show the resolution that we need, so we can focus on a finer resolution phylogenomic tree. And so this just suggests, when we look at -- when we compare the complete genomes of these isolates and look for strains that are similar and different, at least from what we've sequenced so far, the strains from the individuals are highly similar to the heater-cooler unit.

Now, I need to preface this, that in order to do a very systematic study, it's important for us to get background isolates. And so we really need to know the genetic diversity in regions, and we also want to know what's happening in other locations to really understand are there *chimaera* -- are the *chimaera* strains highly similar in different locations, including Europe and other, and what are the implications of that?

So we have strains that have been sent to National Jewish Health that are going to be fed into our pipeline. We're asking for environmental isolates also to really understand the implications of this. But I think, you know, this sets the foundation to really understand this. Also we're a highly collaborative laboratory and want other samples so that we can really

understand this.

And so, if we look at the mean SNP difference within that group that's involved in this study, we have very little SNP diversity among those strains when we look at the genomic comparisons, when we compare them to other strains that we've sequenced. So we want to broaden this tree by including other strains so we can really understand this observation.

So, in essence, our next steps are we want to perform whole genome sequencing on other mycobacterial strains, including ones that are of concern, specifically *Mycobacterium chimaera*. When we started, there wasn't a good reference strain, a reference genome, so we had to actually use technologies to create a very robust reference genome, which we have now. We've sequenced well over 30 to 40 *Mycobacterium chimaera* strains, so we're filling in that phylogenomic tree, and now we can start to analyze sequences that come in, in relation to that information.

We're here to collaborate and help in any manner we can. We're a research lab, but we really want to foster our understanding as well as facilitate efforts by the FDA and the CDC in really understanding implications and potentially identifying markers that could be used to better distinguish if *chimaera* is a problem in these units or in the patients.

So with that, I'll conclude. Thank you.

DR. LANGE: Thank you, Dr. Strong.

I'll ask all three of our speakers if you'll join us here at the table. That will allow us, the Panel, to ask some clarifying questions for the next 15 or 20 minutes. And I'll remind the Panel that if we don't get to the questions early this morning, we'll have other opportunities as well. So with that, let me open this next section up.

Yes, Jeffrey.

MR. RILEY: Dr. Diekema, we're neighbors, and I have three excellent perfusionists from the University of Iowa that trained and graduated from there. Could you confirm which heater-cooler? I think we saw a picture, but I don't think you stated which heater-cooler.

DR. DIEKEMA: I'll ask the Chairman if that's okay. I understand that a spirit of this hearing is to discuss this in general, but I'm happy to --

DR. LANGE: You're welcome to identify. We're going to discuss in toto what we ought to do, but feel free to provide that information.

DR. DIEKEMA: Yeah. So they were Sorin/LivaNova 3T.

MR. RILEY: Thank you. When our infectious disease representatives or nurses and doctors come to visit us, they ask for documentation of cleaning. Were your perfusionists able to provide documentation of the cleaning protocol?

DR. DIEKEMA: I will say that from -- I don't know the exact date, but prior to -- the documentation was improved after this, I think, once this became a sort of public issue and was understood. I think prior to that, I do not know the extent to which it was documented.

MR. RILEY: Thank you.

UNIDENTIFIED SPEAKER: Can I make a comment?

DR. LANGE: We'll hold the comments. We'll be able to talk about it. But to follow up, because I had the same question, it appears that in January it would have been identified, and then from January to May, over that 4- or 5-month period, a lot of the units that were initially negative became positive, and I assume that's during that time period where the disinfection was more vigilant. Is that fair?

DR. DIEKEMA: I would say that it was equally vigilant because, at the time, they were actually exceeding the instructions for use in terms of they were actually changing the tubing more often, even prior to a recognition of a case linked to our institution. However, the assiduous documentation would have absolutely been in place from between January and April. My own view is that this just represents sampling issues. I'm quite sure that the units had *M. chimaera* prior to, you know, January, at least those four units.

DR. LANGE: Very helpful. Thank you.

Dr. Yuh.

DR. YUH: Thank you.

This question is directed towards Dr. Daley. One of the most difficult questions, I think, this Panel is being asked to address is surveillance. In your best opinion or based on your experience, what is the earliest time point after exposure to *M. chimaera* in a cardiothoracic surgical patient would blood cultures or conventional screening modalities present the highest yield? In other words, is there a point beyond which such surveillance would be more effective in identifying infected patients versus just culturing them too early and achieving a very negative -- a low yield?

DR. DALEY: I don't think we know the best time to blood culture someone like this, but I would drive -- my decisions would be driven by clinical presentation. So I wouldn't just do a blood culture because someone had had potentially a high-risk surgery. But if they presented with this constellation of symptoms, laboratory parameters, then I would. Then the issue will be which system you use, which blood culture system and which tubes, and that's going to vary from place to place.

DR. YUH: But on clinical presentation, isn't it a bit too late in terms of treatment?

DR. DALEY: No, I don't know that. Many of these patients that I've consulted on, there was a delay of therapy, but there was also a delay in treatment, and that delay in treatment didn't always need to be so delayed. I think now if we can -- with appropriate case definitions and education of providers, I am hoping we can shorten that, so that when people first present with a fever, that people work them up for NTM and not months later.

DR. LANGE: Dr. Zenilman.

DR. ZENILMAN: This is a question for Drs. Daley and Strong. What I'm also hearing is that, you know, we should be reaching out to pulmonary folks who see the sarcoid cases because we've heard this consistently, that these patients are presenting with unusual manifestations which are misdiagnosed as sarcoid.

My question is what -- you know, in your genomic analysis and maybe looking at function, what is it about *M. chimaera* which lends itself to this, because there are lots of other mycobacteria out there which don't seem to be causing problems. So I'm curious what you are -- you know, what your thinking is on that.

DR. STRONG: I think it was -- you know, as Dr. Daley alluded to, it was somewhat unexpected to see all of these *Mycobacterium chimaera* disseminated --

DR. ZENILMAN: Right.

DR. STRONG: -- diseases. And in the U.S., it's not -- if you look at the diagnostic breakdown, once you speciate things coming in to National Jewish Health that are representative of the U.S., it's not a highly prevalent --

DR. ZENILMAN: Right, exactly.

DR. STRONG: -- organism. And other mycobacterial species can colonize the heater-cooler units and other water sources, and most other water sources have a variety of mycobacteria. So it's not entirely clear. I think once we get samples from other locations, we might be able to better address why it's *chimaera* in the heater-cooler units. I think then you can compare the strains and the sequences and see -- you can understand point sources and other implications of that. I think that may help answer why *chimaera* is in these units. Does that answer your question?

DR. DALEY: Sure. Jonathan, that's an incredible question. It's why we've argued for doing sequencing, whole genome sequencing as opposed to other methods of genotyping. I think you can genotype with other methods, but we don't gain the scientific knowledge that we're going to get here, which is by comparing these isolates with environmental isolates elsewhere, pulmonary isolates, to see are these different in some way. Is this *chimaera* different, because we don't understand why it's so pathogenic in this setting. The attack rate is low. But once it gets there, it's severe. And we assume it's something about its getting stuck to biofilm on these prosthetics and we can't get rid of it.

DR. LANGE: I've got questions both from Dr. Leggett and then Dr. Givner.

DR. LEGGETT: One quick follow-up question pertinent to this. Has *M. chimaera* been seen from any other device than the 3T? It was hard for me, in the material that was sent to us prior to the meeting, to figure that out, but it didn't appear to be.

DR. DIEKEMA: So I think these are two related questions, and you've already heard alluded to yesterday the existence of whole genome sequencing data from Europe that was presented at the ECCMID meeting earlier this year and will be published that I believe will help

to explain the question why *M. chimaera* and why, when we've been using heater-cooler units for over three decades, we suddenly have a multi-state and multi-nation outbreak of *M. chimaera*. However, I also will point you to some of Dr. Falkinham's data from yesterday, which really, I think, points out the characteristics, not just of *chimaera* but NTM in general, that make them absolutely perfectly suited to survive in a fluid environment where they can generate biofilms and also perfectly suited for aerosolization. They seem to live to be aerosolized.

DR. LANGE: Dr. Givner.

DR. GIVNER: I was very intrigued by the University of Iowa investigation. I think a lot of information there is also very, very helpful. So thank you for that.

Two comments that you made really intrigue me, and one is that a lab look-back would not be helpful. And correct me if I misunderstood. A lab look-back would not be helpful, because I think most clinicians would start there, most microbiologists would start there. So I'm very interested to hear that statement. And the other is that routine surveillance of the heating-cooling device is also not helpful, because it seems to me that if there's a high number of NTMs there, that that would be a cause for concern, even if you hadn't yet identified patients affected by it because the infection can take so long to declare itself and of course be diagnosed. So if you could comment on both of those, because I think most people, including me honestly, right or wrong, would think otherwise.

DR. DIEKEMA: So the reason I think that a microbiology lab look-back is likely to be low yield -- and I would welcome, you know, comments from our colleagues in Pennsylvania and CDC about what the yield has been to date -- is that the clinical awareness is so low that

cultures are simply not obtained for AFB in patients who have this disseminated type of presentation. So when you pool your mycobacteriology lab results, you're going to find a lot of MAC, but it's going to be a lot of respiratory samples, and you're not going to be -- unless you have, and until we increase clinical awareness, we're not going to be seeing those invasive, you know, blood cultures, bone cultures, spleen cultures, bone marrow cultures. So that's why I think that's of limited yield.

The answer to your second question is, you know, for any -- you know, I'm a clinical and not an environmental microbiologist. But, you know, to sort of relate it to the clinical realm, the performance characteristics of a test -- sensitivity, specificity, positive and negative predictive value -- are really critical for how they actually inform your response to those test results. And I presented our environmental sampling results because, for example, had we decided we're going to do some kind of tiered response based upon whether *M. chimaera* was present or absent from our devices in January, we would have had three devices that were almost certainly colonized with *M. chimaera* operating in our operating rooms for 3 months -- actually longer than that, 3 months plus 8 weeks before we knew that they were indeed culture-positive for *M. chimaera*.

So for a situation like this where you're making a decision, which I wouldn't recommend, but if you're making a decision about whether to remove a unit based upon results of an NTM culture, it would seem to me you would have to have a negative predictive value well in excess of 90% to do that, given the implications of the exposure for some patients. And I just absolutely don't think that is the -- that it's certainly not known to be that high.

DR. GIVNER: Thank you.

DR. LANGE: Let me follow up in terms of the -- and we'll get to the other questions as well. In terms of the positive predictive value, how are you handling when a unit has been identified as being contaminated but there is no obvious clinical infection yet, which may take obviously years?

DR. DIEKEMA: So we don't really have experience with that because we weren't routinely culturing our units. So we knew we had a link, we knew we had at least one case when we first started culturing, and on the basis of that, we removed the units from the operating room. So we felt that the units, even a "colonized" unit, could be safely operated in an anteroom or hallway, provided that the operating room remained at positive pressure and air handling in the operating room wasn't impacted.

DR. LANGE: Thank you. That's very helpful.

Dr. Aguel and then back to Dr. Leggett.

MR. AGUEL: So to help inform Dr. Leggett's question, I think , from before, if we could --

DR. LANGE: Fernando, I'm sorry, would you speak closer to the mike? Thank you.

MR. AGUEL: To help inform Dr. Leggett's question that you posed before about whether *M. chimaera* was seen in any other units, if we could pull up Slide 78 from FDA's presentation, I think that would help.

DR. LANGE: This is Slide 78 from yesterday's presentation by the FDA. And while we're doing that, I'm going let Dr. Leggett proceed with a question, and then we'll come right back as soon as they pull that up.

DR. LEGGETT: A follow-up question to these, too. Dr. Diekema, when you were giving your presentation I was wondering, okay, if we're not going to do routine NTMs -- everybody's

agreed, negative predictive value. Everybody's agreed. So what did you do in January of 2016 or what the FDA's Advisory Panel is tasked to do? What are we supposed to do with the units that are currently out there for which no outbreaks have yet been ascribed? So do we take all the units that are out there, reservice them or allow the colonized or unknown colonized to be used with your exhaust system until we have an infection? What are you guys -- what would you have done in January if you had not removed all the units? I presume you had them all reserviced and all the tubes cleaned out; is that correct?

DR. DIEKEMA: Yes. So we were looking into obtaining different heater-cooler units, but that's not an overnight process. So what would we have done? In all likelihood, we would have tried to only utilize the new units that we had obtained more recently for elective procedures and used the -- actually, it's hard to say because it's a hypothetical. But I mean, what we did do was remove them from the operating room.

I mean I'm hesitating. I don't know if I should -- I think, as an epidemiologist, you need to think in terms of your response as to whether this is an endemic or epidemic issue, whether it's a routine kind of cause or a special-cause event.

So as a corollary, as a hospital epidemiologist, if I have an outbreak of central line-associated bloodstream infections and then I find out that they're all due to the exact same strain of *Serratia marcescens*, certainly I'm going to continue to focus on the general issue of central line-associated bloodstream infection prevention. But more urgently, I'm going to try to figure out what is the source of this common strain of *Serratia marcescens* to try to halt the outbreak.

So I think one of the challenges that this Panel faces is limited information that, I think,

is going to be critical to address this issue, including the results of whole genome sequencing and of the investigation that occurred in Germany.

DR. LEGGETT: Thank you. Just as a matter of fact, it's not quite hypothetical. In our system, we have four units that are colonized and three other units so far that are not. We don't have any noted outbreak, but we're trying to figure out what to do before we have this data 2 years from now.

DR. DIEKEMA: Yeah. I didn't mean to suggest it was hypothetical for you. I just meant it was a hypothetical question for our institution because we didn't have to face that question, and I acknowledge that that is an extremely difficult decision. We get phone calls on an almost daily basis from institutions around the country struggling with exactly these issues, which I think is why this Panel is meeting.

DR. LANGE: Dr. Aguel, did you want to walk through the slide? Then Dr. Hopkins and then to Al.

MR. AGUEL: Sure. So if you look at the row with *M. chimaera*, acknowledging the limitations of reporting with our MDR systems, you could see the LivaNova device has had the majority of infections, at least reported to FDA, with some -- with four cases from Maquet devices, two important cases to note from the Maquet devices. And I can't speak to the 30 cases with LivaNova. They were all outside of the U.S. occurrences, and they were not associated with patient infections so much as the device being cultured.

DR. LANGE: And you didn't mention it yesterday, but you may or may not be able to talk about the circumstances under which these devices were tested. In other words, there wasn't routine testing of all devices. These were just reports generated for whatever reason. We

don't know why these particular devices were tested.

MR. AGUEL: That's correct.

DR. LANGE: Dr. Hopkins.

DR. HOPKINS: This is for Dr. Diekema. First of all, I'd like to congratulate you on a really good workup of the local problem particularly. Those are very hard to do and particularly when you don't know where it's going in the early parts of the investigation. Just to put a cost number on this, do you have a ballpark figure of what it cost your institution to do this evaluation and follow-up?

DR. DIEKEMA: No, I don't know. I'm sorry, we are going to gather that information. I just don't have it at this point.

DR. HOPKINS: Could you give a log level? A million dollars, 500,000?

DR. DIEKEMA: I don't think I should because it will probably be off by a factor of 10 or more because I don't know how much it costs for, you know, engineering to work through the night to drill a hole in an operating room wall and --

DR. HOPKINS: Yeah. Obviously, almost anything that the Panel recommends is going to cost money. And so having an idea of what, if we don't make improvements, it will cost institutions is helpful to put some parameters around what's realistic and what's not.

DR. LANGE: And I'll say, just for respect to the Panel, we won't -- fortunately or unfortunately, we won't deal with the cost of it that will be borne by institutions, and so what we'll do is provide recommendations that will be independent of that. But your point is well taken.

DR. HOPKINS: Right. But just, I mean there's all kinds of outlandish things you could do,

so just to put some parameters around it.

The second thing is a modern operating room design, at least the last time we went through this iteration, is based upon a zonal concept of increasing microbiological reduction, if you will. So you've got the laminar flow surgical field. You've got the operating room itself that has a certain HVAC air turnover capacity outside that laminar flow field. Then you have the hallways and the areas around that that have people in it that are all in scrubs, etc. There's a limitation of traffic, and there's a formula for the air turnover, and then there's the field around that where there's a reduction in traffic, etc.

So how did you deal with the fact that you were purposefully aerosolizing that zone outside the operating room that is supposed to be a reduced level of microbe?

DR. DIEKEMA: Yeah. I'll just first say that we weren't purposefully doing it, but at that point, you know, we were doing what all of you are doing at your own institutions, I assume, which is weighing risk and benefit in terms of the ability to continue to perform cardiac surgery over against trying to provide the safest possible environment, you know, over the patient.

However, it is an issue, and certainly our own staff have raised it. And, you know, there are -- you know, as we've been in discussions with them, there's not a simple answer to that. It's somewhat a variation of what you heard from Dr. Falkinham yesterday, that every time you shower, you probably inhale more nontuberculous *Mycobacterium* than someone who is walking past that anteroom area would. However, obviously, the ideal situation would be that none of the units would be producing a bioaerosol anywhere near the operating room. So, you know, we continue to ramp up our disinfection beyond the instructions for use. But as I said earlier or during my presentation, I'm only aware of this one reference in the literature that

suggests that you can push the level below detection in a study environment using a peracetic acid approach that involves also complete replacement of all internal tubing.

DR. LANGE: Mr. Stammers, then Dr. Allen and then Mr. McGlamery.

MR. STAMMERS: Thank you very much.

Dr. Diekema, thank you for your presentation. Following up on -- and actually, Dr. Hopkins has touched on this as well. And we heard yesterday from the Pennsylvania Department of Health and CDC that the time of utilization and also the time on bypass is directly related to the infection, and you chose to remove the heater-cooler device to the outside of the operating room, which surely is reasonable and rational. All of these devices are used off label because very rarely do we use them less than 6 hours. I mean, what occurs, for the people who are not aware in the operating room for cardiac surgery, is literally as soon as we enter the operating room at 6:00 or 6:30 in the morning, we turn them on, either a nurse or a perfusionist, and then usually they're not turned off for, you know, it could be 12, 14 hours, or longer.

The question I have for you is you have a very robust ECMO program, and these devices are used always with ECMO 100% of the time. What are you going to do in that environment when you're in an ICU where these devices could be used for weeks on end?

DR. DIEKEMA: That's a very good question. I think that initially, in terms of our risk assessment, we felt it was most urgent to deal with a situation where a patient has an open chest and is having things implanted in an operating room environment. So we felt that the level of risk in an ICU environment, while certainly not zero -- but that's an environment where actually we have other sources of running water that likely also may be colonized with various

different bacteria. So we have not really focused on that at this point.

MR. STAMMERS: And there have been reports of ECMO patients developing these NTMs. So it is critical and perhaps something we should think about perhaps in another Panel or so.

DR. LANGE: Thank you.

MR. STAMMERS: Thank you.

DR. LANGE: Dr. Allen.

DR. ALLEN: Actually, the two previous panelists actually stole my thunder because they asked the two questions I was going to ask. One is the idea that you can move these devices someplace else. I think it's pretty neat that your OR was able to do that. But I think when I look at my OR and how it's structured around a center core, you certainly wouldn't want to move your device into the sterile center core for it to aerosolize on all of your products that are going to go to lots of different operating rooms. And as, I think, Dr. Miller alluded to yesterday, from a public health standpoint, putting these things out in a hallway where traffic is and carts are being -- there are regulations regarding simply not having obstruction in your area. So I think that's very challenging.

The comment on ECMO, though, I think maybe you might underestimate how much. And have you looked at those patients, because as we heard the discussion yesterday, these aerosolized droplets fall down on things. And, for example, if you have somebody with a heater-cooler unit that's VA ECMO for a week or perhaps has an LVAD or something to that nature, all of the IVs and invasive lines, ET tubes that are going into that patient and you've got this perpetual aerosolization in that room, there's a lot of effort for contamination. Have you

guys looked at that specifically?

DR. DIEKEMA: No, we haven't looked at that specifically. And I should also add, we haven't done air cultures. We've only done cultures of the water in the unit. So yeah, we have not.

DR. ALLEN: So I guess to follow up and just to -- so you guys haven't actually then looked at the potential for aerosolization of your devices at the University of Iowa. You simply cultured the machines, but you didn't do any type of filtration, large-volume air filtration coming out around the machine?

DR. DIEKEMA: No, we didn't. We felt initially that we had enough information to generate the response and to guide the response. Just knowing that there was a patient that had exposure to a heater-cooler unit at our institution was enough for us to assume that there had been aerosolization in the past. So that's why we didn't do air sampling, yeah. And as you saw from the typing data or the sequence data that was just presented, in fact, it does look like there's clonality between the isolate from a patient and from the heater-cooler unit.

DR. LANGE: Mr. McGlamery.

MR. McGLAMERY: In our presentation materials for these meetings, it said that there had been no presentation of pulmonary involvement to speak of, although I'm curious because my limited experience as it pertains to this, when my sister had her heart transplant in 2001, about 8 months later she presented with a lung disease and it was nonspecific. They could never identify it. They had to induce coma and feed her extremely strong antibiotics for over a month. She did survive, but I find it interesting, particularly with Dr. Daley's, you know, expression that this is hard to identify, that they couldn't identify it. So I kind of wonder if the

scope of this thing might be much bigger than we're looking at, and there have been a couple of comments about potential pulmonary involvement. And clearly this was a tremendous challenge for her doctors, and it was, you know, 10 years prior to what we're talking about. So I thought it might bear mentioning.

DR. LANGE: Thank you, Mr. McGlamery.

Our final question, Dr. Leggett.

DR. LEGGETT: A follow-up for Dr. Daley or any of you. In terms of the low yield of cultures, we in the Portland, Oregon area, when we are faced with this sort of problem, have been sending tissue specimens, especially from cardiac surgery, up to the University of Washington where they have non-CLIA associated 16S universal or mycobacteria, etc. In our experience in the whole Portland area, it's about a 10% yield, so it's not great.

Any comments on whether something like that is about to be improved upon or could be used in lieu of trying to look for NTMs in the surveillance of that kind of data? It seems farfetched, but I was wondering what we could do in the future.

DR. STRONG: I think that comes down to are there going to be improved methods to more rapidly and robustly and accurately figure out if medical equipment is potentially contaminated, or if the patients -- what species they may have or if they even have an NTM infection? So those molecular methods are improving. At National Jewish Health, for instance, we've moved from a culture-based method that was longstanding, to speciating using rpoB and some other genomic markers to really understand, okay, it's not MAC complex. It's this species or it's this subspecies. And then we've complemented it with whole genome sequencing to say, even within those species or subspecies, there are certain groups that are important. In doing

so, we can identify potential markers that might be unique to each of these species or subspecies, and we can develop assays that would be focused on rapid amplification of certain genomic markers.

And so you know, I didn't go into it, but that's one of the goals of doing this whole genome sequencing. Can you find unique genomic segments that can be amenable to PCR-based methods to quickly identify? And you can use that in quantitative PCR applications in devices or in patients, to look at burden and also to understand are these certain species that you're worried about present, and if so, how abundant are they? And that can be used as more routine, potentially monitoring to understand how fast things are recolonizing or repopulating water or others. So I think those are in development, and they have been developed.

So I think those greatly accelerate. You know, we've always been limited by the speed of division in some of these slow-growing mycobacteria. But if we use non-culture based methods -- we use on a regular basis microbiome profiling, so we can do 16S profiling to understand what are all of -- what's the breakdown of all of the microorganisms that may potentially be in a source. And then if mycobacteria are in there, then we can then focus on that and understand, okay, what are the species/subspecies in there and what do they look like genomically? So I think there's a lot of potential for really speeding up and ramping up the identification and using that to help understand if there's an issue and, if so, how big of an issue possibly?

DR. DALEY: Just to add, I think that these tests are being developed for clinical uses, and if you try to use a molecular-based method to swab the inside of a unit, that's going to be very hard to interpret, given how ubiquitous these organisms are. So I think we have to be very

careful about that and study that to make sure that it means something to have a positive amplification for a mycobacteria in some kind of swab in the OR. Because basically everywhere on earth, if someone is taking a swab, they've found mycobacteria, even in very clean areas. So it could be useful, but probably more useful clinically than surveillance-wise.

DR. LANGE: One final comment.

MR. RILEY: Thank you.

Dr. Diekema, I was remiss. I want to join Dr. Givner and the others and thank you for your case report. I personally used your experience to motivate my 20-perfusionist team to greater diligence earlier this year. Thank you.

DR. DIEKEMA: Thank you very much. And thanks for inviting me.

DR. LANGE: With that, we're going to take a 15-minute break. We're going to come back at 10:15. We have 15 questions the FDA is posing to us. So if you've identified a particular brain food for you, now is the time to buy it.

(Laughter.)

DR. LANGE: 10:15.

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

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

DR. LANGE: Thank you for reconvening. We're about to address the questions posed to us. Before I do that, I've asked Dr. Miller to give us some additional information in under 5 minutes. And then as we deliberate upon the questions, if I need to call one of yesterday's or today's speakers to the podium to clarify some issues, I'm happy to do so.

So Dr. Miller.

DR. MILLER: So I'll reintroduce myself for the Panel. My name is Dr. Jeff Miller, CDC career epi field officer assigned to the State of Pennsylvania. Again, it's best to think of me as a representative of the Pennsylvania Department of Health.

A couple points very quickly that I'd like to make. I reiterate Dr. Diekema's concern about the utility of going back and looking at microbiology data. I would phrase it somewhat differently, however. While he talked about negative predictive value, the way that I would phrase it is that if it's negative, it's potentially falsely reassuring. And so in the right setting where you have a tertiary referral facility where patients are coming back for their care, they may be tested, they may have mycobacterial cultures, and those isolates in your microbiology bank in your look-back may be useful. However, that's not going to be the case for all facilities.

I'll state, in our initial investigation, there were three identified patients, and when we went back and did our microbiology culture, our retrospective look-back, we doubled or tripled that number. So in the right setting with the right patients, it can be useful. Is it the tip of the iceberg? Almost certainly. So that's one point I'd like to make.

I do have some preliminary cost data from a facility in Pennsylvania. So the ongoing tally for patient notification, the clinical costs, the laboratory costs for the patients as well as some of the surveillance costs, $1.6 million. That's also to replace their machines.

The last point that I'd like -- it's actually a question, if I may. You know, we've been talking about --

DR. LANGE: Actually, you may not. Sorry.

DR. MILLER: Okay.

DR. LANGE: Okay.

DR. MILLER: So I would suggest that thinking about how we get potentially contaminated water, whether or not it's heater-cooler units or otherwise, outside of the operating room or controlling the exhaust is potentially useful. I think that there's been some concern among hospitals -- and this is following on some of my comments yesterday about how do we do that safely and whether that is an adulterated device. What is the regulatory pathway for putting a box around the thing to trap the exhaust? And who should be responsible for actually determining whether or not that's a safe thing to do?

Thank you.

DR. LANGE: Dr. Miller, thank you.

We're about to enter the time period where we'd like to address the FDA's questions, and my understanding is, Julia Marders, you'll be asking the questions. We have 15 questions that we'll address between now and the afternoon. I'll try to keep us on focus. So if it looks like we're wandering, I'll try to bring us back. This is a time to gather the collective opinion of the Panel, so I'd like for our experts to speak up as the questions are posed.

So Julia.

MS. MARDERS: If I could have my slides up, please. Okay. Julia Marders, FDA.

The first question is about Mitigating Water Contamination In Heater-Cooler Devices. Some background. Literature provides evidence of nontuberculous mycobacteria transmission through aerosolization of contaminated water in heater-cooler devices. It's important to note that heater-cooler devices are not shipped as sterile devices, nor are they intended to be maintained as sterile in the clinical environment. Therefore, some level of microbial contamination of the water within the heater-cooler device will be unavoidable. To mitigate

risk of NTM exposure and improve the safety margin for patients undergoing cardiothoracic procedures where heater-cooler devices are used, please address the following questions:

a. Should existing standards or limits for microbial water quality (e.g., EPA drinking water standard – 500 CFU/mL HPC or water for hemodialysis – 50 CFU/mL) be used as a surrogate when determining acceptable levels of NTM in the circulating water in the heater-cooler water pathways to minimize/mitigate patient infection?

b. Upon release of a new or serviced heater-cooler device from the manufacturer for shipping to a clinical facility, what is an acceptable level of bacterial contamination in the water pathways of the device?

c. In the clinical environment, should monitoring (i.e., surveillance) of the heater-cooler device water for NTM or bacterial contamination be performed? If yes, please consider the following:

    i. Whether surveillance/monitoring of the heater-cooler device water should be implemented by healthcare facilities as a matter of routine or only at those facilities where patient infections have occurred, and in either case at what frequency

    ii. The entities that should perform the testing (e.g., hospital-based microbiology laboratories or independent laboratories) and what monitoring would consist of (for example, microbial water quality, NTM, etc.)

    iii. The other indicators healthcare facilities should use as part of their

monitoring (visual cues, length of time in service, etc.) whether there is a threshold or trigger that can be identified for removing a device from clinical use

DR. LANGE: Thank you. And I appreciate you putting this up.

So there are three questions, and the third one has three parts. So let's address 1a first, and that is, should existing standards or limits for microbial water quality be used as a surrogate? I'll open it before I call on people. Yeah, we're to going to go around, just -- go ahead, Dr. Givner.

DR. GIVNER: We're discussing whether or not nontuberculous mycobacterial cultures will be helpful. Especially in view of that, I don't think a surrogate would be helpful. So I would suggest that we not have a bacterial surrogate be used when we're concerned about the NTM in the circulating water.

DR. LANGE: Thank you.

Matt.

DR. ARDUINO: So I'm at no regarding NTM. I think when you're doing an investigation, it will be one thing to do that, to look for NTMs because I still think it's a laboratory issue; that if you come out with recommendations to look for NTM across the board, the laboratory capacity in this country who could do that testing right now is small. I would rather prefer to go to -- so the same thing happened 20 years ago in dialysis when we had a couple of outbreaks with *Mycobacterium abscessus,* and we just said don't culture for *abscessus*. Use your standard plate counts that you use for the AAMI-recommended standard, and use that as your indicator because these same bugs will actually grow on the same media. You'll catch the rapid growers,

not really the slow growers, but everything is relative. So if counts are high, you get -- you know, you can almost assume that counts of the NTMs would be as high as well.

DR. LANGE: So Matt, if you'll clarify. So is what I'm hearing you say is that you would use the standard as with hemodialysis?

DR. ARDUINO: So if we say though -- if we pick the standard from dialysis and use dialysis-related -- the calling counts for dialysis-related water, there still has to be some sort of validation that goes on with these heater-cooler units to say, can we actually achieve that? Is it achievable? I mean, when we developed the standards for dialysis, we actually had clinical data that said, you know, if the colony counts in the dialysate bath go up, once you cross certain thresholds we start to have patient reactions. So we take that a log below that threshold.

So that's why, you know, it's 1,000 CFU -- it was 1,000 CFU when we started seeing patient adverse events. It got lowered to, you know, one log lower than that, and then we decided on an action level based on potential for biofilm to be in the system, which is why the action level became 50. We don't have the same sort of data for other devices other than dialysis, but I think going with like 50 CFU/mL is stringent. The question is going to be, with the current state of the heater-cooler units and how they're used today, you know, can we achieve that, and how frequently will you have to test to make sure you're within, you know, that 50?

DR. LANGE: Dr. Leggett.

DR. LEGGETT: I think some of the things that Matt talked about are going to be brought up in the next sections. In my thinking about this first question, sort of the first point is that NTMs are ubiquitous. The second is that biofilm, from what we heard yesterday, begins to form when the CFU is greater than 50. So use of the hemodialysis standard provides us sort of

a relatively simple extra measure of control over the input to control NTMs into these HCDs, and it's something that's already done in most, if not all, facilities that are doing CV surgery using these HCDs because I can't think of where you're going to take somebody from the OR with a really serious cardiac problem and not have dialysis available. So I think that the transfer technology is possible, usually feasible.

The other thought that was brought up and recommended by the FDA -- and I don't know the engineering part of it -- would be to use a simple 0.2 µ filter for the tap water, if machines already don't use distilled water, that they can then sterilize or some other thing. But it seems like a relatively simple engineering thing to just take the hemodialysis standard and apply it to these things and then use of the validation and stuff later.

DR. LANGE: Dr. Allen.

DR. ALLEN: Seeing as a heart surgeon, I think you have to implement realistic features or it will not happen at all. So we can, for example, say we want to be at 50, which is what it is for dialysate, but the heater-cooler units, how they function is very different from dialysate. And so in order -- I don't even know, quite honestly, if you could achieve that level with heater-coolers. So even if you change them after every case, I'm not sure you could obtain that level based on what I know now.

So is that really realistic? I think it is a usable surrogate to set some level, but it needs to be a level that's achievable. So if you've got -- obviously if you've got 1,000, somebody's not doing their job and not cleaning it. But if it's 100 or 150, which may be a more reasonable number, at least that is a surrogate for the fact that you are cleaning this unit and doing what you need to do. I guess we just can't make it so tight that nobody can achieve it, and that then

buys you time, and we'll discuss this later, to -- I think there are some pretty clear engineering issues that need to go on with these devices and needs to be changed, but that's a longer-term goal.

DR. ARDUINO: So what's actually here for dialysis is the action limit, which is half the limit. So the actual limit for dialysis, for both water and the final bath for conventional dialysis, is 100 CFU. And the 50 mL, the action limit is basically set. If you start seeing that in your cultures, dialysis unit, think about doing something because you don't want to get to 100 and then chase a problem. So the 50 limit was set to get them to start putting an intervention in place to do that, so that -- because what happens when you typically reach your limit, it takes several rounds of disinfection, maybe, to bring you back down under it. This way, when you hit an action limit and you do something, you'd never get to your MAC.

DR. ALLEN: And I get that.

DR. ARDUINO: Yeah.

DR. LANGE: Go ahead, Dr. Allen.

DR. ALLEN: I mean, I get that. But your action limit for dialysis, where you actually have contact and so forth, maybe is very different from this device because, quite honestly, it may be that you could have -- if you had a device that didn't aerosolize, your counts could maybe be 1,000, and as long as it doesn't aerosolize, then you wouldn't even have an issue to begin with. So I think relying on those counts in a very specific way, you know, some legislative rule, I think, would be a mistake and would be burdensome to both institutions and the industry. But I think some general recommendations to -- until we get some standards for how you clean and what you should use and how often tubing should be replaced and until engineering design changes

can be made, I think that might be appropriate.

DR. LANGE: Jeff.

MR. RILEY: I agree with Dr. Allen. It's my sense that we'll never get these devices that clean. The devices across the United States are soiled now, generally speaking, and I think drinking water would be very clean in the operating room. So I'd go for the 1,000 if we had guidelines. I just got a text last night from a West Coast perfusionist asking if at Mayo we do plate counts and what our limits are. So I think perfusionists are being encouraged to do these daily across the United States. So I think we need to make a statement about it.

DR. LANGE: Dr. Roselle.

DR. ROSELLE: I think I wouldn't call it a surrogate for the NTMs. What you're really doing is validating cleaning. Did you clean it right? Did you clean it on time? Drinking water doesn't sound bad to me. There's no known safe level. You don't have a clue. It could be one particulate in certain patients or it could be more. So you can't get too granular because you don't have any data. Drinking water is kind of standard. I don't know if it's good, bad, or indifferent. But once you have an SOP for cleaning, competencies for cleaning and a monitor that would be helpful to know if you're cleaning, that may be the best you can do while data is being accumulated.

DR. LANGE: Go ahead, Matt.

DR. ARDUINO: Yeah, I still think even with the microbiology here, I think whatever we do before even settling it is what is achievable in these machines right now, the ones in use. Even if we set a drinking water limit, which is 500, with the current state of machines in use now, can we even measure -- can we get 500? Do you know what I mean? So there needs to

be some sort of validation here to say what threshold can we reach? What is achievable?

DR. LANGE: Dr. Leggett.

DR. LEGGETT: Perhaps this would be a time that some of the presenters could tell us if they have done any HPC data or have any of that on the machines, either at the manufacturing level or after the results of these outbreaks. For instance, perhaps Dr. Sax or someone, Dr. Miller perhaps, they've done that.

DR. LANGE: So let me ask Dr. Sax and Dr. Miller and then let me ask the three industry representatives as well, in terms of -- so for each of the companies, if each of them will have a representative come up and address have you done HPCs and what have the results been? I see one. Thank you.

So go ahead, Dr. Miller, then Dr. Sax, and then our three industry reps.

DR. MILLER: So the Pennsylvania Department of Health has not done this type of testing and validation directly. I think it would be great to have that type of data from the manufacturers. We don't have visibility of that validation data. We have heard anecdotally from a number of hospitals that our recommendation for a 500 CFU/mL is difficult to achieve. They are achieving it with multiple devices, but they are doing it in excess of the manufacturer's IFU.

DR. LANGE: Thank you very much.

Dr. Sax.

DR. SAX: We have not measured other bacteria in the levels. We have identified other bacteria like *Pseudomonas*, *Legionella*, and -- as a type of bacteria, but we don't -- we didn't look at the levels otherwise.

DR. LANGE: Thank you.

And then by the way, for our industry reps, just for recording, if you'll give your name for the transcriptionist.

MR. PLATT: Doug Platt, CardioQuip.

We have validated and verified at EPA drinking standard levels, you know, after cleaning. I would say that in some of our 90-day runs, that those levels won't stay there. But we've also not seen them rise above 1,000 CFU.

DR. LANGE: And can you give the Panel an idea, of the machines you've tested, are these machines that are fairly newer or that have been in use for a year or two?

MR. PLATT: We did testing on what we would call a trial unit or a demo unit. These are units that have been in the field and back to us. So all of our testing was done with trial units. So averaging maybe 400 to 500 hours per unit.

DR. LANGE: Very helpful. Thank you.

DR. ALLEN: Could he clarify? Because he said 1,000, was his threshold 500, or was it 1,000? Because drinking water --

MR. PLATT: Our threshold for --

DR. ALLEN: -- is 500.

MR. PLATT: Right. Our threshold for after cleaning was to meet all EPA drinking water standards, which is less than 500 after cleaning. And we would be down less than 100 after cleaning, but obviously over a period of time that rises, and so you know -- and we've done some extended-run testing looking towards ECMO-type uses. And so in those extended runs, we've seen those rise.

DR. ALLEN: Did you ever have it get below 50?

MR. PLATT: No. I take it back. Yes. With Pine-Sol we actually did, yes.

DR. LANGE: I have a feeling we're going to have millions of patients running around the country smelling like Pine-Sol.

(Laughter.)

DR. LANGE: Doug, before you leave, I have one other question to follow up on that. When you got below 100 and they cleaned and you did continuous runs, how long did it take before the count went up above 500?

MR. PLATT: I don't have that data right now.

DR. LANGE: Thanks.

MR. PLATT: I really couldn't address that.

DR. LANGE: Okay, very well.

MR. PEIS: So my name is Christian Peis, from LivaNova.

We have a long experience on this hetero plate count measurements because, in 2011, we have set a new standard for our devices. So we went on expert -- water hygiene expert, renowned expert Professor Dr. Exner from the University of Bonn, and we defined a standard for our device, and Professor Exner told us that the minimum level we should achieve with our devices is drinking water quality. He referred to the hemodialysis equipment. At that time it was 200 CFU/mL. He referred to dental equipment. In the U.S., it's drinking water standard. In Europe, it's the German drinking water standard having less than 100 CFU/mL. We have validated this standard.

So one additional comment with this standard. The drinking water standard or also the

U.S. drinking water standard is only referring to heterotrophic plate count. Professor Exner did even require additional tests. So he asked to have less than 1 CFU/100 mL *Pseudomonas*. So this was an additional requirement. He also asked to add coliforms less than -- we should have less than 1 CFU/100 mL coliforms. So this was our standard test in 2011 and implemented in 2012 also in our IFU.

We did a lot of validation activities. So we have tested the devices, and I can confirm that our devices, new devices can meet this standard. So if you have a new device, a clean device, and if you follow our IFU, you will meet the drinking water standard and the standard for *Pseudomonas* coliforms. In 2015 we have added to our standard a requirement for NTM. So now our standard includes to have less than 1 CFU/100 mL for nontuberculous mycobacteria. How can we --

DR. LANGE: Oh, I'm sorry. Go ahead.

MR. PEIS: Yeah. How can we achieve the drinking water standard? One is you need to have a very effective disinfection. So it's very important that you set the device to 0 CFU at the beginning. And then you need clean water. So we are using filtrated water. So we are adding filtrated water via 0.22 µm filter, water into our system. Our first tests have shown that within 2, 3 days, even if the water was filtrated, we did see some growth though. After certain days, water would colonize, the counts would increase.

And so we had two options. One option was to ask the customer to replace the water every 2 days or every day. If they are doing that, disinfecting the system every 2 weeks and changing the water every day on a new machine, they will always be below 50 CFU -- below 100 CFU, which is our standard, and they would have a very clean and safe device. Our customers

in the past have not replaced the water daily. So they have used the system for several days, for 1 week, for 2 weeks until they have changed the water.

To meet the drinking water standard, we had to add some preservative to the water to keep the bacteria low, and we have added, based on the recommendation of Professor Exner, a low -- very low concentration of hydrogen peroxide to the water. Hydrogen peroxide is bacteriostatic and keeps the water at a drinking water level over 7 days, according to our new validation, and after 7 days you are changing the water, you would add hydrogen peroxide. And I'm very confident that this system works. And we have a lot of positive feedback from our customers in Europe, that you can keep your system within this drinking water limit.

DR. LANGE: Thank you.

Dr. Yuh, do you want to address this particular speaker?

DR. YUH: No, he actually addressed the question already --

DR. LANGE: Okay.

DR. YUH: -- in his talk.

DR. LANGE: Thank you.

And before -- go ahead, Al.

MR. STAMMERS: Thank you very much.

Two very quick questions. If you follow the current IFU, which states replace your water at 1 week with hydrogen peroxide supplementation, will you be at the drinking water level, assuming that you followed the disinfection to protocol, as you've described, per week?

MR. PEIS: For a new device and a clean device, yes. For a device which is on the market for several years, you will not meet the drinking water quality because the hydrogen peroxide

will decrease tremendously over the first day and you will see some growth already on the second day. Why? Because of the biofilm which is present. As soon as you have a machine where you have biofilm in the water circuit, this standard cannot be met with such a machine. You have to take additional actions to remove the biofilm to clean the machine, to bring it back to a clean machine, and then you will be able to meet the drinking water standard.

MR. STAMMERS: Okay. So that's a lot of additional work to do to get the drinking water standard down. I mean, it will work effectively with a new device that is delivered, but existing devices, which are clearly the majority, really would not be affected if we went to the drinking water standard.

The second question I had is on hydrogen peroxide.

MR. PEIS: Yes.

MR. STAMMERS: There are some manufacturers of oxygenators that have said hydrogen peroxide should not be used in the water of the heater-cooler devices. Can you comment on that? And some have said that it actually will traverse the fiber and end up in the blood.

MR. PEIS: We are in the process of evaluating this information. So we got this information also from European authorities. We are only aware of one manufacturer who has made this statement, and we are working on that, and we will decide, together with FDA, how to act on this information from this competitor.

DR. LANGE: Thank you very much.

And our representative from Cincinnati Sub-Zero.

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

We have focused on making sure primarily that our unit does not aerosolize. And that was where we focused all our original tests on, and we are undergoing tests currently with regards to the HPC counts and -- but no matter what you do to keep cleaning the water, keep replacing the water, you're killing everything else and giving nutrients to the mycobacteria, from what I've learned over the years -- I mean, over the last 6 months. And so we keep cleaning the water, but are you really getting rid of the mycobacteria? And regardless if it's there, can you isolate it and keep it from getting to the patient? And I think that's a real focus here and not putting things in and then being reactive, but verifying and making sure that everything is stable. And like it's been for us, you know, we have not had any incidents in the 35 years that I've been dealing with this.

DR. LANGE: If there are no other comments from the Panel -- Jeff, go ahead.

MR. RILEY: Is it true to say that none of the manufacturers' instructions for use recommend surveillance now?

MR. BERKE: We don't.

DR. LANGE: That's fair. I think that's true.

Go ahead.

MR. PEIS: With surveillance --

DR. LANGE: I'm sorry, go ahead and identify yourself for the transcriptionist again.

MR. PEIS: My name is Christian Peis, LivaNova.

With surveillance, do you mean monitoring, if we're requiring monitoring from -- we did not -- pardon?

MR. RILEY: Culturing.

MR. PEIS: Culturing, yeah. In the past, we did not require that. Based on this topic with mycobacteria, we have sent out a customer letter, 2015, and asked all the customers worldwide to culture their heater-coolers to understand that they are contaminated with NTM or other bacteria, and we asked them to culture for NTM, *Pseudomonas* coliforms, and heterotrophic plate counts. Now, we are in the process of implementing monitoring in our IFU, and we had a lot of discussions also in Europe with our experts. What shall we require from our customers? Shall we ask them to test for NTM? And our information from the market was that not all hospitals can do that, it's expensive, it is time consuming, and so on.

So our proposal now in our next version of the IFU was to test for heterotrophic plate count, though less than 100 CFU/mL, and to test for *Pseudomonas*. Why *Pseudomonas*? Professor Exner mentioned that *Pseudomonas* is a very good indicator for biofilm. So if you have biofilm presence in the system, you will always find *Pseudomonas*. So I'm not a microbiologist; I'm just repeating what I got from Professor Exner.

DR. LANGE: Yes, Dr. Givner.

DR. GIVNER: You mentioned asking for cultures from your customers. What were the results of those? That's my number one question.

Number two is you've talked about new heating-cooler devices and being able to get the colony counts down and them being down for some period of time. But, of course, there are many that are going to be used for a long period of time, there are many currently in use that have been used for a long period of time. Do you have any idea of the period of time, even with good following of the IFU, that those counts then go up? So a two-part question.

MR. PEIS: Yeah, it's not easy to answer that. We got a lot of feedback in Europe from

these monitoring activities, and if a customer had five devices, he was able, with following our new instructions for use and having every 2 weeks the disinfection and so on, to bring some devices back to clean devices. But there are some others, you can treat them for 1 year, and they will not get back to a clean device because biofilm has been built up in the circuit, on the tubing, and the only ways to bring them back is to make -- do a kind of deep cleaning, deep disinfection, to replace tubing, to mechanically remove the biofilm from those devices. So this is one option how to bring them back, yeah.

DR. GIVNER: But those are added steps besides the routine cleaning that now you're recommending or that some have undertaken removing the biofilm, etc.

MR. PEIS: In Europe and -- Europe, Australia, Japan, we have established a process in our service department to deep disinfect devices. So devices have been returned to us to Munich, to our service facility. We have a special room. We have special processes how to clean such devices. And we are in the process to set up this deep cleaning process or deep disinfection process in the U.S. as well, and we are working close with FDA on getting this process implemented for the U.S. customers.

DR. GIVNER: Thank you.

MR. PEIS: Yeah.

DR. LANGE: Dr. Yuh.

DR. YUH: If I can just editorialize a bit. I think, you know, I agree with Dr. Roselle in terms of this threshold we're being asked to specify is really only going to be a marker for adequate maintenance of a device. It is impossible for me to believe that even a new device maintained well is going to maintain this, that this is going to be achievable over years of use.

In the rollicking environment of a busy cardiac operating room, as well intentioned as our perfusionists and dedicated perfusionists would be in maintaining the IFU, I just don't think it's practical and achievable unless you buy a whole new fleet of heater-cooler devices every year. So I really think we should take this question as with the limited amount of data that we have, in terms of just a practical recommendation of a marker for adequate maintenance of the device rather than a stringent, you know, requirement.

DR. LANGE: Two questions to the Panel members I'll pose. To our perfusionists, how easy or difficult is it to remove the water, that is, to drain the water on a daily basis once it's been used and then to refill it?

MR. RILEY: We spend --

DR. LANGE: Jeffrey, go ahead.

MR. RILEY: Thank you. Jeff Riley.

We spend 25 minutes per unit per day, and we have 11 units. We spend 0.5 FTEs of perfusionists to follow the manufacturer's instructions with the 3T. So 20 minutes per day per device.

DR. LANGE: So I just want to make sure that I understand. So the time it takes, technically it's not difficult to either drain it and/or fill it, is that --

MR. STAMMERS: That is correct. We own several hundred of these devices in 200 hospitals throughout the country, and we have instituted the strict IFUs that LivaNova has put forth, and it does put a significant burden on the company right now, just an aside. There's an extreme shortage of perfusionists from a population perspective, so it is affecting cases since we have a limited number -- a large number of opportunities for job employment and limited

people to fill those roles. So we're having to hire additional individuals, non-perfusionists, to perform these functions.

DR. LANGE: So if I was to summarize for the FDA, I think what the Panel is saying is that it is possible, in the new machines or the old machines, to get to a CFU level or an HPC level that meets the water standards. Getting too stringent may not be achievable. It's a marker not for NTM but of how well or how often the machine is cleaned, and I think the Panel is pretty uniform upon that. What we've heard is that cleaning regularly and frequently and draining the water will help to decrease these counts.

And what there hasn't been consensus on is what to do with the older machines. In other words, these HPC counts are a marker for how well you are cleaning new equipment, but in terms of end of life, that is, at what time should we say that a machine will either get too infected or the possibility again is to send it back to the company for deep disinfection? And I think that the Panel would agree that that carries some interest, and that is, at some point, this may be an end-of-life issue where you can't get it sterile enough, and at that point it may be wise to send it back to the company or do something else to remove the biofilm and to decrease the counts.

So is there anything I haven't represented? Matt?

DR. ARDUINO: Could I just bring up some old literature that looks at growth of microorganisms in distilled water and the time period? There's a paper by Favero and Bond from 1971 in *Science* that basically says *aeruginosa* will grow up 10^5 at ambient room temperature in distilled water within 72 hours and stay there. And there's similar work done with *B. cepacia* at a variety of -- and that's by Loretta Carson in 1973 in *Applied and*

Environmental Micro. So when you think about this, you have to remember, you know, your Pseudomonads are going to -- you know, within 48, 72 hours, going from like 10^1 to 10^5, 10^6 and then be there forever because they reach a stationary phase in water that doesn't have much carbon.

DR. LANGE: I would say there is some enthusiasm, by the way, to the FDA, of using the most uncontaminated water available, okay?

Dr. Leggett, anything you want to add? I'm sorry. Dr. Givner. I'm sorry. And then Dr. Leggett.

DR. GIVNER: In the Panel's discussion, was there an upper limit set for what the CFU counts would be?

DR. LANGE: So let me poll the Panel. By a show of hands, how many of you think 50 should be the upper limit?

(Show of hands.)

DR. LANGE: How many of you think 100 should be the upper limit?

(Show of hands.)

DR. LANGE: Several. How many 500?

(Show of hands.)

DR. LANGE: And how many of you don't know the upper limit?

(Laughter.)

DR. ZENILMAN: Rich, are we voting? What's our voting/non-voting status?

DR. LANGE: Actually, we're not voting on anything.

DR. ZENILMAN: Okay.

DR. LANGE: We're just making recommendations to the FDA. So thanks.

Dr. Leggett.

DR. LEGGETT: It was my understanding that it's useful to the FDA to get each of our own opinions so we'd have a broad spectrum as to come up with a consensus statement. The second point I had in terms of our consensus statement was that the European water standard is actually the United States' hemodialysis standard, which was the 100, and that we have found that it can be achieved currently. And then the other parts dealt with maintenance issues later.

DR. LANGE: Great. Dr. Schwartz, does this give you all sufficient guidance about what the opinions are here of the Panel?

DR. SCHWARTZ: At this time, yes. Thank you.

DR. LANGE: Is there anything else we can do to clarify that?

Dr. Hopkins.

DR. HOPKINS: Just a quick question. Are we discussing all three components, (a), (b), and (c), or are we just still on (a)?

DR. LANGE: Just still on (a) right now.

DR. HOPKINS: Okay.

DR. LANGE: We'll get to (b) --

(Off microphone comment.)

DR. LANGE: Yeah. Fourteen to go.

(Laughter.)

DR. HOPKINS: That was actually not my point. They are interrelated, and we're starting

to get into comments that deal with (b) and (c).

DR. LANGE: They are. And so we'll address the specific question. But as those points come up, we'll apply them to the other --

DR. HOPKINS: Okay.

DR. LANGE: -- issues as well. And the last comment, Dr. Givner.

DR. GIVNER: If you don't mind -- and I apologize. Would you be willing to restate what our recommendations are? I just want to make sure I understand them.

DR. LANGE: Sure, and that is the Panel takes the HPC as a level of whether it's being regularly cleaned and adequately cleaned or not, number one. Number two is to make sure that we choose an achievable level. Third is to use the cleanest water possible. Again, to disinfect frequently and document. And the suggestion has been made to change the water daily. And the last thing is -- and those are primarily for new machines. And for those, the machines that have been in use and consistently exceed, to consider other measures to remove the biofilm or to deep disinfect it.

Al.

MR. STAMMERS: Just a very quick question. Thank you. Could I ask a question? Instead of the cleanest water possible, we've had several presentations that have talked about filtering it through a 0.22 µ filter and which is readily easily done in the operating room right now by perfusionists. So I wonder if we could add that.

DR. LANGE: Thanks. Does anyone say cleanest? I should have specified that, that would be to do that.

Julia.

MS. MARDERS: In regard to the show of hands, what was the consensus, please?

DR. LANGE: Okay. A show of hands again for those that think 50.

(Show of hands.)

DR. LANGE: Those that think 100.

(Show of hands.)

DR. LANGE: It looks like there's six or seven. And those that think it should be 500.

(Show of hands.)

DR. LANGE: One, two, three, four, five, six. And I would probably vote there as well. So about equally split between 100 and 500. I'm sorry, you don't get to vote, Dr. Miller.

Yes, Jeff.

MR. RILEY: Just to clarify, what was the FDA's definition of the cleanest water possible?

DR. LANGE: I would say, again, not the FDA's but our recommendation is to use filtered water through 0.22 μ filters.

DR. SCHWARTZ: And that's -- yeah.

UNIDENTIFIED SPEAKER: Or less.

DR. LANGE: Or less.

DR. SCHWARTZ: Which is consistent with the communications that we had previously issued.

DR. LANGE: All right. Let's move on to Question 1b. Upon release of a new or serviced heater-cooler device from the manufacturer for shipping to a clinical facility, what is an acceptable level of bacterial contamination in the water pathways of the device?

Dr. Hopkins.

DR. HOPKINS: Yeah. There was some evidence or at least some discussion in some of the manufacturers' presentations yesterday that when you started off clean there was an ability to postpone the inevitable for a relatively prolonged period of time with more assiduous cleaning, etc. You know, mass sterilization of large objects is very easy in the industrial setting and very hard in the hospital setting. So with a device coming essentially organism free, you start off at 0.0. I also completely agree with using sterile distilled water. We have a rule in our OR that no tap water, no unsterile water is allowed in the operating rooms in any format, and I think that's pretty universal.

So it seems that for new devices and subsequent to deep cleaning devices, those devices that are starting off at an exceedingly low contamination rate, that utilizing sterile distilled water, first of all, it will prolong the metal elements, but secondly, it is a first surgical principle of just irrigating out contaminated spaces and reducing the overall colony count for a period of time. And starting off at zero, it seems to me it would be relatively low cost and would give you a running start.

I do worry a little bit about filtering in the operating room. We do that a lot in our laboratories, etc. It is a little fidgety. People are sometimes good at it, sometimes sloppy with it. It's best done with closed devices. We're talking about gallons of water here, not 500 cc. So simply buying distilled sterile water in jugs is going to be probably less expensive in the long run. But, you know, I think that's more of a technical decision by perfusion, etc. And if you can couple that with adding some hydrogen peroxide and some other ways that are being validated and ultimately need to be validated by the manufacturers as to postponing the development of biofilm -- and hydrogen peroxide does do that. I mean it's used in dental

applications specifically for that -- then starting off at zero makes ultimate sense to me.

DR. LANGE: I'll come to you, Dr. Givner.

So what I'm hearing you say, Dr. Hopkins, is you want the bacterial contamination or the HPC to be zero when it comes out?

DR. HOPKINS: Yeah, as delivered, it should be zero.

DR. LANGE: Dr. Givner.

(Off microphone response.)

DR. LANGE: Dr. Christensen.

DR. CHRISTENSEN: I just want to make one point. This whole discussion would be moot if the instruments didn't actually produce an aerosol. So that would be -- you know, if it's contained within the unit and there's no aerosolization happening in the OR space, then this discussion of levels wouldn't be as critical.

DR. HOPKINS: Actually, can I challenge that thought a little bit? I don't think I'd be very happy, in my OR, of having a bottle of contaminated water full of *Pseudomonas* sitting over in the corner, even sealed. I mean, I think aerosolization is a bad thing, but also little drip holes occur, other ways of violating that space occur. So I don't think you want to contain a bag of *Pseudomonas* in your OR.

DR. LANGE: Al.

MR. STAMMERS: Thank you very much.

If I can make one comment, too. It's hard to visualize what's going on with the oxygenators and the cardioplegia systems that we attach these to, but these devices are separated by pieces of -- water in these devices are separated by a piece of plastic and

occasionally a piece of stainless steel. In historical development, some of these were semi-permeable. I agree with Dr. Hopkins. Even if they weren't aerosolizing, they are in such close proximity to the entire blood of patients that passes through them thousands of times in an operation, you know, at a normal flow rate, so I think we have to keep that in mind. As Dr. Hopkins pointed out, I agree with, you know, whatever we do, we do have to come to a safe level of the water within the devices, regardless of whether or not they are aerosolized.

DR. LANGE: Dr. Christensen.

DR. CHRISTENSEN: Yeah, I'm not saying using pond water, so just --

(Laughter.)

DR. CHRISTENSEN: -- a reference to yesterday. But no, I agree that it needs to be clean water and even filtered water. But I think the length of our discussion, you know, would be a lot different if they just didn't aerosolize.

DR. LANGE: It certainly does add to it, and we'll talk a little bit more about that when we talk about the machines. Thank you, Dr. Christensen.

Jeffrey.

MR. RILEY: I will comment, it's a common practice, probably until this year, for perfusionists to walk outside of the operating room with the overflow canister, fill it with tap water, come back in the operating room, and fill the heater-cooler to bring it up to the level of water, and I think that's the first educational point we'll have to make. So tap water moves in and out of the OR, filtered and unfiltered. We just put the rule in place at our place, that if you're going to top off the heater-cooler to bring the level indicator up, you go get the filtered water from the filtered water source to do it in a clean container. So there are a lot of human

habits. And we'll game this. I'll throw that comment in now. We'll put fresh water in with hydrogen peroxide the day before the cultures are due.

(Laughter.)

DR. LANGE: So noted. If there is a consensus around the table --

MR. RILEY: Except at SpecialtyCare, their perfusionists don't bother.

DR. LANGE: Dr. Hopkins' point was that there should be zero bacterial contamination.

Dr. Leggett.

DR. LEGGETT: Zero is hard to always achieve. So I mean, I would think if we have the standard of the hemodialysis of less than 50, that probably should do the trick.

DR. HOPKINS: Except the question was, when it comes from the manufacturer, should we start -- and you can gas sterilize very large equipment at the industrial level quite inexpensively, and it can be wrapped and brought and started off sterile. You know, why start mixing -- I don't know where these are made, but why start mixing bacterial populations from different parts of the country or the world into your OR, even at very low levels? I would prefer they come zero.

DR. LANGE: Dr. Allen.

DR. ALLEN: I think that's unrealistic. I would agree with Dr. Leggett. I don't think you can have zero. As soon as you unpackage these things, whatever's floating in the air contaminates them, and my understanding of these particular organisms, you know, I could go around the room and swab in 100 different places and I'd probably grow this organism. So I think that's not achievable and unrealistic. I think having it come from the manufacturer, you should be able to realistically put fluid in this machine when you open it fresh out of the

manufacturer and do an HPC count, and it better doggone well be below 50. That would be what I would recommend.

DR. LANGE: Dr. Fennal.

DR. FENNAL: Mildred Fennal.

Since zero is impossible, why not say 0 to 50 and let that be the standard?

DR. LANGE: Thank you. Keith, if you'll turn off your mike.

Comment, Matt?

DR. ARDUINO: Okay, here's the comment. There is no such -- in microbiology, when we're talking about plate counts, there is no such thing as zero. It all depends on what your denominator is. It's less than whatever your sample volume is.

The other thing, too, is I'm going to do a déjà vu. A different device, mid-2000s, Vapotherm, a device, and *Ralstonia mannitolilytica* infections in pediatric patients in the U.S. and then again in 2011 in Israel. The device was tested at the manufacturing plant with tap water and then sent -- you know, they were shipped to users here in the States. Well, the *mannitolilytica* was never -- we were never able to clear it from the device, here. And then working with FDA, the manufacturer had to come up with whole disinfection protocols to get it done. Well, then those changes went into place here for the U.S. customers, and then 6 years later, the same clone of *Ralstonia* appeared in a hospital in Jerusalem. Our PFGE results were the same.

So instead of shipping devices, is there a way to ship devices that we know are dry, so that there's no residual water left in the device? Because as long as there's residual water left, you have stuff that can -- if it's damp, it's going to grow something. So if there's a way that

devices can be shipped to users, like a new device and you know it's dry, that way when you fill water or that there's some way to scavenge the water that was used to test the device from the -- out of the device, whether that's -- you know, for endoscopes we usually say, follow that with an alcohol rinse and then force-air dry because, you know --

DR. ALLEN: I think that drying process was alluded to by at least one of the manufacturers. I think it was LivaNova suggested that they had implemented drying. I can't speak -- I don't know that any of the other manufacturers did that, but I do think that's an interesting point. Yeah, if you put water in them at the beginning to test them, you got to get that water out so that it doesn't sit. But I think the bottom line is that when the thing comes to you from the manufacturer, I think it's not unreasonable to say that when you do your first HPC, it should be less than 50.

DR. ARDUINO: A brand new device that you receive should be well below whatever limits we say that we should be maintaining.

DR. LANGE: So to that point, let me see -- I'm going to summarize, and I'm not trying to truncate it, but I think it's fair to say we want these items shipped dry. It shouldn't be wet, okay? That should be clear.

And the second is no matter what standard you set as your first -- when it comes out of the box, if on the second run, the very first time you put water in it, then you say it should be below 100, then it doesn't make sense to make it any more stringent the first time out. In other words, if we're going to say it ought to come out -- you know, we're going to use an HPC of 100 for every run after the first one, then it doesn't make any sense that it ought to be any more stringent for the first time.

DR. ALLEN: No, I disagree with that. I think these devices inherently, over a period of time, you will see them approach their end of life, and you will get colony counts that then would require either them to be gotten rid of and a new one purchased. So I think actually the time course of how you'll get these organisms and a biofilm to form, I think you can't have disparate signals early on versus later on. So I think when it comes out of the box, it ought to be pretty good.

DR. LANGE: So let me take a straw poll again. A show of hands. Those on the Panel that feel like there ought to be an HPC count of less than 50 straight of the box.

(Show of hands.)

DR. LANGE: Good. So Dr. Schwartz, does this answer Question 1b to your satisfaction? Have we addressed it?

DR. SCHWARTZ: Yes, it does. Thank you.

DR. LANGE: Okay. And again just to summarize, dry and clean, clean being an HPC of less than 50. Great.

I'm going to move on to 1c. In the clinical environment, should monitoring of the HCD water for NTM or bacterial contamination be performed? And then if yes, we'll answer (i), (ii), and (iii). So before we start points (i), (ii), and (iii), let's start with (c) and hear the Panel's opinion. Should monitoring of the heater-cooler device for NTM or bacterial contamination be performed?

Dr. Allen.

DR. ALLEN: So I think we already essentially concluded that yes, it should be HPC, which will do bacterial, and we're going to use that as a surrogate. I think it is absolutely impossible,

at least in the current state, from what I understand for every hospital that does open heart procedures, to monitor for NTM. I think that is not feasible and completely unrealistic.

DR. LANGE: So let me break this out for the FDA. Your point is well taken, Keith. If you'll hit your microphone for a second -- and that is we've already talked about doing heterophilic counts, which are different. So I'm going to say, should we be routinely monitoring for NTM? So let me break that out first.

And so Dr. Givner, Dr. Zenilman, and then Matt.

DR. GIVNER: He already mentioned what I was going to mention. Thank you.

DR. LANGE: Okay. Dr. Zenilman.

DR. ZENILMAN: I think we heard -- I mean, I think there's an important -- there's a big issue here. So I think we heard yesterday that for Sub-Question (ii), that there are no -- there are very few resources available and laboratories that can do this. And I think we just ran into this at our -- at Johns Hopkins. Johns Hopkins's clinical labs do not do this, and it has to be sent out to contract labs, and we heard yesterday from Matthew that there are very few contract labs that do this well.

DR. LANGE: Matt.

DR. ARDUINO: So I don't think we should be doing it routinely. As part of an investigation, yes, go ahead and do it.

(Off microphone comment.)

DR. ARDUINO: NTMs, yes. The problem I have with doing surveillance cultures for NTM is the results are not actionable. It takes 8 weeks. That machine is still in -- I mean, you're still using the machine. You know, it doesn't give you results quick enough for you to take some

sort of action to prevent, you know, something else from happening.

DR. LANGE: Al, were you going to say something?

MR. STAMMERS: Not really. But very quickly, we do this at -- our organization is the biggest user of these heater-coolers in the world, as to my knowledge, and we do have a lab set in Columbus, Ohio that we send these for, for HPC, NTB -- NTM, excuse me, and several others that we identified, but it's hospital specific. We do not require our associates to send these samples unless the specific hospital requires it, for what that's worth. So we have that policy, but it's by individual facility.

DR. LANGE: Dr. Yuh.

DR. YUH: Aside from being not that feasible with the current lab availability, the gist of what I gathered from Dr. Diekema's presentation earlier on is in terms of the utility of NTM monitoring of the water has really limited value in the first place. So I think the question specifically asked about surveillance of the water -- and it seems like that's pretty apparent.

DR. LANGE: So FDA, when you talk about water, do you talk about the water in the HCD device, not the water, tap water or --

DR. SCHWARTZ: Yeah, the question is specific to water within the device.

DR. LANGE: Is there anybody here that feels that there should be monitoring of HCD water for NTM routinely? So I think the message you're getting from the Panel is we don't think that would be useful. I think I'm going to speak for the Panel because -- for investigations, yes, that is, there's an outbreak in the hospital or concerns. If there's something that would drive that, the answer would be yes? Great. And the feeling is that if it's negative, you're not really sure whether it means anything. If it's positive, you're not sure what to do with the information

and you get it weeks to months later.

Now, with regard to bacterial contamination, obviously, we've talked about doing that for HPC just as a surrogate for whether it's being disinfected and/or cleaned appropriately. Great.

So, Dr. Schwartz, does that address the questions that the FDA -- is there any further clarification or any other information you'd like from the Panel?

DR. SCHWARTZ: Can we clarify with regard to using it as a surrogate or as a marker for maintenance and adequacy of cleaning, the frequency that would be recommended for that? Would that follow with at the time of changing or prior to changing the water?

DR. LANGE: Sure, we appreciate that. So Panel, I mean obviously we've recommended certain standards. How often should the devices be assessed?

Dr. Allen.

DR. ALLEN: I think that's an excellent question, and I think maybe we could get into that with recommendations down the road because I don't really think we know that. Right now, all we can do is follow the IFU per the manufacturers of each the individual units, and I would suggest that the HPC counts should be done at the intervals suggested for cleaning by each individual unit, at least right now. I personally think there should be an industry standard that should be applied to all units. And that's a long-term fix, not a short-term fix.

DR. LANGE: Matt, let me direct -- based upon your expertise in hemodialysis, how often is that?

DR. ARDUINO: Dialysis is at least monthly. So for new systems in the dialysis setting, we recommend -- we've recommended weekly until they have an established pattern, and then

they usually pump back to at least monthly. But there are some facilities that do it more frequently.

DR. LANGE: Dr. Zenilman.

DR. ZENILMAN: With specifics of dialysis -- and this is just a question for my own knowledge. What we're hearing about, the HCUs are closed-circuit systems, and dialysis, aren't they more open circuit, or is the bath a closed bath?

DR. ARDUINO: I would say it's closed because even the storage tank has a lid with an air filter on it.

DR. ZENILMAN: Okay.

DR. ARDUINO: So you're producing water, and it goes to the storage tank, and it gets distributed to the dialysis machines, and that's where the dialysate bath proportions are mixed at the machine. But for the most part, that's a closed system.

DR. ALLEN: I don't think that all of these devices are equal. And I'm not educated enough about each device, but I don't think you can say all heater-coolers are closed or open. There's a mix apparently out on the market, and I think that is something that the FDA is going to have to standardize.

DR. LANGE: So the number of 1 month has been thrown out for dialysis. Is there anybody on the Panel that feels that it should be -- that that is too frequent?

DR. LEGGETT: I would reiterate that it should be done per the current IFUs to maintain safety for this 2 in 1,000 event, infection.

DR. LANGE: And so let me probe because obviously some manufacturers have recommended things to be done quarterly. Do you feel comfortable with it?

DR. LEGGETT: As long as their systems stay clean. I agree with Dr. Allen. Why do it more often if their systems are cleaned quarterly?

DR. ALLEN: If the manufacturer has done testing and validated that their particular disinfection or cleaning or washing method works at once a quarter, then I think that's appropriate. What you'll find, though, is that that's a marker that a hospital perfusionist can use to gauge the adequacy of how well they're following that IFU. So I wouldn't change what the manufacturers recommend, at least not right now.

DR. LANGE: Dr. Givner, were you going to say something?

DR. GIVNER: No, thank you.

DR. LANGE: Jeff.

MR. RILEY: Jeff Riley.

Do we monitor at the end before we clean, or do we monitor after we clean in that cycle?

DR. ALLEN: No gaming. So you need to monitor at the end of your cleaning because that's going to reflect the adequacy of your processes up until that moment.

MR. RILEY: Well stated.

DR. LANGE: Dr. Hopkins.

DR. HOPKINS: Actually, I was going to ask that question of our microbiologists. Is there value of knowing your starting point before cleaning? If, in fact, the point of doing the colony counts is to assess the quality of your cleaning, should you know you're taking it from 10^8 down to 50?

DR. ARDUINO: From the dialysis --

DR. HOPKINS: That's a microbiology question.

DR. ARDUINO: Yes. So from the dialysis side, it used to be that facilities would base their disinfection strategy on their testing. So they would do their monthly testing, and when they saw their colony counts begin to go up, that's when they would do something. The newer standards are basically saying you should be producing all of this good quality water. The testing now is done as a confirmation that your control strategies are effective. So it's moved from the worst-case scenario, kind of to after your disinfection processes. And as a measure of that you have adequate control of your system. So that's where the ISO/AAMI documents have kind of moved, is that way. But you're also assuming that our processes in place are for producing, you know, low colony count water.

DR. LANGE: Dr. Gallagher.

MR. RILEY: Thank you.

DR. LANGE: I'm sorry, then I'll come back. I'm sorry.

DR. GALLAGHER: Thank you.

I think wrapping my head around some of these different scientific principles is one thing, but I'm thinking for a moment like a patient, and I want to know that the devices that are being used are ones that are maintained at a very strict level, because I want to make sure that if I'm going to be operated on, I've got the best of what's available. So for me to think about that is to say that I think you do need to make the difference between what you have and then you clean it and then you do -- you want to see if there's been improvement, that it makes a difference and the people are paying attention to that, because I mean -- I know this is a silly analogy, but I could take a frying pan at home and I can put oil and cook in that and do

whatever, and in a period of time, depending upon how well I clean, whether I use steel wool to clean it or I use an SOS pad or something else, there's going to be a buildup of grease even on the outside of the pan, unless I'm very stringent about how I clean it. So if I'm thinking about biofilm kind of the same way, that it's going to grow inside this thing, I want to make sure that we've gone from oh, there's a little bit there to oh, my gosh, there's a lot there. Now I've been able to clean and get it strong. So silly analogy, but for me that makes a big difference.

DR. LANGE: So I'm going to state something that's up for either confirmation or discussion, and that is there is enthusiasm for testing after the device is cleaned to make sure that the process is adequate in achieving the HPC counts that we consider to be the lower limits. If anybody disagrees with that statement --

DR. ALLEN: Yeah, I disagree with that. So I don't really care. So let's say you clean it, you're quarterly cleaning it, and you clean it and then you test it and it's clean.

DR. LANGE: Hold on a second. I'm not saying it's the only testing.

DR. ALLEN: Ah, okay.

DR. LANGE: Okay.

DR. ALLEN: That's what I thought you were leaving it at, because I want to know what it is while I'm using the device. So I don't care. I think it's interesting to clean it, to test it afterwards, but you got to know where it is right before you clean it to know whether you're effective.

DR. ARDUINO: So if you're doing, say, quarterly disinfection or whatever, cleaning and disinfection, and if you do monthly testing, you may find out that quarterly is not going to do it for you. We're going to have to change our schedule. So even if you're following the IFUs,

there might be -- because of the testing parameters that you're using.

DR. ALLEN: So I think that's --

DR. LANGE: Hold on. Hold on a second. Either let me come to -- in other words, I'll address you by name for the transcriptionist. I don't want to cut you off, but they're looking around here trying to find out who's talking. So it was Matt first and now Keith. Go ahead. Your comment.

DR. ALLEN: I absolutely agree with that. But I think for us to mandate ahead of time and beyond what each manufacturer's IFU is, I think what you're talking about is absolutely correct, and that's a moving target going forward. But as far as recommendations to the FDA, until we can gather more information -- and I think you need to follow the IFU. If a particular manufacturer says it's every quarter and over a period of time hospitals using that device note that, hey, this is not working every quarter, they either aren't doing it correctly and need to be re-in-serviced, or then the manufacturer then needs to be looking at how do they change their recommendations and their IFUs? But for us to start out the gate and just say let's do it every month, I think that's burdensome.

DR. LANGE: Jeff.

MR. RILEY: Yeah, I think -- and our statistician might comment -- I'd add the word "random" and "by a third party" into this. If you have somebody on the cardiac surgical team doing it, I think it will be biased, personally. But if we add random by a third party and we get enough samples and we'll get it during different parts of the cleaning cycle, after a year we'll have information. And I'd recommend monthly to start, until you get the pattern that we've heard about to confirm your cleaning processes. If we're going to do this, I'd recommend

adding randomization by a third party.

DR. LANGE: Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

A quick question. I think if you're going by the IFU, which recommends in some cases the quarterly type of testing and cleaning, wouldn't it be important to also make sure of the type or the quality of the water that is being put into the system at different hospitals? If it's different from what the manufacturer tested, then the IFU would not always be applicable.

DR. LANGE: And I think you certainly hit that. In other words, if you tested after you cleaned it and immediately it wasn't clean, it could be the water or it could be the cleaning device that would certainly drive you towards that. Absolutely.

So to summarize, there's enthusiasm from the Panel to check after the recommended cleaning, both -- primarily to see if it's cleaned appropriately. And then the recommendation is, based upon the company's IFU, to test just before then, and that will drive the companies to appropriately recommend the cleaning cycle. It may be different from company to company. One may say it's a week or 2 weeks or 4 weeks, but to document just before you clean it that, in fact, you haven't exceeded that level. And if they have, then that should drive us back to saying is the cycle not appropriate or the disinfecting mechanism not appropriate or is there something else going on with the machine and it needs to be deeply disinfected?

Dr. Schwartz, I see you shaking your head. Let me go back to the Panel.

DR. SCHWARTZ: Yeah.

DR. LANGE: The recommendation obviously is to test just after cleaning. A show of hands. Does the Panel feel like it should be tested just before the next cleaning as well, at the

end of the cycle? Let me see your hands if you -- whatever the manufacturer recommends, no --

(Show of hands.)

DR. LANGE: Okay. The people that feel like we shouldn't be testing after that.

DR. ARDUINO: After the cleaning.

DR. LANGE: Well, in other words --

DR. ARDUINO: At end of cycle.

DR. LANGE: At end of cycle. Okay, great. So we're recommending two testings, that is, after the cleaning and then at end of cycle. Is there anybody here that feels like it should be done more frequently than end of cycle?

(Show of hands.)

DR. LANGE: Dr. Schwartz, does that give you sufficient --

DR. SCHWARTZ: Yes, thank you. Thank you.

DR. LANGE: Well, since the answer to (c) was no, that we shouldn't be doing routine monitoring of the HCD, of the heater-cooler device for NTM, we haven't addressed (i), (ii), or (iii), other than just the routine testing cycles we've mentioned. Is there anything else in there that you would like the Panel's opinion on? This is directed towards the FDA. So Dr. Schwartz, anything else with regard to Question (i)?

DR. SCHWARTZ: So more of, I guess, a clarifying comment or question back to the Panel. I think, you know, where you came to in terms of a recommendation for testing at the end of a cycle and then at the time of -- and after cleaning, so on both sides of a cycle, as per the manufacturer's IFU, does get to the concern that we would have based upon one of the

speakers yesterday who discussed that if you have biofilm building up within a device, cleaning the device and/or disinfecting the device and then testing it right afterwards may give you that kind of false sense of confidence or false sense of security that everything is good. However, over time, in that lapse, in that duration, you're going to have continued ongoing buildup of biofilm. So that was one of our concerns, and I wanted to make sure that in clarifying the idea of doing testing at the end of a cycle and then repeating it again afterwards, we would have a mechanism of being able to control for that or examine that. Is that correct?

DR. LANGE: I think that's correct. Good.

Two comments, Jeff and then Dr. Hopkins.

MR. RILEY: Just to clarify, we're recommending per HCD, each individual HCD?

DR. LANGE: The answer is yes.

MR. RILEY: Yeah. For us, that would be 26 pairs per machine per year of heterotrophic plate counts.

DR. LANGE: The answer obviously is that would vary according to how many HCDs each institution has, but the answer would be yes. I'm speaking on behalf of the Panel. Anybody that feels otherwise? We're talking about per HCD device. The answer is yes, okay?

Dr. Hopkins.

DR. HOPKINS: This is sort of a devil-in-the-details question for the manufacturers and for our perfusionists. When you do the post-testing, since part of the issue is the biofilm and we have testimony that as the machine vibration goes on over a few hours, even without any other introduction, your colony counts start to go up. So how do you currently do your post-cleaning assay? Is it done just washing a little bit of water through after you've put through the

Pine-Sol? Or do you actually run the unit with distilled water for 3 hours and then do it? Because that's going to begin to sample your biofilm efficacy of the cleaning. So the way that assay is done after cleaning is going to impact the data tremendously. And the manufacturers may -- that may already be in the IFU. I just don't know.

DR. LANGE: Al.

MR. STAMMERS: Thank you.

And a very good point, because I could tell you right now, we don't have a standard for that with our devices, but it is something that we will internally create. And I don't believe the manufacturers state -- I could be wrong -- exactly the interval for testing the device. Right now we recirculate the device -- they all have internal recirculation modes -- for whatever period of time the individual clinician feels. So it's random, and then we sample at that point. We don't run it through a patient first. We go ahead and we'll just test it before we hook it to a device.

DR. HOPKINS: But you don't run it for 3 hours and then test?

MR. STAMMERS: No, sir, we don't have a time that we're doing this, although it's -- we will standardize it now to be consistent.

DR. HOPKINS: So I throw out the recommendation that that be a standardized procedure.

DR. LANGE: And I think that I would probably speak for the Panel. Is it we want the same procedure to be followed by all the institutions so they're comparable and nothing less? Great.

Anything else about 1c?

(No response.)

DR. LANGE: Or are you prepared to move to Question 2?

MS. MARDERS: Sure. Can you advance the slide, please?

Okay, Question 2. Mitigating Biofilm Formation in HCDs: Overgrowth of bacteria in HCDs is problematic and can lead to biofilm formation. The prevention, detection and removal of biofilm can be challenging.

a. Given the consistent low level of water contamination in the water pathways, device labeling indicates that regular preventative maintenance is necessary to mitigate/minimize risk of patient infections. What factors would have the most impact on minimization of biofilm formation? Please consider the following points in your response:
    i. Frequency of mechanical and/or chemical cleaning before disinfection, and factors that impact frequency (e.g., microbial monitoring, visual cues, operating hours, etc.)
    ii. Maintenance intervals and maintenance procedures as part of regular servicing at hospital facilities
    iii. Device materials, water system designs, microbicidal processes or chemical treatment methods (e.g., combination of cleaning and disinfecting agents)
b. Should cleaning/disinfection servicing performed by the manufacturer be part of routine maintenance to demonstrate an acceptable level of contamination (as discussed in question 1a)? If so, at what frequency?

DR. LANGE: Great. Okay, as we're digesting it, what factors would have the most

impact on minimization of biofilm formation? I'll open it up to the Panel.

Dr. Allen.

DR. ALLEN: So I think, in essence, we already somewhat discussed this, and I think the issue is that on new machines, getting ahead of the curve, keeping the machine clean in a consistent fashion, using HPC as a surrogate to know that you're actually getting the job done is a good way to prevent biofilm. I think on older machines, from what I know, it's impossible to take a machine that's been out there for 6 years, and even if you get low HPC counts, as far as NTMs are concerned, that probably isn't going to be reflective, and those are going to require some type of a deep dive deep clean by the manufacturer. That probably can't be performed on site.

I do think that the hosing -- you know, when I look at the insides of these devices, there's a water containment system, which that's easily gotten to, or maybe it's not so easy on some machines, but that can be cleaned. What concerns me are the PVC, polyethylene hosing that is in these machines that sounds like, even by IFU, aren't replaced that often. And while I don't know what the right time frame to replace those is, we need to come up with some recommendations either by visual clues -- we saw pictures yesterday; those were disgusting. I mean, who would open the back of a machine and see brown hoses and not think those didn't need to be replaced? So probably some visual clues and a more frequent replacement of even these tubings that supposedly are designed to prevent biofilm and so forth needs to be considered.

DR. LANGE: Dr. Givner.

DR. GIVNER: Are Questions 2a(i), (ii), and (iii), are they questions that we're asked to

make a recommendation on, or they just questions like what do you think?

DR. LANGE: What do you think? And based upon that, what's your recommendation?

(Laughter.)

DR. GIVNER: I recommend that we think about it.

DR. LANGE: What are your thoughts, Dr. Givner?

DR. GIVNER: It seems to me they're just saying what do you think? I mean, we're not going to make a recommendation about (i), (ii), or (iii). Which one do you think is important? Oh, I don't know. But then what are you going to do about it? The only one that there is concern about, of course, is the visual clues. I think all of us would agree that that's an issue. But other than that, I don't know what I would say to (i), (ii), or (iii).

DR. LANGE: Dr. Leggett.

DR. LEGGETT: I would add to Dr. Allen's and Dr. Givner's point and bring into discussion the fact that we know that mechanical and/or chemical cleaning is of the utmost importance to eliminate proteinaceous debris, or even high-level disinfection as shown in duodenoscopes, or even ethylene oxide sterilization won't work if you don't clean them. So that, to me, is the most paramount thing in biofilm elimination.

DR. LANGE: Jeff.

DR. LEGGETT: Oh, and then -- sorry. And to add on to Dr. Allen, in the machines that are already in use, there was data presented by Garvey's paper looking at two cycles with peracetic acid as opposed to the one-cycle cleaning. So that is something to think about but not to recommend, according to you.

(Laughter.)

DR. LANGE: Jeff.

MR. RILEY: Jeff Riley.

One of the comments that was just made, we already have the recommendation from the CDC and the FDA that soiled units should be taken out of service, and I don't think that recommendation got followed because half of the heater-coolers in the United States are soiled on visual inspection. So that's already in place. The other thing that I learned from Dr. Falkinham was that detergents were helpful in breaking down biofilm, and I'm not sure if bleach or Pine-Sol falls into a detergent category, but it goes back to proper cleaning with a detergent like -- at least I think I learned that.

DR. LANGE: Matt and then Dr. Hopkins.

DR. ARDUINO: Okay. So I'm going to just give you a little background on things that you have to look for and that cause biofilm. Stagnancy. So if the unit isn't running and it's just sitting for a period of time just full of water, that's an issue, which is one of the reasons why, if you look at dialysis water systems in the old days, they were direct feed, a lot of them, which meant you went from the RO in a straight line out, hit all your machines, and then went to drain. So at the end of the night, what you do is you turn the thing off. Those were hard to maintain.

And then we started looking at minimum flow velocity through the distribution system. And then you have to look at shear and other things that happen within the system, and some of those all impact, you know, formation of biofilm. And biofilm actually starts within hours because if you introduce -- if bugs get introduced into the system, where do they want to be? They'll attach to the surface. And, you know, there's a period of time where that's temporary

attachment, and then it becomes permanent and then they begin to grow. So part of this, too, also has to be what you have to think about is if I use this and I'm going to keep water in it for X period of time when it's not cycling, you know, you may want to minimize the time that you're just sitting stagnant, full of water.

DR. HOPKINS: Yeah, I actually read this question a couple of times trying to figure out what FDA needed, and if I understand the intent of the question, it seems to me that I would propose that while we have no knowledge to make recommendations, it does appear that progress could be made in device material and system design elements as well as improving the processes and chemicals used for cleaning. So if we had to vote, I would probably vote that Number (iii) is where a lot of the improvement can be made. But again, that's going to be dependent upon research and development, primarily by the manufacturers.

DR. LANGE: Mr. McGlamery.

MR. McGLAMERY: My question speaks to that as well. I mean, if you look at these machines, there are a number of different materials used. Is biofilm agnostic, it sticks to everything? Or are there some materials that would be better suited, some that maybe are not even used right now but should be used in future devices?

DR. ARDUINO: Okay. So here's another biofilm thing. Even antimicrobial-containing materials, all it does is slow the process down. They don't prevent the formation of biofilm. So like silver-containing impregnated catheters or this sort of surface, all you're doing is slowing the process down. Now, when I look at water distribution systems, there are materials that are more helpful than others. So if I have a distribution loop, the lowest grade material you can get is PVC. If you do a scanning electron microscopy on PVC, it's not a flat surface. There are all of

these little nooks and valleys, and what happens is, is bugs stick down in the nooks and crannies and form. So when designing our laboratory building, we have centralized -- on one portion of our lab building, for each floor there's a centralized water system just like we have in dialysis, a recirculating loop. And I wanted a choice. So I was like -- I went to the architect that said 316L or PVDF? We went with PVDF because it had a 50-year lifespan. And we do monthly monitoring on that water, and it's sanitized on a quarterly basis, and I still produce water in that distribution loop that's less than 1 CFU/100 mL, and endotoxin is basically not detected in that system. And, you know, that's with it flowing all the time.

But here's where I think device materials would be helpful because many of the materials we have now are not compatible with some of the disinfectants and cleaning agents that we would need to remove scale and biofilm. So, you know, you may want to look at choices of materials and choices of chemicals and the appropriate biocides to use in cleaning and removal.

MR. McGLAMERY: I'm just curious, too.

DR. LANGE: Please identify yourself, Raymond.

MR. McGLAMERY: I beg your pardon? Oh, Raymond McGlamery.

Have other methods, has any sonication, any ultrasound methods been tried to loosen the biofilm quicker, move it out? I mean, has any of that stuff been attempted?

DR. ARDUINO: So in a laboratory setting we use a combination of sonication and physical, you know, kind of scrubbing. What we used to tell dialysis facilities with storage tanks is that at some point you pull the lid off a storage tank and you actually get in there and scrub, scrub, scrub. Nowadays, what people are doing with these types of water systems that are like

this, is they put an ozone generator inside the storage tank and you ozonate, and then you wait until you can detect the ozonated water being returned to the tank, because usually it takes awhile for that process to do.

So there are chemical agents that are effective against biofilm. So there are things like chlorine dioxide and -- which helps then to minimize it. Do we actually remove the whole biofilm without the physical getting in there and scrubbing it off in some way? What you end up doing is killing cells leaving the house. So you end up with the matrix is still behind, which is then easier to, you know, recolonize. And in some cases, even with disinfection, depending how thick your biofilm is, you get the sister cells. So while you kill off some, the sister cells are still there, and then you get the regrowth of biofilm.

DR. LANGE: Dr. Yuh.

DR. YUH: Yes. In trying to strictly address the question, you know, I think all the factors in (a)(i), (ii), and (iii) are equally important given the lack of information that we really have. So in trying to strictly answer the question, I'm not sure we can necessarily rank or prioritize any of them. And they're on different scales; (i) and (ii) are kind of more immediate measures, whereas (iii), in terms of device material system designs, are more long-term priorities that may have equal impact. I think we should, you know, focus on (b) when the time comes because I think that's a more difficult question to answer in terms of whether or not the manufacturers should be brought in to look at these devices on a periodic basis.

DR. LANGE: Dr. Givner.

DR. GIVNER: We're going to get to Question, later on, 4b that says, for devices in development, what design features, instructions for use and/or environmental/use-related

considerations might you suggest? I think we're going to get to a lot of this. So I really do think that (i), (ii), and (iii) are just kind of food for thought. Although, where it says, "Please consider the following points in your response," that reminds me of exams in college, but I don't think we really have to answer this or make a recommendation.

DR. LANGE: Two questions I'll pose to our experts. One is we've made the recommendations for water not to stagnate, and that is to drain it every day, considerations of the time involved notwithstanding.

The first question to you, Matt. Does that decrease or slow down biofilm? I might not get away with this. And the second question to our infectious disease experts that was brought is the use *Pseudomonas* counts as a surrogate for the extent of biofilm and whether we should act upon that.

So Matt, if you'll address the first question.

DR. ARDUINO: Okay. So what helped was if you drain the machine, you still have to be able to say I've drained it. If it's still wet, you still have a problem. There has to be a way that you could actually dry that fluid pathway, because if it's just sitting there wet with just some residual moisture on there, that's -- some of these bugs just need that.

DR. LANGE: Having said that, I mean, there are two -- one that you can completely dry. But even you can't -- that is, if you just drain it and there's some residual drops on it, does that still slow down the growth of biofilm or not?

DR. ARDUINO: I can't really answer that. I could tell you what happens with dialysis jugs. So if the jugs that they use for the concentrates -- so they're supposed to be cleaned, and you know, our recommendation is clean and disinfect at the end of the day. AAMI says weekly

disinfect the jugs. But if there's residual water left in there, you can have amplification occur in that jug so that when you go refill it with bicarb, now your colony counts may exceed your limit. Will there be biofilm? Maybe not. But the bugs are still, you know, there to grow.

DR. LANGE: Al.

MR. STAMMERS: A point of clarification. Draining the devices every day, did you say we made that recommendation? Because that's infeasible; that cannot be done in America today using these devices. It's just impossible to drain these every day, every night and then refill them. Once a week is extremely difficult. On a daily basis, it's impossible.

DR. LANGE: Okay, I want to come back to that because in our first recommendation, one of the things we recommended was changing the water, and that is draining it and replacing it. What you're saying is that's done without draining it?

MR. STAMMERS: Yeah, we cannot drain these devices every day. I mean, it's physically impossible. They're in operating rooms. Most of them are of greater than 20 L of tank, and they would physically have to be removed to an area someplace else in the operating room where that volume can be removed safely without contaminating the OR environment, then brought back refilled. It would take an hour to an hour and a half for each device. So like a center like the Mayo Clinic, you know, which has 12 operating rooms or something, it would delay surgeries, and it's just feasibly -- and I defer to our cardiac surgeons if they would agree with that.

DR. ALLEN: Yeah. And maybe I misunderstood. I didn't know we had made the recommendation to change daily. I think our recommendation was that we follow the IFU of the manufacturers. That was the recommendation.

DR. LANGE: Thank you.

DR. ALLEN: Not to change daily.

DR. LANGE: Thank you.

Jeff.

DR. ALLEN: Because that's impossible.

MR. RILEY: We can't drain the waterlines daily. We can empty them when we're done, and that's our current practice now. But I agree that daily emptying of the machine, no.

DR. LANGE: Great. Other comments?

Dr. Givner.

DR. GIVNER: I did have my last recommendation we made: change water daily. And I don't know if, Dr. Schwartz, you had the same, but -- and I have no problem re-discussing it, but I thought we kind of did recommend that.

DR. ALLEN: Yeah, that's not what I heard, and that's not -- that's not what I would recommend, and I think that's --

DR. SCHWARTZ: Yeah, I don't have that in my notes.

DR. LANGE: Hold on. Hold on a second.

DR. ALLEN: -- practically impossible.

DR. LANGE: Let me call on somebody.

Dr. Schwartz.

DR. SCHWARTZ: Yeah. In looking over the notes from Question 1, I don't have in my notes anything about draining and changing the water daily, but rather sticking to the manufacturer's IFU with respect to the cleaning and disinfection, which is going to involve

obviously changing the water too.

DR. LANGE: Thank you for clarifying that.

DR. LEGGETT: I think that may have come up in the context of --

DR. LANGE: This is Dr. Leggett.

DR. LEGGETT: This is Dr. Leggett -- in the context of an outbreak, and Dr. Sax, where they were doing it daily. So I think that once you're dealing with an outbreak, then things have to change, but we're talking about routine.

DR. LANGE: Thank you.

Dr. Roselle.

DR. ROSELLE: The biofilm is going to win. You're not going to get rid of it. It's a nice thought. The chemicals you would use to clean it out will probably destroy the machine. It will eat the pipes and the connectors and everything else. It's going to be very, very difficult. You can slow it down, we talked about. And, in fact, it's what is said here in 2a(i). You're going to do microbial monitoring, you're going to do visual cues, theoretically. You're going to do maintenance and make sure you've done it and document it and make sure people know how. And it may not be the perfusionists. Sometimes you're better off to have somebody else do it who is -- that is what they do, and they're trained to do the same thing all the time, instead of being torn between 50 different jobs. But the materials can be useful, but it's not going to fix it.

Remember, most medical devices are not designed to be cleaned. It's a fantasy if you think they are. And I could give you a whole list of them that aren't, so you have to do the best you can as designs change. There are tubings and there are coils, and they're going this way and that. There are connectors that are kind of rammed up. They work, but you're going to kill

the planktonic bacteria, most of them, and you're probably not going to kill all the bacteria in the biofilm. So all you can do is the best you can do as you monitor it because you're not -- it's very unlikely that you're actually going to get rid of the biofilm entirely, unless somebody else thinks differently.

DR. LANGE: Dr. Leggett.

DR. LEGGETT: Jim Leggett.

Just something to add. I would think that intermediate-level disinfection, however, would be better than the low-level disinfection.

DR. ROSELLE: It's Roselle.

DR. LANGE: Dr. Roselle.

DR. ROSELLE: I'm not saying you don't do all of these things, but I don't think we should try to convince ourselves that the biofilm is going to go away and that everything will be fine. I think you do everything you can to make it as safe as possible, just the same with all the equipment in the operating room, and that's what you do. And you make sure -- the hard part, that it's done right, it's done right all the time every day.

DR. LANGE: Dr. Allen.

DR. ALLEN: So to keep us on track, I think I don't want to focus on or I don't think we should be focusing on how to keep these machines ultra clean because it's clear they're never going to be ultra clean. Let me use this analogy. You know, we used asbestos all the time, and asbestos in a building or house is okay, unless you disturb it. So I think the key is we need to be thinking more long term. How can we design these devices so that they don't aerosolize? We're never going to prevent the biofilm. Our experts tell us that. We're never going to make

these machines absolutely bacterial or protozoa or NTM free. But what we could do is just like asbestos, if you leave it alone and keep it as clean as possible, then you might fix the problem.

DR. LANGE: So let me see if I can summarize. The consensus is we're not going to get rid of biofilm; that again, there ought to be routine visual inspection and there ought to be some recommendations about how frequently that should be done; that the manufacturers should make the devices easy to inspect so we don't have to take things apart and work our way through it -- that wasn't a recommendation of the Panel, but I would say the pictures from yesterday that showed that things you could see looked fine and things you couldn't see didn't quite look so well; that again, it comes back to the routine cleaning and disinfecting with appropriate detergents that are biocompatible. Low-level disinfection is probably not appropriate. We're going to continue to use the HPC as a marker for how well we're cleaning and disinfecting. And then longer term, to the manufacturers, is to develop materials that are biocompatible with better detergents and that are more likely to slow down the growth of biofilm. I think that summarizes what I've heard.

Dr. Schwartz, does that give you enough guidance about this?

DR. SCHWARTZ: Well, let me ask. We have not considered Part (b) yet of this question; is that correct?

DR. LANGE: That is correct. We're going to do Part (b) after lunch.

DR. SCHWARTZ: Okay. Well, because I think that Part (b) raises the issue of, as you've just stated, we're never going to get rid of biofilm in currently used devices. Our question gets to whether routine maintenance in order to remove biofilm needs to encompass the manufacturers doing a deep clean/disinfection service of the device at certain intervals. I think

that it's sort of tied into the first part of the question as well.

DR. LANGE: Okay. And that's why I want to keep that, I want to come back to that. I see people that are being hypoglycemic now.

(Laughter.)

DR. LANGE: And so a little bit more brain food. Have we addressed (a)(i), (ii), and (iii) to your satisfaction? Anything else we need to do?

DR. SCHWARTZ: Yes, that's fine. Thank you.

DR. LANGE: Okay.

DR. SCHWARTZ: Thank you.

DR. LANGE: Before we break, a couple things. One, for the guest speakers, if you have planned on an early departure, and I'm not sure why you would, this is so titillating --

(Laughter.)

DR. LANGE: -- see AnnMarie, Ms. AnnMarie, so that she can make those arrangements for you. When we come back again, we need to identify who we are before we speak so we give you proper attestation in the transcription.

Anything else, Evella?

(Off microphone response.)

DR. LANGE: Great. It is now 12:04. We're going to take a 56-minute lunch and be back here at 1:00. Thank you.

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

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

(1:01 p.m.)

DR. LANGE: I'd like to reconvene the Panel at this time. And I'll ask Ms. Julia Marders to reread Question 2b. And then after you've read the question, Ms. Marders, I'll ask Dr. Schwartz to give us some guidance about how the FDA would like us to approach this. So please, please read 2b.

MS. MARDERS: Julia Marders, FDA.

Question 2b. This is the second part of the Mitigating Biofilm Formation in HCDs. Should cleaning/disinfection servicing performed by the manufacturers be part of routine maintenance to demonstrate an acceptable level of contamination (as discussed in question 1a)? If so, at what frequency?

DR. LANGE: And Dr. Schwartz, I assume you're talking about heater-cooler devices that are currently being used?

DR. SCHWARTZ: That's correct. So this gets back to the discussion that we were having right before our lunch break where the discussion focused on mitigation, a removal of biofilm, and the question that we've been grappling with at FDA and that we're putting to the Panel is whether, indeed, knowing the limitations of being able to totally eliminate biofilm or even reduce it to an acceptable -- whatever that acceptable level is, whether maintenance performed, whether cleaning and disinfection, deep cleaning and disinfection servicing is provided by the manufacturer needs to be considered as part of routine maintenance of some of these devices at various intervals.

DR. LANGE: And again, just for clarification for the Panel, is it important to you that it be

performed by the manufacturer or just that a qualified person or persons outside, or you specifically want it addressed by the manufacturer?

DR. SCHWARTZ: That's an interesting question. I think that we would like it addressed with respect to the manufacturer performing that or someone who is trained according to the manufacturer's validation for that procedure to be undertaken.

DR. LANGE: So the question before us, should we be doing something more intensive either from the manufacturer or from somebody trained from the manufacturer?

Al.

MR. STAMMERS: Thank you, Dr. Lange.

I just want to -- in the instructions for use, the ones that I've been able to obtain online, the manufacturer LivaNova does state that after -- I'll read it exactly, it's one sentence. "Every 1,000 operating hours or yearly, notify the authorized service technician for the regular preventive maintenance check of the heater-cooler." It's kind of generic, but I think perhaps they're even revising that because I think that is a stop-point where we, as users, are required to go beyond the normal maintenance requirement to use their own service or an authorized individual to provide that internal care. I don't mean to think more so than what their idea is, but I would imagine in the IFUs, there is some hourly time period where the device needs to be serviced by themselves or an authorized representative.

DR. LANGE: I'm going to ask a representative from LivaNova to come up because it talks about routine maintenance, but specifically, is the manufacturer recommending, as a part of that, that a deep disinfection be performed?

MR. PEIS: Christian Peis from LivaNova.

Yeah, it's true we require yearly or annual maintenance of the heater-coolers. And regarding this topic, we have updated this maintenance guidance document, and now we require from the service technician to check the tubing, if there is biofilm present, and if there are some signs of biofilm, to replace the tubing sets, for example. So those things have been included in the annual maintenance guidance.

DR. LANGE: Now, the Panel's already talked about two distinct things. One is changing the tubing and the other is -- it's an entirely different thing. It's a deep disinfection of the entire device.

MR. PEIS: Yeah.

DR. LANGE: So as a part of the annual maintenance right now, is the company only recommending changing the tubing if there's biofilm or doing a deep disinfection of the entire device?

MR. PEIS: Um-hum. We only recommend -- so, first of all, he has to check the status of the machine, if biofilm is present in the tubing. And if biofilm is present, we ask the service technician to replace the tubing. It's limited to replacing the tubing. Because the deep disinfection process is a very complex process, it cannot be performed at the customer site or at the hospital. You have to disassemble the device, you have to scrape surfaces, and you have to apply certain disinfection processes which need some equipment. So like heat, we are doing some heat disinfection and so on, and those equipment is only available at the service site.

DR. LANGE: That's very helpful, thank you.

MR. PEIS: Yeah.

DR. LEGGETT: This is Jim Leggett.

Before you leave --

DR. LANGE: I'm sorry. Dr. Leggett.

DR. LEGGETT: -- do you already have protocols for when you would opt to do the deep cleaning?

MR. PEIS: In our customer letter we have sent out, 2015, in June 2015, we asked customers to take samples, microbiological samples, and if they're not able to bring the device back to a clean device, we ask them to contact our company. And in this case we recommend the customer to perform a deep cleaning or deep disinfection.

DR. LANGE: Dr. Yuh and then Dr. Allen.

DR. YUH: Is that involved process something that perfusionists at a community practice would be capable of doing with any kind of quality assurance, disassembling the device and cleaning it to the extent you just described? I mean, because if -- and that's what the question here is asking, is if somebody from your company would be willing to come out and do that. I understand that it seems unlikely that that would be feasible of all the heater-cooler devices that are in the United States alone. But what you just described was a deep cleaning process, and I'm just not sure, you know, the -- you know, the perfusionist in a community practice is going to be qualified to do.

MR. PEIS: No. This deep cleaning can only be performed by service people, trained service people from LivaNova. It cannot be done by any perfusionist or -- it's impossible. The perfusionist is also not allowed to open the device or to disassemble the electronic parts. This needs to be done by a qualified person.

DR. YUH: So is that programmed into your program where you would have a qualified

technician come out to each center with your product and do that on a periodic basis?

MR. PEIS: Um-hum. Yeah.

DR. YUH: Because I'm not getting that from what you just said.

MR. PEIS: So again, we have these annual maintenance guidelines, and the service is getting to the customer, checking the machines for safety, for maintaining the machine, and during this regular maintenance he's checking the status of the machine and changing the tubing. But he cannot do more on site. If the machine is fully contaminated, the machine needs to be sent back to the facility for deep cleaning.

DR. LANGE: Dr. Allen.

DR. ALLEN: So I think if the FDA is asking, cleaning and disinfection, you mean a deep clean, which I think is what you mean. I think that has to be performed by the manufacturer.

DR. SCHWARTZ: Yes.

DR. ALLEN: Secondly, though, I personally do not think that that should be part of routine maintenance. I think that should be driven by your inability to maintain appropriate HPC counts, if we're going to use that. If you consistently are cleaning the device and you're having elevations and/or you have an incident, you have a sentinel event, then that would indicate it.

Can I ask manufacturers or -- and perhaps maybe to get an unbiased from the two perfusionists, what does one of these heater-cooler units cost? And for perspective, if I sent -- if I'm Hospital A and I sent my product back to LivaNova, how much does it cost to get it deep cleaned? So how much are these devices, broad strokes, and how much does it cost to -- you get what I'm getting at is, is it cheaper to junk it or is it cheaper -- and buy a new one than it is

to deep clean it?

DR. LANGE: And so I'm going to take us back to the question. That's interesting, no doubt, Dr. Allen, but it's a little bit far afield of this particular question. But the first point you made is good, and I want to bring us back. But we all can sit down. You can stand there if you want to but -- unless I call on you, okay?

(Laughter.)

DR. ALLEN: Well, I do think that --

DR. LANGE: But your point's taken. Is it what you would -- your recommendation is that deep cleaning can only be done if there's an indication, not routinely?

DR. ALLEN: Right. So deep cleaning, though, costs $10?

UNIDENTIFIED SPEAKER: No.

DR. ALLEN: Okay. So if deep cleaning costs $10, by all means, let's do it routinely. If deep cleaning costs more than replacing the machine, then clearly that's not practical or feasible. So some idea of cost in being able to make practical, usable recommendations to the FDA is important.

DR. LANGE: So is it more expensive than doctors and less expensive than a Beamer?

(Laughter.)

DR. LANGE: Okay. Al.

MR. STAMMERS: Just this question, I think, is answered in the IFUs, just so we don't spend a lot of time here. And I know a couple other companies are here, but in the LivaNova they specifically say at 1,000 hours it has to be serviced, which I think answers this (b) question in 2 very accurately, so I don't know if we have to spend a lot of time.

DR. LANGE: No, this is different because routine maintenance is different. Because what the FDA is asking for --

DR. ALLEN: Deep cleaning.

DR. LANGE: -- is not should routine maintenance be performed, but should routine cleaning and disinfection; is that correct, Dr. Schwartz?

DR. SCHWARTZ: Should the deeper cleaning, the deeper cleaning/disinfection be incorporated --

DR. LANGE: Okay.

DR. SCHWARTZ: -- as part of, under the general maintenance of the device, was the question.

DR. LANGE: So what the FDA is asking us, as a group, is would we recommend that routine cleaning and disinfection be done on a specified time period or hour period?

Al.

MR. STAMMERS: Just quickly following up. I believe, if I heard the LivaNova representatives correctly, once they do this assessment at 1,000 hours, which in their research and their validation of their devices up front, they came up with this number to say that's the point where it has to be assessed in regards to the presence of biofilm and other aspects of the working components of the device that needed to be checked. So I think this does -- in my experience as a perfusionist, this is the routine maintenance; it's just not the weekly or bi-weekly or monthly. This is a 1,000 hours of use or a year, whichever comes first. This maintenance needs to be performed by the company or an authorized representative.

DR. LANGE: So I mean, again, that puts it in a different category because at that point

it's not being routinely disinfected, it's being inspected, and on the basis of that, then it's being cleaned. And what the FDA wants to know is, is that good enough, or does the Panel think, regardless of what it looks like, if it just needs to be routinely cleaned?

MR. DUPOUX: Dr. Lange, maybe I can answer Dr. Allen's question. So Thierry Dupoux, LivaNova.

So the cost of a deep cleaning is less than the cost of a new machine; otherwise, nobody would have ordered it. However, for U.S., there is no cost yet available because the process is not approved yet. So whenever it's going to be approved and made available for U.S. customers, then there will be a value associated which would be communicated. But for sure, it is less expensive than getting a new machine.

DR. LANGE: Thank you.

MR. McGLAMERY: I mean, to me, maintenance speaks specifically to maintaining the mechanical parts on the machine, the tubing, as you said, but it doesn't say cleaning at all, to me. It just says maintaining the operational, whether that's the touch screen or just the operational parts. And I think the question is, is should that also include cleaning? But I think there's another part of this, unfortunately, to speak to the economics, is that you're going to have to ship the machine, and it's going to have to go overseas. So there's another cost beside the cleaning that's going to add a significant amount to it.

MR. DUPOUX: Not exactly.

DR. LANGE: So I'll ask again, I'm going to ask the company -- I mean, I'm not trying to be disrespectful --

MR. DUPOUX: Sure.

DR. LANGE: -- but the people in the audience, unless I call on you specifically, won't respond. But again, I want to take the cost out for just a little bit, in other words, because if we determine as a Panel -- and I'm not saying we should, but if we determine that routine maintenance should be performed, then the onus will be for the FDA and the company to work with how that's accomplished, whether overseas or here, and that will be obviously a part of the cost of it. So I want to take us away from that and I just want to answer -- I want to focus on this particular question and that is -- and I'm not offering an opinion. I want the opinion of the Panel. Should there be routine cleaning?

Keith.

DR. ALLEN: Al, I disagree. I really read this very different than you. I think Rick has kind of said it. I read that as we're going to come out, look at the hoses, change them if they're dirty, but I don't -- that does not include deep cleaning. That is in no way involved in deep cleaning. They're totally separate issues. And while I would follow the IFU and they would change the hoses and do what they need to do, but I would not recommend taking it a step further, and I would not recommend to the FDA that they put a rule in place that all of these machines at some set period of time have to be shipped back to the manufacturer or a service authorized person to be deep cleaned. I would not make that recommendation.

DR. LANGE: Thank you. And that's what I'm looking for is how the Panel feels.

Dr. Gallagher. Thank you.

DR. GALLAGHER: So I think that saying routine at so many hours or at this time interval really doesn't make sense because if, in fact, as our perfusionists have said, someone turns on the machine in the morning and it doesn't get turned off until the end of the day, that's real use

for the running of the machine, but they might not count it that way. It may be the use when it's being used directly by the patient. So I think that hours of use is a misnomer of a way to determine it. I would think that the most reasonable is as soon as you cannot achieve the appropriate numbers that we've indicated earlier that says your machine needs something more than the routine whatever, and that would be when I would say that it would require some kind of deeper-level fix.

DR. LANGE: Thank you, Dr. Gallagher.

Other opinions? Dr. Leggett.

DR. LEGGETT: If it ain't broken, don't fix it. I mean, I think that sums up what we're saying.

DR. LANGE: Yes, Dr. Fennal. Yes.

DR. FENNAL: Mildred Fennal.

I agree, if it's not broken, don't fix it, but sometimes what happens is if we don't maintain it, it gets broken. And so I think maybe my opinion is routine maintenance means that it's going to be checked every so often to see if it's functioning properly, and what FDA is asking about is the deep cleaning process, which is usually done when there is a problem; is that correct? When it's a problem?

DR. LANGE: Yes.

DR. FENNAL: So it would have to be taken out and immediately deep cleaned if there was a problem that was found. But routine maintenance may get you to the problem sooner. And if everyone was doing what they were supposed to do to maintain the machine and the protocols were being used, it's not likely that it's going to get to the point where you have to do

that. I mean, we just need to do our job and keep it clean.

DR. LANGE: So what I'm hearing from the Panel is there's enthusiasm for doing routine -- I'm sorry, do you want to say something, Dr. Givner?

DR. GIVNER: I was just going to ask, I know we kind of concentrated on LivaNova with these questions, but do the other manufacturers also have annual maintenance, etc.? I just want to be sure all three have them because I don't know if that's something we're going to recommend or we're just going to say according to the manufacturer's recommendations.

DR. LANGE: So Doug, please.

MR. PLATT: Doug Platt, CardioQuip. I'm assuming you're asking a question, so I came up here anyway.

We recommend annual maintenance, routine maintenance on an annual basis or every 1,000 hours. It's pretty much a standard thing. I do want to say, though, I don't think you all really understand what routine maintenance is. It's basically a functional check of the machine. We do check water quality, but we only make an indication that this is what the water quality is and report that to the hospital. In our basis, there is nothing for us to do with water quality other than to inspect the machine.

I would say that in the case of replacing the tubing inside the machine, that is absolutely useless. There are many more places where the biofilm would be on the machine. The second thing is if you replace the tubing inside the machine, what you've really done is you opened up the machine and allowed the bacteria to escape from where it really was. So there are things to be added, but to say that routine maintenance would include any kind of cleaning which is not accomplished by the manufacturers, and to say that routine maintenance -- or to say that a

deep cleaning could be done in the hospital environment, that is also not possible.

DR. LANGE: Thank you very much. And from our other -- thank you very much. And do you recommend routine maintenance, and does that include disinfection or cleaning?

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

We do recommend routine cleaning on a quarterly basis and a maintenance check, checking all the safeties and things like that to make sure it runs properly and performs its normal performance. We do not include disinfection.

DR. LANGE: So Dr. Givner, does that address your question?

DR. GIVNER: Is that recommended annually? What you just mentioned, the maintenance, routine maintenance, is that annual?

MR. BERKE: It's quarterly.

DR. GIVNER: Quarterly.

DR. LANGE: So there are several people around the room that have mentioned -- I'm sorry. Mildred, if you'll turn your speaker off -- microphone. Several people around the room that have mentioned doing it if there's an indication, that is maintenance, if the tubing looks like it's got biofilm on it during routine inspection, and if it doesn't meet our quality standards. Is there anybody here that feels otherwise on the Panel before we --

(No response.)

DR. LANGE: Dr. Schwartz, does that address 2b to your satisfaction?

DR. SCHWARTZ: Yes, thank you.

DR. LANGE: Great. Any other comments from the Panel about that?

(No response.)

DR. LANGE: Okay. Thank you. And thank you for the manufacturers.

If we can move on to Question 3, then.

MS. MARDERS: Question 3. Case Definition and Patient and Provider Notifications: Once NTM has been detected in the hospital environment or via retrospective review,

a. What case definition should be used for patient identification and stratification for communication with patients?
b. Please discuss what methods could be implemented for identification and tracking of potentially infected patients (for example, registries, electronic health records, etc.)?
c. Understanding the latency period for the onset of symptomatology of NTM infection, what would be the best approach and appropriate time periods for healthcare providers to communicate with their potentially infected patients?

DR. LANGE: We'll take each of these individually, and let's start with (a). What case definition should be used for patient identification and stratification for communication with patients?

Dr. Givner.

DR. GIVNER: Before we get to (a), (b), and (c), I'd like a little clarification on the question that 3 is asking because it says, "Once NTM has been detected in the hospital environment or via retrospective review." I'm not sure what that really implies.

DR. SCHWARTZ: So let me clarify. "Once NTM has been detected in the" --

DR. GIVNER: Sorry?

DR. SCHWARTZ: -- "hospital environment," we're speaking specifically about NTM in the

heater-cooler device in the hospital environment as opposed to the other environments.

DR. GIVNER: So particularly in these devices?

DR. SCHWARTZ: I'm sorry?

DR. GIVNER: Particularly in these devices?

DR. SCHWARTZ: That's correct.

DR. GIVNER: That's the hospital environment?

DR. SCHWARTZ: That's correct.

DR. GIVNER: And then the retrospective review is that you find a patient who's been infected?

DR. SCHWARTZ: Yes. Also, alternatively, if a patient has been identified through retrospective review of electronic health records with NTM, and what needs to happen, you know, with regard to looking to determine whether that patient was a cardiothoracic patient and so on and so forth.

DR. LANGE: Great. Larry, does that address the -- is the question clarified to your satisfaction?

DR. GIVNER: The patient part, is that -- is it when you find a patient who's been affected or you know your machine's been infected, that then you go back and look for a patient notification?

DR. SCHWARTZ: It's a two-part question, in a sense. So there's two parts to it, right? And that's what we're asking the Panel. If, for example, NTM has been detected within HCDs, should that hospital take on an evaluation, pursuing analysis in terms of patients that were previously exposed to that HCD and notify them, identify those patients and notify them of the

potential of exposure? Or another approach is for hospitals to take a look through their electronic health records to determine if they have patients who have been identified or diagnosed with NTM and then match those back to whether they've undergone cardiothoracic surgery. Does that help?

DR. GIVNER: Yes. So I guess what you're asking is when you find out a patient has NTM, there's kind of -- kind of it is expected, then, that you will go back and find out if that patient had cardiothoracic surgery.

DR. SCHWARTZ: We're asking. Basically, we're saying what should be the mode of determining patient exposure, number one, and then how would that further -- what kind of protocol, how would that inform patient notification and potential identification?

DR. GIVNER: I don't mean to be picky, and I'll quit whenever you want, but we've heard that the lab review may not be helpful, but if you look at -- there's plenty of patients who have NTM infection who would be identified in our lab. So are you saying we need to go to the lab, identify each of those reports, and then find out if each of those patients had cardiothoracic surgery?

DR. SCHWARTZ: You can consider that as part of the question.

DR. GIVNER: Okay.

DR. SCHWARTZ: We don't know enough about this to really be able to provide various options, and so we'd like to leave this as open as possible and have the Panel provide some suggestions.

DR. GIVNER: Thank you. I just wanted to understand what we're being asked. Thank you.

DR. LANGE: Yeah, thanks for that direction. Very helpful, Dr. Schwartz.

Dr. Zenilman.

DR. ZENILMAN: Yeah. I think part of the problem is that this is actually -- this is more -- it's a public health service, it's a CDC/FDA question, because I had a couple -- one issue here is that, for example, whether or not there's NTM in the units now is really irrelevant because many hospitals have followed the directives that came through, and based on what we've heard about the incubation, the point in time is actually maybe 3 or 4 years ago whether there was NTM in the machine, and we don't know what that status was at that time. So I think this may be more of a global thing.

The second thing is, is that perhaps -- we also heard that at least a third of the cases in some of the series were misdiagnosed as sarcoid, and maybe this, you know, really needs to be looked at, you know, for example, as part of a workup in patients diagnosed at least with disseminated or unusual manifestations of sarcoid.

And the third point was that based on the Iowa reports, it was that the rate was about 1 in 500 in Iowa based on what data and, you know, that's a very rough log scale type of estimate, so -- which translates in 200,000 cardiac surgery patients a year, that's about 400 patients potentially if we kind of -- if we assume all the machines were infected.

So I think where I'm going, I think this really needs -- I think this -- some type of systemic look-back which actually incorporates multiple modalities may be required here.

DR. LANGE: Mildred.

DR. FENNAL: Mildred Fennal.

In looking at the question, it asks case definition, how do you define the case? How are

you going to determine what is the case once this infection has been noted? If you find it, then every possible exposure, particularly by the most vulnerable population, they are going to have to be considered a possible case, and that's where the notification would have to start within a certain time frame when it's found, when the virus is found. Those people would have to be considered a possible case, and it would be a time frame from -- you could get the dates of when this happened. That's just my opinion on that.

DR. LANGE: Dr. Allen.

DR. ALLEN: So I think perhaps the FDA, in hindsight, having heard the last couple of days of discussions, maybe would write this question a little bit differently, because first of all, if we recommended earlier that we're not going to do routine HTM -- or NTM surveillance -- so the whole idea that it's been detected in a hospital environment, we know it's already there, we know it's in the machines, so it's not practical to do that. I think really you have to do what was done, you know, in Iowa and in Philadelphia when you have case outbreaks. Then perhaps we can give guidance to the FDA that when there are case outbreaks, that then those have to be specifically looked for, subspecies typing with genome testing in order then to determine some epidemiology around that particular outbreak. But once again, from a practical implementation standpoint, making sweeping recommendations, I think, is quite impractical.

DR. LANGE: If you'll turn your microphones off, Dr. Zenilman.

Other comments? Dr. Leggett.

DR. LEGGETT: Jim Leggett.

Usually, case definitions are, as it was noted, in outbreak situations, and we have a very well-developed, iterated case definition that was brought forward by Dr. Miller in Slide 67, the

final slide of Dr. Perz, Appendix G that you gave us, the CDC interim guide and the University of Iowa examples. So I think in terms of an outbreak case definition, you've already got it. I think the question becomes what do we do with the machines out there that people are in the process now have determined, oops, we've got an NTM? They don't quite know how to go about figuring out what it is.

So maybe there's a way to do something in between, going onto the local radio and TV as an outbreak and then looking to see if there's a problem. So I think that we might have to come up with, for the purposes of what you're trying to get at, I think, which is how do we make sure that we're trying to do something to find potential other cases without going all the way to an outbreak, manhunt, big resources. I don't know that I know exactly how to do that.

DR. LANGE: Dr. Gallagher.

DR. GALLAGHER: So I think one of the issues is, you know, we're talking about NTM, which is a larger category, and yet most of what we saw in terms of the specific case outbreaks -- and that was a particular one, and that was the *chimaera*. So I think, you know, we have to be careful not to say, oh, let's look at just all of them because we're, you know, running scared about something.

So I think if we see that there may be an outbreak based on the case definition that does exist, I think then some of that whole genome sequencing becomes important to say is it this? And then you go about doing notification. I think just running crazy might be hard. So I think in terms of provider notifications, that's where you start to get your possible cases. Because if things are being diagnosed inappropriately, as has been suggested -- we don't know whether that's true or not true -- we can say if you have a patient who looks like this in any

way, then let's do a test, let's find out for sure.

So I think the provider notification almost has to come before patient notification. So just rewording the question, I would probably reverse it a little bit so that you can actually find those possible cases because patients aren't going to know. And even if you say -- you know, I can imagine somebody going and saying, well, everybody who ever had this surgery done, you know, come forward and say something, you'd have a massive overrun of many systems to try to deal with that problem. So I think provider notification is the first place to start.

DR. LANGE: Dr. Schwartz.

DR. SCHWARTZ: I'd like to reframe the question slightly based upon the presentations that we've heard this morning and particularly the presentation by Dr. Daley, who really underscored the concern with respect to the delays in actual diagnosis of patients who are probably under-detected, who may be walking around with symptoms that are vaguer kinds of symptoms, and that because of that delay in diagnosis, there is a delay in therapeutic intervention, and those patients end up with, therefore, a much poorer outcome.

And really what we're trying to get at here is knowing that there is this, first of all, lag in time and there's a period, there's a point of exposure, and patients who are potentially symptomatic but the pieces are not being put together in terms of the potential for this diagnosis, how do we get at reaching those patients? Is it through provider-type notifications? What is it that is going to be able to raise that level of awareness among providers in order to be able to bring this to the attention of the clinical community?

DR. LANGE: So reframed. The question is since this is under-recognized right now and/or under-reported, under-diagnosed, how do we get the information out? Is that fair,

Dr. Schwartz?

DR. SCHWARTZ: Yes.

DR. GIVNER: Dr. Givner.

DR. GIVNER: I wonder if we should break this down into two scenarios. One is what do we do with the knowledge that all of us already have? What communications do we recommend to who? And then if there's a patient identified in your institution, then what do you do? So what do we recommend every hospital do right now? They're not aware of any patients. What do we recommend they do? Who do they notify, patients, providers, whatever? And then once there is one identified at your institution, it seems like that's a whole different set of notifications, etc., that would go forward. So that's what I'm wondering, should we -- and I don't know what's already been sent forward, quite honestly. I'm sure you know better than I do. But that's what I wonder, if it's what should you do now? What do you do when you have a problem in terms of communication?

DR. LANGE: Dr. Hopkins.

DR. HOPKINS: Just a couple of serial statements. Currently, every patient who has undergone cardiac surgery has theoretically been exposed to NTM, if I understand the last two days. So everybody has been theoretically potentially exposed. So if there is one patient that pops up in a hospital population of open heart surgery patients or ECMO patients with invasive NTM, one patient is not an outbreak, correct? For the infectious disease people.

(Off microphone response.)

DR. HOPKINS: But one patient is --

(Off microphone comment.)

DR. HOPKINS: A disease.

(Off microphone comment.)

DR. HOPKINS: So my question to the group is, if there is one patient diagnosed who had cardiac surgery at X hospital 2½ years ago, does that -- are you asking should that initiate a $1.5 million investigation? Is that the question or -- and along with that, if there are three and they all have genomic identity, then I think there'd be no disagreement. So somewhere between that first case and the three cases. But I understood our perfusionists properly, and I think what goes on in our hospital is the disposable parts of a perfusion system, that serial number is recorded on the perfusion sheet. The actual heart/lung machine, cardiopulmonary bypass machine is -- you know, Number A43 is on the sheet, but I don't think the heater-cooler is identified on --

(Off microphone comment.)

DR. HOPKINS: It is? So that would be a best practice for all perfusion. Okay, so if all three occurred, all three had the same heater-cooler, and all three had the same genomic pattern, then you've got an outbreak. But where between that first case and the third case -- and maybe, Dr. Zenilman, you can educate me. I'm a little loath to make a recommendation that's going to cost a hospital a million and a half dollars based on one case.

DR. LANGE: Dr. Zenilman.

DR. ZENILMAN: Well, Dr. Miller is probably closer to this in terms of the EIS course than I am and my infectious disease colleagues, but I was taught that an outbreak is a significant increase over what's expected. So in these -- you know, some examples. One case of anthrax is an outbreak. In these settings you could make the case that one case is an outbreak. Now, the

problem is, is I think you pointed out the problem, is that basically in this environment, if there was a case of NTM at the facility, *M. chimaera*, I think you have a pretty good idea of where that came from. And I'm not sure. So I think the -- and the intervention would be required to look at what happened over 4 -- you know, over a long period of time in the past. I think the investigation would be actually uncovering more cases.

DR. HOPKINS: So one case.

DR. LANGE: So -- yes?

MS. MARDERS: From the hospitals we've spoken with, I'm not certain that they could all identify the actual heater-cooler that was used in the cases.

DR. LANGE: Jeff.

DR. RILEY: Yeah, I'm going to take the opposite stand that Al said. It is best practice, but it hasn't started occurring until this year.

DR. LEGGETT: Jim Leggett.

I would second that. Only now --

DR. LANGE: I'm sorry, this is Dr. Leggett talking.

DR. LEGGETT: Only with the Epic update have we been able to download the thing to put the serial number on, and that sort of like just got done. So we're at the -- that's the hardest thing to do, is change Epic.

DR. LANGE: Al.

MR. STAMMERS: Just to follow up, the standards and guidelines published by our professional organization since 1996 stated that the serial number for -- all devices involved in cardiopulmonary bypass should be recorded, and it was just revised 2 years ago, 13 months

ago, that they say the same. So it is in our professional register that this information is recorded. So if this group didn't have it, hopefully they're more an outlier than the current state of practice.

DR. LANGE: So I want to address this in two aspects because I think the FDA is asking for two things. One is what do we do with the knowledge we have now to make the public, providers, and patients more aware in a general sense, without specifics?

Dr. Allen, do you have any recommendations or thoughts about that?

DR. ALLEN: I think it behooves all of us, I can tell you, in talking -- there are three heart surgeons sitting over on this side, and in talking to each of us, we had absolutely no clue until -- it sounds like ID people know about it, public health people know about it, maybe even perfusion knows about it, but as far as the heart surgery community, no clue, nothing.

So the first thing I'm going to do when I leave here is I need to go back and educate your facility. But more importantly, we need to educate our society, whether it's the ACC or -- through the ACC or the AHA, whether it's through the STS, with publications, some white papers in major journals, editorial-type comments that can let this bubble to the surface and let it be disseminated because I do think that the diagnosis and the delay in diagnosis, how these patients presents and the latency, if you disseminate this out enough, I think you're going to see that this tip of the iceberg is going to become quite substantial. We had a patient just in this short period of time, it's anecdotal, but we had a transplant patient die 2 months ago, 3 years after a cardiac transplant, from disseminated *Mycobacterium,* and I'm trying to find out what his -- but it wasn't TB.

DR. LANGE: Dr. Yuh.

DR. YUH: You know, this kind of reminds me of the aprotinin situation long ago. When that became publicly known in terms of the adverse effects in a very, very small subset of patients, our office at Hopkins got deluged with every patient that had even the remote chance of having been exposed to aprotinin, to no benefit of the patient. They had no -- nothing was done proactively in terms of treatment or surveillance, but it just raised anxiety based on limited information and did no service. This kind of reminds me of that situation. I agree with Dr. Allen that awareness on behalf of the care providers, you know, including cardiac surgeons, probably is the most efficacious strategy for addressing what the FDA is asking about in terms of notification.

DR. LANGE: So you would say notification of the providers, widespread, but not necessarily just the public at large?

DR. YUH: Right. I mean, I think that certainly notifying the public in the generic sense is -- you know, there's no downside to that. But I think that, you know, in terms of the most efficacious way of disseminating the information and raising awareness, to pick up those very, very few cases -- very, very few patients that are affected, that that is the most logical way of going about it.

DR. LANGE: Mr. McGlamery.

MR. McGLAMERY: And I would add to that. My personal experience is that none of these patients feel good. So the symptoms that you're asking to describe this, they all are going to have them, I mean -- and, you know, for a certain amount of time. Particularly if somebody's on heavy anti-rejection drugs, I mean, these are symptoms that are going to pop up in their mind, and everyone's going to say, oh no, this may be me. So the caseload would be

overwhelming.

DR. LANGE: Al and then Dr. Givner and then Dr. Leggett.

MR. STAMMERS: I appreciate Dr. Allen's comments and Dr. Yuh's and all the surgeons, but it's weird to think that with a CDC and -- not DOH, excuse me, an FDA alert that went out, a safety alert that goes to all risk managers -- correct me if I'm wrong -- in every healthcare facility in the country so that that would not be trickled down. There's nothing that has occurred in our profession as perfusionists in the last decade that has got us more energized to respond to this information, and I think the point is we might have failed to go to our surgeons and let them know. That could be a point. But I tell you, I would check with your risk managers, because immediately, within hours of this occurring, every manager in perfusion in all 1,100 hospitals in the United States was alerted to this outbreak. But isn't that how the information is distributed to the hospitals and --

DR. LANGE: Dr. Givner.

DR. GIVNER: A couple things. One is I agree with Dr. Zenilman. In infectious diseases, there are cases where one case demands a very detailed investigation, and one that comes to mind in pediatrics is group A beta strep. One nosocomial case requires a very, very deep investigation, and that's only one case. With the University of Iowa presentation, I think they noted after their patient, with a notification to providers, then they identified two more. So I think one case is very significant in what we're talking about here.

And again, I think we need to break it down into what we should do now when your hospital doesn't know there is a problem. And as I said before, maybe enough has already been done, but I'm not clear what's been done. And then, of course, when there's a problem that

you've identified in your hospital for whatever reason, that's -- you know, that a patient has been affected, that's a whole different story. But maybe if it's okay, maybe you could tell us what has already been done. Is it provider notification, or are there other things that have already been done by the CDC, FDA, whatever?

DR. SCHWARTZ: So with regard to FDA, we have released a safety communication back in October of 2015. We also released a safety communication prior to this meeting with respect to making greater -- increasing awareness around the exposure to *M. chimaera* in certain heater-cooler units so that providers can be aware and patients can be aware of those risks.

DR. GIVNER: So it went to providers and patients, is that --

DR. SCHWARTZ: When we write a safety communication, it's written as a message to providers, to an audience, and those -- that audience includes providers. And in this case, patients as well. But among the providers, we break it down by subspecialties.

DR. LANGE: I'm going to ask Dr. Leggett, but I want to follow up on that for just a second. Could you have a number of providers here, and that went out in 2015, and show of hands, how many of you saw that and --

(Show of hands.)

DR. LANGE: Okay. So it just goes to show we have work to do, and that's -- we'll get to that, about how do we disseminate that information a little bit better?

Dr. Leggett.

DR. LEGGETT: That was exactly where I was going. So I think I would propose that the step before we have an outbreak situation, however you define it, is that the FDA needs to

come up with a new interim guidance, perhaps more specific or more broader, sort of saying that infection preventionists need to maybe think about in their hospital, their system, going back 4 to 5 years and trying to come up with a list of people that fit those three circles that have been in sort of the Venn diagrams, sort of taking it another step in the next interim guidance without doing anything in practice except letting more people know. So, for instance, in our hospitals, all the perfusionists knew, all the infection preventionists knew, all the risk management people knew, all the ID doctors knew, and I had to send the e-mails to our cardiac surgeons who didn't, had never heard of it because that's not what their job is. But I think that one step would be for us to sort of recommend that you guys come up with it in the next iteration of stuff to send out.

DR. SCHWARTZ: So just to fill in a little bit more detail here, because we covered this in broad strokes in our presentation yesterday, we have taken multiple steps to try to really raise awareness around this. In fact, we did, together with CDC, a 50 states call to the departments of public health across the United States, and I will say that -- and I don't remember what the numbers are, but among these states that actually participated in the call, it was probably under 10. And we will utilize, as much as we can, various mechanisms to really try to get that word out, knowing that those are the entities or the organizations that would then feed into their jurisdictions and the healthcare organizations that are part of that particular, again, region.

So between that as well as a public webpage that we posted that just provided a lot of information about this issue and what resources are available and really just trying to create education around it, working together as well with CDC on this, working very closely with CDC,

and CDC has put out interim guidance that gets to the type of knowledge that providers should be aware of and what they can be doing in order to be able to further identify cases. But we're -- you know, we're looking for what other feasible and effective means there are in order to be able to get this message out in spite of what we have done this far, reminding that FDA, in terms of blasting information out, uses all kinds of social media as well and utilizes lots of different societies and lists. And yet, as has been described here, there hasn't been much recognition or awareness of this issue, and as a result of that, we really don't know the scope of it.

DR. LANGE: So some of the recommendations have been working with some of the professional societies, the Society of Thoracic Surgery, American Heart Association, American College of Cardiology, IDSA, Society of General Internal Medicine, because these are the individuals that will see the patients 2 and 3 and 4 years afterwards. The recommendation was for high-impact journals that are read. The excellent article by Dr. Sax would not have been read by most of the people here in the United States, so high-impact journals. And I would assume that they would be interested in that information as well. So those are two recommendations that came out of the Committee. Anything else?

(No response.)

DR. LANGE: And with regard to the second point, and that is identification of individuals, once a person with disseminated MAC or disseminated NTM has been identified without risk factors -- and specifically, it's important to ask if they've had a device which has been exposed to a heater-cooler unit. And if they have had such, then I think what the Panel would say is we have to assume that that's an index case and go back to wherever their surgery

was done to inform them, and that would be two practices at that point: Notify other patients that may have been operated around that time, and then secondly is to look at their current practices. Because although they're separated in time by 2 or 3 or 4 years, what you still want to know is at that current time, even though there was an infection that seeded 2 or 3 years ago, what is their -- it's an opportunity to look at what their current practice is, whether it's being properly disinfected, properly sterilized, properly monitored and properly utilized, even though it's, again, a 2- or 3- or 4-year difference. You've identified a location where that's occurred, and that gives you an opportunity to see what their current practices are. Would that be a fair -- Dr. Leggett and then --

DR. LEGGETT: In terms of the methods we use for the part (b), a couple things I thought about. Since these fall out of the normal infection control-type infections, it might be worthwhile thinking about whether laboratories should be sending their NTMs and fungal, because I noted in the talk today, there was fungal overgrowth of one of these machines, whether that should be sent routinely to infection prevention folks to log in as part of their nosocomial infection-type stuff to monitor. And then we also mentioned the Epic best practice alert for things that should be sort of sent out as the things to do -- that was the University of Iowa this morning -- in addition to the -- adding the -- making sure that serial numbers get recorded in all the OR notes.

DR. LANGE: So before -- Mr. Thuramalla. The issue with the lab is an important one, and that is once you suspect a case, how is it properly -- where does that information go to get the proper lab identification?

Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

In terms of patient identification, would there be any additional symptoms or factors to be considered in case of pediatric patients?

DR. GIVNER: Not that I'm aware of. Except I was interested to see the failure to thrive noted in the symptomatology. That usually does refer to infants and young children. But honestly, I'm not aware of anything in particular that applies to pediatrics that doesn't apply to the adult world. And that may just be lack of knowledge.

DR. LANGE: One other thing I want to bring as a part of this summary that was mentioned, and several times, and that is patients misdiagnosed with sarcoid. And so a patient who has been diagnosed with sarcoid and has undergone cardiothoracic surgery in which they've been exposed, that needs to be reevaluated and the proper laboratories done. And that's an important public information piece, public information as well.

So Dr. Schwartz, have we sufficiently addressed this, or are there other areas with regard to Question (a) that you'd like for us to address?

DR. SCHWARTZ: Yeah, I think we have the information that we need. Thank you.

DR. LANGE: Moving to Question (b), discuss what methods could be implemented for identifying and tracking of potentially infected patients. We've had electronic health record already mentioned. I'm looking to the Panel. Keep in mind that these individuals may have been operated at Hospital X and now live in a different area of the country. So recommendations from the Panel.

Dr. Givner.

DR. GIVNER: I do think it was presented -- I forget if it was -- I think it was Pennsylvania.

I do think all patients who have cardiothoracic surgery with a heater-cooler device should be notified, and I think there should be some proof that the notification has actually reached them, whether as was done, a phone call through an 800 number, whatever it is, but I think we need to know that all those patients were reached. Now, obviously for large hospitals, that's going to be a large notification and a large process, but I do think we need to do that. When we identify one case in a hospital, I think we need to do that for all the other patients who had cardiothoracic surgery there with an HCD.

DR. LANGE: Is that a general Panel consensus? Is there a dissenting view?

Dr. Allen.

DR. ALLEN: I think that walks a bit of a tricky path for that to come from the FDA. Once again, I'm all about practicality and the ability to implement something like that based on, you know, one case. I think I would -- all politics is local, and I would probably leave that to the discretion of hospitals rather than have that come from higher up.

DR. LANGE: Dr. Givner.

DR. GIVNER: Whoops, I left it on again. So the question is, I guess, should the FDA recommend -- I think you're asking, should the FDA recommend with one patient, then, that this notification process go on, or when there's only one case, should the institution make their own decision? And I guess my only question there would be where will the cutoff be, then? Would it be two cases, three cases? What would the number be where we should be recommending that the FDA should be recommending that then this process be put under way? And again, I do think it should be one case, but I -- you know, I'm always happy to hear what the Panel has to say, of course.

DR. ALLEN: Well, if I can just follow that up.

DR. LANGE: Dr. Allen.

DR. ALLEN: If I could follow that up. I think, to take your line of argument one step further then, the reality is that we shouldn't wait for a case, and that every patient that's had cardiopulmonary bypass in the last 5 years should get a letter, period. Because we do know that these patients are undiagnosed, there's a latency period, there's a lot of people that probably had infection that weren't diagnosed. So I think if you're going to send out letters, I think you need to have very specific reasons to do that with not only an index case, but a specific investigation into a hospital. Otherwise, you're really biasing against a lot of other people, and I think to send it out to everybody that's had open heart, that's a lot of letters. It's a lot of angst.

DR. LANGE: Dr. Gallagher.

DR. GALLAGHER: Thank you.

I think I'm going to use an example from the research world. When something happens that goes wrong or is unexpected, you have to notify OHRP, and you have to tell them what your corrective action plan is, what you're going to do with it. So a kind of a mix of letting people know but still allowing it to be local. I wonder if FDA could be -- yes, you have to report it to the FDA, but along with that, you tell them how you are going to go about notifying and who you're going to notify in terms of a class of people or something like that, so that you give a plan for how you're going to do that. So the planning of how to do that and everything is local, but the acknowledgment that that's being done is given to the FDA so that it can be watched and that kind of thing. So it's kind of a mix of the two would be my recommendation.

DR. LANGE: Jeff.

MR. RILEY: Thank you. Jeff Riley.

Is the underlying assumption of this is that we found NTM in one heater-cooler and therefore we will notify all the patients, or is this we've done an investigation, that heater-cooler's have been the source of an NTM infection in a patient and we have this key case?

DR. LANGE: This is not device centered, but patient centered. Once a patient has been identified that has been infected, an NTM infection, what method is implemented to track other potentially -- so we've heard Dr. Givner say that he thinks, in his opinion, there should be a look-back, and Dr. Allen's a little bit more circumspect about it.

Dr. Roselle.

DR. ROSELLE: I think it's also a matter of what lane people are in. If somebody gets an illness, it would be reported to the FDA. The FDA is a regulatory body, not a patient care body. And it makes me a little nervous that we would have a regulation in place that would say you will send 4,000 letters to patients, because that's really what you're talking about. Maybe that's okay, but it's a little worrisome, I think, as opposed to saying you will report it. The FDA can analyze it and heckle people all they want, that's fine. Usually you talk to the CDC when it comes to what's your clinical steps beyond your case investigation and things like that. So I just get a little nervous when the regulatory agency is going to define how I communicate with patients. Maybe I'm being overly nervous.

DR. SCHWARTZ: So if I could just clarify, that's not the purpose of this question, and FDA surely does recognize what its authority is as a regulator. But this is a question that has been manifest in many of the discussions that we have had with healthcare institutions as we've

been dealing with this, and we know that this is a tough, complex area. And so we are bringing it up really more for community discussion so that a path forward can be established, not that the FDA is undertaking that process or saying you must do the following or you should do the following. I hope that that clarification helps.

DR. LANGE: Dr. Hopkins.

DR. HOPKINS: I'd just like to drill down a little bit more on this single case issue. If we have a case operated on 3½ years ago, was on ECMO for 5 days, bridge to transplant, has had three episodes of rejection, and then was recently diagnosed with an invasive NTM, does that initiate this whole sequence?

DR. LANGE: Dr. Leggett.

DR. LEGGETT: Sort of a follow-up and clarification. Oregon may be the only state or one of the few states where nontuberculous mycobacteria are now reportable. So one thing that might -- we might consider -- and I agree with the statement about I don't think this is sort of the FDA's ball field, but we might consider moving forward to make these non-pulmonary, if you like, or some sort of thing, nontuberculous mycobacteria a reportable disease so that somebody at the CDC and the local health departments knows about this. That might help a lot to get things spread out further.

DR. LANGE: Mr. McGlamery.

MR. McGLAMERY: So through all of the testimony, it sounds like some hospitals do have a record of which HCD unit is in the operating room at times and others don't; is that correct? And if it is, if people do have a record of which unit was in the room with this particular patient, would it not be easier to notify the people that were in the room with that

specific unit instead of notifying everybody? I mean, to me it sounds like this is unit-specific. If it's one case in a hospital that has multiple units but this one was in the room when this occurred, it lowers the number of people that you have to notify, and it does specify that this is potentially the unit.

DR. LANGE: So I think there's a fair sentiment from the Panel, is that when a patient's identified, is to go to the hospital. I mean, that's with that question. And see what current practices are.

I'm just going to take straw vote here among the Panel members, is should other patients who have received operations in that hospital with a heater-cooler device be notified? We'll talk about time period later, but in other words, other potentially exposed people. Those of you that believe that there should be routine notification, I'm going to ask for a show of hands, and those that think that that's not necessary with the first case. So if you think that the patients potentially exposed should be notified, let me see a show of hands.

(Show of hands.)

DR. LANGE: Okay, I would've voted there as well. And those that think that they should not be.

(Show of hands.)

DR. LANGE: Dr. Gallagher.

DR. GALLAGHER: I just want to add a clarification that I think that you don't notify everybody every time, but I think if you can identify the machine and you have more accuracy to be able to do it, then you would do it. But if you don't have that kind of accuracy, you scare an awful lot of people needlessly if you don't have something you could offer them to fix the

problem.

DR. LEGGETT: And my no vote was a local decision.

DR. LANGE: I'm sorry. This is Dr. Leggett.

DR. LEGGETT: My no vote was a local decision on who to notify.

DR. LANGE: Dr. Zenilman.

DR. ZENILMAN: I want to respond to Dr. Hopkins in his specific case because kids who have transplants or adults who have transplants are independently at risk for NTM infections whether these things are used or not. So I think it requires a little bit more of a drill-down review whether it's -- so if it's a *chimaera*, I would say yes. If it was *fortuitum* or *chelonae*, it probably is not.

DR. LANGE: So I'm going to --

DR. HOPKINS: That was the point of my question. Oh, sorry.

DR. LANGE: This is Dr. Hopkins.

DR. HOPKINS: That was kind of the point of my question, is that just the occurrence of a single case, assuming that this was 3½ years ago, we probably don't know which heater-cooler it was. So there would be no ability to match the genomic -- you know, whether there really was a fomite, which was Heater-Cooler 42, and you've got an at-risk patient, anyway does that really kick off this whole thing? So I think if, in fact, there's going to be an FDA regulatory recommendation, it's going to have to be carefully written because it can't just be a positive NTM culture. It has to be a specific subtype, it has to be a *chimaera*, it has to be in a patient who would not -- who normally would be zero risk, etc., and then that kicks off.

DR. LANGE: Dr. Yuh.

DR. YUH: Thank you.

I'm just not sure how this global notification based on one diagnosed patient really helps the other patients. So you're not going to institute any kind of prophylaxis, you're not going to culture them up. If they start feeling badly, they're going to come in to a doctor, and those are the providers that really need to know about this potential to adequately diagnose and treat them. I just don't see how this effectively helps those other patients that were at risk, but at exceedingly low risk, a microscopic risk almost.

DR. LANGE: So what you're saying, Dr. Yuh, if I were to paraphrase, is you'd focus on the providers to make sure that that association of cardiac surgery and NTM is clearly on their mind and allow them to make the diagnosis?

DR. YUH: Right. I just don't see how this really effectively, in any substantive way, actually helps the patient treat themselves or -- you know. I mean, with such a small number of affected patients, I just don't see how it really helps them in any way.

DR. LANGE: So Matt.

DR. ARDUINO: Well, one case, I think, would trigger an investigation, and you call the state or health department in that. And then depending on results of that investigation, it may trigger you to go do other things which may even begin with a provider notification before you get to the -- and then the state would work with the institution to figure out.

DR. LANGE: So what I'm hearing and I'll -- what I'm hearing is that there's a lot of enthusiasm for making sure that the providers are the point of -- primary point of contact and point of information.

MS. MARDERS: Just one quick clarifying question for those who -- of those on the Panel

who are not inclined to notify everyone in general after finding one case, would you notify any of those patients who had prosthetic material placed or who have received a transplant or artificial heart or an LVAD or ECMO? Any of those categories? Would that raise your level of alert?

DR. LANGE: So I'm going to ask, for those who voted to routinely notify everybody, keep your hands down. For those that voted not to routinely, I want to see hands up for a second.

(Show of hands.)

DR. LANGE: Okay. Keep them up for a second. Would you notify any of the patients that got prosthetic material? Would that change your opinion?

(Show of hands.)

DR. LANGE: Answer is no. Okay, hands back up. Would that change if there were two or three individuals?

(Show of hands.)

DR. LANGE: Okay. So what I'm hearing is that if it's more than one case, then the Panel is more receptive to notifying all subsequent patients.

DR. LEGGETT: Jim Leggett.

But that's because you've already undertaken the steps to notify the local health department and go through your own local facility, talking to your own hospital and system lawyers who are going to tell you what to do, that then you do that.

DR. ALLEN: Yeah.

DR. LANGE: Dr. Hopkins and then Dr. Allen.

DR. HOPKINS: With one exception. I'm voting not to jump the gun but to go through

that sequence except if, in fact, now we're talking 5 years from now and we have the recorded heater-cooler devices and we've got their culture, pre- and post-cleaning history, and we've got a suspect heater-cooler and all of a sudden the patient shows up that got that heater-cooler exposure. Well, then yes, that one case should probably prompt a little more aggressive notification scheme for the patients who were exposed to that heater-cooler. But I think what we're recommending now is under the assumption that we have an absence of that information for the historical patients, the patients we're going to be seeing with the infections now. So assuming that, I wouldn't jump the gun. But if we had evidence of a true vector process, then yeah, I think you'd be more aggressive.

DR. LANGE: Dr. Allen.

DR. ALLEN: Yeah. I mean, I think Matt and Jim summarized. I think it's local, and one case starts a discussion at a local level, involve your healthcare, and then that progresses from there. It's kind of following a chain of command.

DR. LANGE: Does that provide guidance as to the Panel's opinion and -- sufficient guidance to the FDA?

DR. SCHWARTZ: Yes, it does. Thank you.

DR. LANGE: So let's go to (c), and let's assume that for whatever circumstance, however you voted, that we're going to notify patients. What is the latency period? What is the best approach? What time period? How far would you look back?

Dr. Leggett.

DR. LEGGETT: Jim Leggett.

Well, we have the data that was presented to us, which in the MDR reports said zero

months was the shortest time frame in that table. Then we have the other data that I think said 2 weeks. But in general, it was between sort of -- between 1 and 3 months time, then up to maybe 4, and this morning we heard 5 years. So given that's the data that we have so far --

DR. LANGE: Is there anybody that would want to look past 5 years? If you would, let me see your hands.

(Show of hands.)

DR. LANGE: Okay. And has anybody said no, 4 years and not 5 years?

(Show of hands.)

DR. LANGE: So the consensus of the Panel would be is anybody -- if a notification's going to be issued for whatever the reason, the indication is, is it would extend to 5 years. Okay. Does that address the FDA's question?

DR. SCHWARTZ: Yes, thank you.

DR. LANGE: With regard to Question 3, as the FDA looks at it, are there any remaining issues you would like the Panel to address?

DR. SCHWARTZ: Thank you. There are no remaining issues. I just do want to reemphasize that the FDA isn't looking to take any particular regulatory action, regulatory recommendation here. But what I do want to highlight as well is that there is a feedback loop here in the sense that the ability to identify patients that had been infected where an association is made with a particular medical device and where you have a serious injury, FDA relies on receiving that information in a timely manner in order to further, then, do its analysis and inform the public and inform providers with regard to where we see increased risk. And so that's where, also, if this information becomes important to us in terms of there being some

kind of established process or approach towards looking at this in a systematic way, so that then we are able to receive the information that we do need regarding medical device injuries or, you know, serious adverse events and deaths in order to then further inform the public.

DR. LANGE: And to that point, your point's well taken. Your engagement of the local public health departments is incredibly important because the patient in Bexar County who has the infection now got operated in Denton County, and then the person in some other country and the people that are going to put that together are the people at the local department, number one, and then the hospital as well. So I agree with you. And a recommendation to make routine reporting atypical, non-pulmonary atypical mycobacteria, I think, carries some merit as well.

Any other questions?

(No response.)

DR. LANGE: Let's move to Question 4. I'm sorry. Mr. Thuramalla.

MR. THURAMALLA: A quick comment. I was not clear about when you said 5-year period. What is the starting point of the 5-year period? From the day the patient was operated? Because if that is the case, and if we know that this patient was operated and a particular heater-cooler device was used, we don't know how far back did the HCD get infected. So I'm trying to understand what does this 5-year -- or when does this 5-year period start from?

DR. LANGE: So when does the 5-year period? Panel?

Dr. Leggett.

DR. LEGGETT: Whenever the FDA decides to tell us that that's going to happen, from that day on backwards. I mean then leave it up to the local facilities. I mean, I plan on going

back to my facility and start this process.

DR. LANGE: So if a person's identified on June 2nd, 2016, the recommendation would be to go back to look as far as 2011, is the recommendation.

Please read Question 4.

MS. MARDERS: Question 4. Present and Future Device Considerations for Reducing Risk of NTM Infections:

a. In addition to the recommendations in the FDA HCD safety communication and FDA's HCD webpage, what other suggestions do you have for devices already on the market that may help mitigate/minimize patient infections from aerosolized NTM? Things to consider would include revisions to the device labeling/instructions for use; device related considerations that would not adversely affect device performance; and/or environment/use-related considerations.
b. For devices in development, what design features, instructions for use and/or environmental/use-related considerations might you suggest to mitigate aerosolization and minimize patient infection?
c. In order to develop a validated disinfection process both currently in use and for future devices, how should manufacturers properly challenge the device in a lab environment that would replicate real-world use (i.e., test organism, mixture versus individual organisms, simulated use, parts of the device to test, microbicidal threshold (6-log, intermediate, high-level disinfection), etc.)?

DR. LANGE: I'm sorry. So let's start with (a). Suggestions for devices already on the

market that may help mitigate or minimize patient infection from aerosolized NTMs.

Al, you look like you're about to pounce. Go ahead.

MR. STAMMERS: At the risk of being very redundant, I think the last 2 days we've spent a lot of time emphasizing the importance of human factors here, and I could tell you, from the perspective of perfusionists, this is really extremely prominent in our minds, and it would be interesting, starting from October 27th and 15th, the two days of the CDC and FDA approval moving forward, to see how -- I wouldn't say sophisticated, but how more regimented we are right now with paying attention to the heater-coolers. It really gives us an opportunity to start at a particular time frame looking forward.

So I think so much of it is just going to come down to those of us in the field who are charged with maintaining these devices, very well aware of the consequences by not doing it. And in the past, personal experience, we weren't paying attention to this, and we are now; it's got our attention.

DR. LANGE: Dr. Allen.

DR. ALLEN: Yeah, a follow-up on Al. I think there is very little that the FDA can do to regulate devices that are already on the market, making off-the-shelf suggestions that you encase the device or vent it to some outside corridor, or there are lot of things that you can think of, but none of those are practical, and none of those can really be implemented. We don't even know if they might cause more problems than they would help.

So I think what Al is suggesting is really all you can do, which is to follow the IFU for the devices, be diligent in how you take care of that device. When you do have devices that can't be cleaned and their HPCs are abnormal and continue to be abnormal, those machines either

need to be put out of service or deep cleaned. I think there's a lot of things you can do going down the road, is you look at devices that might come on the market and how companies might design new devices. But you're stuck with what you've got.

DR. LANGE: Dr. Yuh. And Keith, I'll ask you to turn your phone off.

DR. YUH: No, I agree. I think, you know, all hospitals are different, all OR designs are different. I mean, the concept of removing the device from the OR itself makes a lot of sense. But on a day-to-day basis with all the different hospitals that do cardiac surgery in the U.S., I just don't think it's universally applicable and not practical and something that, you know, taking into consideration the different kind of configurations of OR suites, you may be venting into an area that you don't want to.

So I think that, you know, vigilance and adherence to IFUs and learning from the surveillance that is done in terms of signals where an IFU may not be adequate in certain regards and then proving up from that perspective on current devices is really the only strategy that I can think of rather than, in a Band-Aid type fashion, just trying to figure out ways to plug holes in the way these devices are maintained and used.

DR. LANGE: Dr. Hopkins.

DR. HOPKINS: I think I'm going to hold off for (b).

DR. LANGE: I'm specifically asking obviously our surgeons.

Dr. Givner. Yes, I'd like your opinion.

DR. GIVNER: I think we've already talked about measuring colony counts, and I think that's -- besides colony counts, you know, visual changes should be paid attention to. But I don't think I agree with Dr. Yuh. I don't think that we should ask devices to be outside of the

OR, or anything like that. So I think the recommendations we've already made are the ones that I would recommend.

DR. LANGE: Dr. Leggett.

DR. LEGGETT: Yeah, I didn't say anything because I really have nothing to add, just repeating it. And I don't know that we have to do anything with devices that have not yet been shown to be colonized. So I don't think it needs to be every device has to suddenly be exhausted or some sort of other ad hoc thing. I think we would sort of start by looking where we've identified a problem.

DR. LANGE: Al.

MR. STAMMERS: Yeah, I apologize for speaking so soon again, but a real problem comes up with what we've all seen in regards to how these devices have got through the FDA and cleared or however, and none of them are rated more than 6 hours. Yet I don't mean to be redundant on that, but I really think that -- with no disrespect to the manufacturers, you know, that really has to be reexamined because -- and the Pennsylvania data has shown us that it was statistically significant in regards to the outbreak, but yet none of us in this room uses them on-label, I mean, very rarely, very infrequently.

So I just throw that out because I don't want to get off of Question 4 here, but that may be a prominent thing to examine moving forward in regards to prospective science, and we talked about that already with worse-case scenario models that the manufacturers are perhaps looking at in regards to the longevity of how their devices are used over time.

DR. LANGE: To my perfusionist colleagues, is it feasible to turn the device off and on? It sounds like it's turned on in the morning, it runs all day, and then it's turned off at night. Would

it be feasible to start and stop it in between cases?

MR. RILEY: Jeff Riley.

No. We depend on the temperatures in the tanks to be maintained to provide sufficient radiance, so it would be unrealistic. There might be times we could turn it off, but we'd be just turning it back on in a half hour.

DR. LANGE: Dr. Leggett.

DR. LEGGETT: Can I ask you a question? So when you guys count up your thousand hours, are you counting the 8 or 10 hours a day? Because that comes to be like 125 days if it's 8 hours a day.

MR. RILEY: Yeah, I did the math, too. A thousand hours for us is about 3 months, and we do preventive maintenance every 6 months, so we're not following the manufacturer's instructions.

MR. STAMMERS: And these devices do have counters on them. Just like if you were driving a tractor or something, you'd see them. So they are monitoring themselves. We just have to be vigilant and record it.

DR. LANGE: I'm going to ask for a show of hands. I think what you're hearing from the Panel is that we feel somewhat constrained by what our current equipment is and current OR configuration. And as a result of that, we're trying to develop recommendations that are feasible and can actually be accomplished, and we feel a little hamstrung, handcuffed, by the fact that we can't.

So let me ask a question of the Panel to propose to the FDA. If in a particular OR it is feasible to have the pump outside the room or to exhaust it outside, would you recommend

that be accomplished, if possible? Or would you say no? So if you would recommend, if possible, let me see your hands.

(Show of hands.)

DR. LANGE: And if you would not recommend, even if it was possible.

(Show of hands.)

DR. LANGE: Does that confuse or clarify things for the FDA?

DR. SCHWARTZ: I think we get the picture.

(Laughter.)

DR. LANGE: Al.

MR. STAMMERS: Sorry to bring this up, but we have evacuation systems throughout each operating room. They're already in place to scavenge inhalation anesthetic agents, and I just wonder -- that's about my total knowledge on this, they're vacuum sources that go through a filtration system in the hospital. I wonder if that's an opportunity because they're in every operating room in America.

DR. LANGE: Dr. Hopkins.

DR. HOPKINS: Yes. I was going to bring this up in 4b when we talk about designs going forward. But actually, we've built a clean room inside of our operating room suite, and it turns out that hospitals do have gas evacuation conduits all over the place that they can tap into. However, to make that effective, the way I'm kind of conceptualizing it with a unit like this is you'd have to have a locking system where you locked in, you know, a vacuum cleaner hose to the evacuation port. It would then go through a HEPA filter and UV lights, the way they do now. But there are all kinds of noxious gases that have to be vented, and they have systems all

over the hospitals to do that. So I think that would be feasible, and that was going to be one of the recommendations. I think the manufacturers should try to pursue, if they can't put filters around it, like we talked about earlier, whether they can actually create a system that can be a closed evacuation system, and the revisions to most operating rooms to do that wouldn't be that extensive.

DR. LANGE: Any other comments regarding that?

Al.

MR. STAMMERS: Yeah. I apologize for kind of continuing to talk, but there are certain aspects of the IFUs that I think the manufacturers need to address, and one of them is the aspiration or evacuation of the water from the device itself because that uses -- that entrains air. It goes through just like siphoned drainage, removes the water from the cardioplegia system or the heat exchange around the oxygenator. And something simplistic as not performing that function, which is basically aspirating air in and purging air out until the patient has left the room, I mean, that's a simple free fix that can be put into the IFUs for the device and doesn't slow down any aspect of the operation. So I mean just some of the basic way these devices operate, you know, can be simply modified without cost to anybody.

DR. LANGE: Did you get that, Dr. Aguel?

(Off microphone response.)

DR. LANGE: Okay. Other comments regarding ways to mitigate or minimize? If there was an effective way, cost-effective way and practical way to redirect the exhaust outside of the room, does the Panel feel that that would be helpful or not? Let me see hands. Would that be helpful if we could do that practically and cost effectively?

(Show of hands.)

DR. LANGE: Those that feel it wouldn't be effective?

(Show of hands.)

DR. LANGE: So I think you can see where we stand. We're concerned about the aerosolization not only on the patient but on the devices in particular as well, and if we could redirect that somewhere else.

Dr. Yuh.

DR. YUH: Yeah. I have another strategy in terms of mitigating risk and trying to eliminate the whole potential for biofilm formation altogether. Is there a way -- and I don't know how onerous this would be from a design standpoint, but in terms of disposable tanks and liners or liners that could be disposed of after each use, eliminating the possibility of colonization. It just seems to me that it's within the realm of design possibility for this conceptually relatively simple device. It's a tank that cools and, you know, heats water and circulates it around. It just seems to me that you'd be able to develop some sort of system where you could dispose of the water-bearing surfaces on a regular basis, maybe on a case-by-case basis. You eliminate the venting problem altogether because aerosolization would be of no consequence.

DR. LANGE: Excellent suggestion, and we're going to talk a little bit more about that when talking about other design features. That's an excellent point.

Dr. Christensen.

DR. CHRISTENSEN: I think this will lead into the next question, but one of the things that would be helpful, I think, is to get a true assessment of the aerosol coming off a machine. And I

think that we know that certain machines do create an aerosol and a bioaerosol, and I hope everyone understands the difference between an aerosol and a bioaerosol. But I think that that's an important thing to know, is how far do these aerosols actually travel from the equipment? Is it, you know -- and how big are the sizes? Because, you know, the different size particles, they will survive in the air or stay in the air longer before dropping out. So I think those are things to kind of consider, of doing a true characterization of the aerosol of these machines, especially the ones that are currently on the market and then the ones moving forward.

You know, moving forward, I would want a machine in an OR suite to produce zero aerosol. I mean, that would be the ideal situation, especially if you're using a water source with it. I mean those two things should go hand in hand, fan and water, especially in a sterile field. But I think that that's something that might be helpful, is to kind of get a true understanding of what actually is going on with these instruments, with or without laminar flow, so you actually know kind of -- you know, following up with what Dr. Sax did, you know, more -- a bigger, better assessment basically.

DR. LANGE: So what you're hearing is some sentiment of having some standardized way of evaluating various machines.

DR. SCHWARTZ: Thank you.

DR. LANGE: Let's go to Question (b). For devices in development, what design features, instructions for use and/or environmental/use-related considerations might you suggest to mitigate aerosolization and minimize patient infection? We've had one already from Dr. Yuh, using disposable -- we've already talked about biocompatibility and in terms of surfaces, either

slow growth or allow better disinfection or detergent.

Mr. McGlamery.

MR. McGLAMERY: So in my life outside of here, I work with architects that build stadiums, and I think if you actually take this a step further and go to the architects that are building new hospitals and retrofitting old hospitals, the opportunity to actually build a space in or outside of the OR with a control panel that is on the wall in the OR so you have access to what you need to, but the machine is out, it is less complicated in the OR, which seems to me would be a good thing. And you could actually have the entire device with a removable feature where the entire contents could be pulled out, disinfected, put back in and your control panel stays in place. And believe me, architects is -- insanely complex is a stadium, or a hospital is. They love these kinds of challenges and these kind of suggestions, and once again, it's one less thing in the operating room.

DR. LANGE: Dr. Hopkins.

DR. HOPKINS: So I actually enjoyed this question a lot and kind of thought about it. I also direct a bioengineering laboratory, so that's another reason I thought it was interesting. I think we're going to have to rely on the manufacturers to come up with new designs, and I'm sure they've all got teams that are doing just that.

But I've got a car at home that's got a dead battery. As most of you know, there are closed battery systems and open battery systems. The closed ones don't have outside venting to protect people from hydrochloric acid and all that. So one suggestion is to explore a closed fluidic system. That would allow you also to put better heat transfer additions to the water, antibiotics, all kinds of other things. I thought the disposable fluidic pathway makes an awful

lot of sense. A bag with tubes coming out of it that can be dropped into a warming and cooling device seems to make a lot of sense in this day in which individual patient personalized disposable materials are the norm for almost everything that touches the patients. The evacuation gas systems which can be done centralized or to each OR makes a lot of sense. And one of the things that the experts on NTM kind of taught me was the lack of water vapor is extremely important in these systems.

So the thing that occurred to me is why, with the input and output port, can't you just put a little device on at the end of the day that has a hydroscopic material and a UV light plugs into the wall and it dries the whole pathway out and kills everything that's in the gas? So I think there's a lot of novel ways that we could retrofit current devices to make them less colonized, and then going forward, really new designs either at the macro level of the actual architecture of the OR, or at the device level.

DR. LANGE: Dr. Allen.

DR. ALLEN: So to me it's pretty simple. There are ways, and we rely on people like Dr. Christensen who have expertise in bioaerosolization, and products moving forward, there's no longer 510(k) predicate approval for any heater-cooler device coming onto the market unless it has zero ability to aerosolize, period. They can't aerosolize.

I would also implement a rule -- I don't know what the lifespan of these devices are, whether they're 10 or 12 years or 8 years, but I would put into effect that at certain intervals, new devices that are being replaced, you need to give these companies time to prove that their devices do not aerosolize, period. And at certain intervals, their devices, when they come out of service, if a company can't replace it with a new device that doesn't aerosolize, then it's not

allowed onto the market. So it's like light bulbs. You know, you had a period of time when you could use old incandescent light bulbs and then you couldn't buy them anymore. Same thing. You implement that. You have to be reasonable about it in a time frame that allows them to do it, but to me that's a simple fix. A lot of this all revolves around aerosolization.

DR. LANGE: Matt.

DR. ARDUINO: And on new equipment, you want to be able to visualize the tubing in the fluid pathway, so without -- you know, without having to invalidate a warranty so that you've taken the thing apart. But you should be able to -- they should all be easily accessible so you can actually see what's going on.

DR. LANGE: Mr. Thuramalla.

And Keith, I'll have you turn your microphone off.

MR. THURAMALLA: In terms of design features, it will be nice to have a mechanism to automatically dry out the system, especially after cleaning. And this becomes even more important in the case of backup devices. If these devices were cleaned and being stored for some potential future use, if we can't make sure they're dry, then it's actually not completely clean. So a feature to automatically dry would be very beneficial.

DR. LANGE: Keith, will turn your microphone off, please?

Al and then Matt.

MR. STAMMERS: Yeah. It would be very nice to have also some mechanism on the device itself to show that the maintenance that is performed by the IFUs was actually performed, and perhaps even a litmus paper or something that could be used to assess the adequacy of the liquid that is in the device itself. But right now, you could say a checklist is

being performed every 2 weeks, a certain function, draining the water, putting through a disinfectant was occurred, but something to -- or excuse me, to chemically assess the -- whether or not it was actually performed.

DR. LANGE: Matt and then Dr. Zenilman.

DR. ARDUINO: Okay. So here's another take from the dialysis industry. If you buy a new dialysis machine nowadays, they all come with a heat pasteurization cycle. So on a daily basis, after use, you push a button, and it cooks up to 82.5°C, and within the machine it circulates, and then there are some water treatment systems where it's integrated. So your RO all the way to the machine is heat disinfected. Of course, there's still a once-a-week or something chemical clean and a chemical disinfectant that's used, but if somehow these devices could also do heat pasteurization, that might be helpful as well.

DR. LANGE: Dr. Zenilman.

DR. ZENILMAN: This is more of a basic question, but I think the dialysis analogy is -- I mean dialysis, the objective in dialysis is completely different in terms of the clinical objective. Here it's strictly heating and cooling, and we're using dialysis because there's a lot of similarities. I would argue that, you know, I think there's a basic question in looking at the technology of heating, because basically are there other ways of doing this outside of a water or exchange coil, which is certainly -- because this is no different, boiled down, than a car radiator. And I think -- so is there -- are there other ways of doing it which would disrupt the current technology?

DR. LANGE: So let me summarize suggestions that were given. Improved materials that would slow growth, biofilm growth specifically, and allow higher disinfectant level. Disposable

fluid pathways. Architectural involvement in OR configuration. Consider a closed system. Improve evacuated gas systems. Use of a UV light or other disinfecting mechanisms when the machines are not being used, which can be done at night. When new equipment, new and improved equipment is made, is use the current equipment until it's reached end of life and then replace it with the newer equipment instead of just saying everything that we have currently can't be used. Better visualization of the water pathways. Improved drying mechanisms. Some indicator that confirms that maintenance has been performed and is adequate, an automatic biologic indicator. A heat pasteurization cycle and newer heat exchange devices. Disruptive technology.

Is there anything I missed? And by the way, if any of these are patentable, we have the intellectual property right here. We said it, okay? It's been documented.

(Laughter.)

DR. LANGE: Matt.

DR. ARDUINO: Yeah, I think we said UV at some point.

DR. LANGE: Yeah, I did say UV sterilization at night. I think that's a great suggestion. Anything else I missed?

Dr. Hopkins.

DR. HOPKINS: A question for the FDA. Is this going to extend to other potential aerosol originators in the OR, such as Bair Huggers, the cardioplegia units that are sometimes separate from both the heart/lung machine and this? Is this going to be a more general device to anything that could create an aerosol? Because one of the things that Dr. Christensen said is if you get rid of the aerosolization, you get rid of the problem. So are we extending this to other

devices?

DR. SCHWARTZ: At this time, the scope of this issue has been, again, specifically on heater-cooler devices. That's not to say that this might not apply, more broadly speaking, to other aerosol-generating equipment within the operating room. I think that we also would need to make an assessment with respect to risk involved with these other devices and have a better understanding of the interaction of the device with the environment.

DR. HOPKINS: Dr. Hopkins.

Because the Bair Hugger, for example, has been implicated in cardiac infections at the time of surgery. So I think some of these other devices are -- maybe not for NTM, but are utilizing similar pathogenic pathways.

DR. LANGE: Jeffrey and then Dr. Givner.

MR. RILEY: Jeff Riley.

Al brought this up two times, and it keeps plaguing me. I think we should go back to the very opening statement where it says cardiothoracic procedures and we should include the word "extracorporeal." There are so many times that we are using extracorporeal circuits with heater-cooler, cooler-heater devices. Limb perfusions, abdominal lavages, transplant procedures, ECMO, everything we've said applies to all of those areas. So we should broaden the definition at the front end in the first opening statement, change it from cardiothoracic procedures to any extracorporeal procedure.

DR. LANGE: And to our perfusionist colleagues again, are there circumstances where a heater-cooler device may be on an entire day, where there's a cardiac case done, a non-cardiac case done, and a cardiac case done?

(No audible response.)

DR. LANGE: So the recommendation to the FDA is -- you know where I'm going with this, is cases -- people at risk are not only those that have cardiothoracic surgery, but those that are exposed to the heater-cooler device and have any type of implant done.

Dr. Givner.

DR. GIVNER: I just want to clarify. I think the recommendation for UV light is internal in the machine. Is that the recommendation?

DR. LANGE: Yes.

DR. GIVNER: Okay, thanks.

DR. LANGE: Either as a part of the machine or something that you can put on top of the machine somehow.

Matt.

DR. ARDUINO: It could be done several ways. One is in the box itself, so that if air is escaping, UV irradiating whatever's being thrown out or blown out of the machine. The other one is internal for the tank, but that just maintains the water in the tank.

DR. LANGE: Al and then Jeff.

MR. STAMMERS: Yeah, I believe -- and Suzanne, maybe -- the indications for use for these devices are not specific to cardiac surgery, correct?

MR. AGUEL: That's right.

MR. STAMMERS: Okay. One other thing, if it would be okay to suggest to add, would be to determine -- and several of the panelists have already mentioned this, to determine the life utilization, when these devices are beyond their prime, because we, as clinicians, struggle with

our hospitals to convince them that it's time to put a device to bed or to decommission it. And I think the manufacturers, with all of their experience and consecutive sequential data, could tell us that yes, at so many hours these devices do become problematic, because having that information going to a hospital administration from the manufacturers for utility of life would be very valuable. Obviously, a center like Jeff's would go through that quickly, but other centers performing a lot fewer procedures with less usage, you know, it's not just how many years in service, it's hours.

DR. LANGE: And the routine monitoring that we're going to do, I think that would help inform that decision.

Jeff and then Dr. Allen.

MR. RILEY: Just a quick comment. I believe Maquet provides a device in Europe that has UV light internally sterilizing now.

DR. LANGE: Terrific. So it sounds quite feasible. Good.

Dr. Allen.

DR. ALLEN: I just want to get a little clarity, though, to Jeff's comment about -- I would be cautious about keying in to extracorporeal circulation because you'll miss a lot of open heart operations done around the world. Eighteen, twenty percent of those are done off pump, for example, if you're doing routine coronary bypass grafting and the pump may be in the room and the heater-cooler may actually be on in those cases. But if you went to search and you were specifically searching with extracorporeal bypass used, it won't have been used. So you'll miss those cases. So be cautious about -- I would continue to look at, you know, cardiac operations, but you don't want to miss the liver transplant that uses bypass.

DR. LANGE: (c). Any other comments? And FDA, have we addressed sufficiently Question (b)?

DR. SCHWARTZ: Yes, thank you.

DR. LANGE: Okay. And Question (c). What would you recommend to the manufacturers to properly challenge the device in a lab environment that would replicate real-world use? Don't try this in your garage, okay?

Dr. Yuh, do you have an opinion?

DR. YUH: The first thing that came to mind was pond water, but I don't think that's really practical.

DR. LANGE: Pond water and Pine-Sol?

DR. YUH: Right. No, I don't know. You know, the different water sources that are being used around the country are so variegated that it's hard to know how to simulate real-world use because it's just so different, unless you establish a standard for filtering all the water to be placed in these devices. So I think, since we've identified this chimaeric species of *Mycobacterium* as an offending agent, that that should be in the inoculum in some way, shape, or form. But I think we'd be missing out on other potential problems by not including other commonly found or as was found in generic water that's used for these devices.

DR. LANGE: Dr. Christensen.

DR. CHRISTENSEN: The one thought I had was to potentially use fluorescent microspheres and use that in your system.: (1) You can use it for aerosol testing; (2) You could also check to see how well you're actually cleaning the system. Depending on the type of microsphere, you can detect with flow cytometer. So you'd have to have the right lab setup,

but it's actually a unique way to kind of use a surrogate instead of actually using a true test organism.

DR. LANGE: So again, this would be done by the company, so with the appropriate facilities, fluorescent microspheres, both assess aerosolization and adequacy of disinfection.

DR. ARDUINO: Well, cleaning, because you can't kill a microsphere. You're still going to have to use an organism mix of some sort, and what you might do is pick a couple of gram negatives and pick a mycobacteria, whether it's *chimaera*, *abscessus*, *mucogenicum*. And you might want to choose one of the rapid growers only because you get your lab results a lot quicker. But if you can kill an *abscessus* or a *fortuitum*, I would presume you'd kill other mycobacteria as well, including the slow growers, and then try to figure out -- and then, you know, seed the machine, let it sit for a little while. And I'm not sure what that time frame would be. And maybe throw in some organic material and -- I don't know. We could ask FDA what they would like to use. I don't know if ATS, or artificial test soil, in this case would really work. And you might want to use hard water, you know.

So when EPA does disinfectant challenges, the water they use is always hard because it's kind of a worst-case scenario, and then go through your disinfection processes to see if you get -- and I'm almost thinking, you know, some of the concentrations of stuff I've seen in unfiltered tap water going into some of these things, you're almost going to need like at least at 6-log reduction in some cases.

DR. LANGE: Dr. Leggett.

DR. LEGGETT: To add to those which were on my list, except I didn't know about fluorescent microspheres, I think that the mixed bacteria should include the ones that are most

likely the aerosolized, which I believe were mentioned were *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas*; and certainly to an intermediate-level standard with repeated cycles and testing of the tubing tanks, filters, and connections, and of course the aerosolization risk, which hopefully will be done away with.

DR. LANGE: So what I've heard so far, two things. One is fluorescent microspheres, so talk about the adequacy of cleaning. Not disinfection, but cleaning. And aerosolization. Two is gram negatives and organisms that are most likely to be aerosolized, *Pseudomonas*, *Acinetobacter*, *Steno*. Looking at the tubing, the tanks, and repeated cycles. Any other opinions? And hard water, I forgot to mention hard water. Keeping in mind that the recommendation of the Committee is that the only water put in the device is filtered. But this is, again, stressing the system.

Dr. Gallagher.

DR. GALLAGHER: I think one of the things that we heard is that sometimes they're easy to clean and sometimes they're not. So I think 56 steps sounds like a lot of steps, but that's okay if they're easy to do. So I think one of the things that also needs to be considered in this is the capabilities of the persons who clean it. They're not all going to be perfusionists. You have people in different roles. So I think, you know, looking at the process and what is the process, not just the organisms and those kind of things, but the actual human factor process involved to make it as simple as possible and make it something that is in the capability of a variety of professionals.

DR. LANGE: So simple procedures, not simple people. Okay. Any other opinions on the Panel? Have we exhausted the opinions or just exhausted the Panel?

(Laughter.)

DR. LANGE: Dr. Schwartz, is that sufficient guidance? Dr. Aguel?

DR. SCHWARTZ: So going back to the presentation that our subject matter expert provided yesterday, Dr. Mayhall, I think she presented a few slides with regard to disinfection endpoints and level, and we need a little bit more clarity on what the Panel thinks is adequate as a disinfection level and with those endpoints.

DR. LANGE: I'll ask our infectious disease experts.

So Dr. Leggett.

DR. LEGGETT: I think I mentioned that for me, it would be intermediate level.

DR. LANGE: Do you have an opinion, Dr. Givner?

DR. GIVNER: I agree with Dr. Leggett.

DR. LANGE: Dr. Zenilman?

DR. ZENILMAN: The same.

DR. LANGE: Dr. Roselle?

DR. ROSELLE: The same.

DR. LANGE: Any dissenting views?

Jeff, were you going to say something, or did you just wave?

MR. RILEY: I was trying to remember the rankings. It struck me that that was a little bit high when I read it yesterday, but that was me remembering.

DR. LANGE: So noted from our perfusionists and overridden by the four infectious disease people.

(Laughter.)

MR. RILEY: Who don't do the procedures.

DR. LANGE: Your opinion is valued. It is valued.

So before we close, I'd like to thank our Industry Representative, our Patient Representative, our Consumer Representative and ask you for any comments.

Mildred, we'll start with you.

DR. FENNAL: I say thank you, and I'm not going to call you Richard. I would like to say thank you for the opportunity to serve on this Panel. This is my first time with this group. I'm on loan to you. I enjoyed being here and always happy to, so you can call me again.

DR. LANGE: And when I do, what would you like me to call you?

MR. McGLAMERY: The same. I'm --

DR. LANGE: I'm sorry, this is Raymond McGlamery.

MR. McGLAMERY: Raymond McGlamery.

I'm very happy to be here. I enjoy serving on the CDER panels, and being loaned over was a great surprise and a great opportunity for me. I always enjoy learning and getting my brain stimulated because my outside world is not quite as stimulating. So I appreciate the hospitality and the kindness of everyone. Thank you very much, and thank you for running a great Panel with some good humor to it as well.

MR. THURAMALLA: So to go along with that, I want to say I'm very happy to be part of this Panel.

DR. LANGE: I'm sorry, this is Mr. Thuramalla.

MR. THURAMALLA: Naveen Thuramalla.

So to go along with the same thing, I should also mention that I'm very happy to be part

of the Panel. But I would also like to thank FDA and the industry representatives, CDC, and all the other guest speakers who spend their time explaining the importance of this problem and bringing it to this Panel for a very detailed discussion. I'd like to also thank the Panel for a very thorough discussion, point by point, to understand the problem and provide necessary guidance to the FDA.

In the context of Question No. 1 discussion that we had this morning regarding the best thing right after disinfection and also at the end of the cycle, it has come to my attention that testing right after disinfection may not be as important because if it is done and the IFU is correctly implemented, the result is going to be zero or very close to zero. So the actual utility to the user facility of testing right after disinfection may not be as important. Our subject matter experts have also told us that the biofilm becomes more active after a few hours of running liquid, 4 hours. So that might become a cost issue as well.

I want to agree with the Panel that informing the providers first and then to the affected patients would be very important to control the anxiety and do the necessary service to the patients.

Lastly, from a long-term perspective, it would be very beneficial if FDA could work with the industry and develop a guidance providing specifics on the outline for evaluation testing, the frequency of testing, endpoints for disinfection and things like that. Once a guidance will come out, it will be very helpful for the industry to apply this in a standardized manner.

Ultimately, I think the user facility who is generally responsible for maintaining these devices should have a surveillance program with documented evidence of implementation, if feasible, and this would be of big help because it could flag the problems and involve the

manufacturers in the right time. Therefore, the problem could be addressed in a timely manner.

Thank you.

DR. LANGE: Thank you, Mr. Thuramalla. I've served on several panels with you. It's always a joy. Raymond, good to have you. Dr. Fennal, it's good to have you guys as well. Thank you very much for joining us.

FDA, I'd like to give the floor to Dr. Schwartz and Dr. Aguel for any final comments or any clarifications you need from us.

DR. SCHWARTZ: Well, I think we want to really thank the Panel and thank all of the invited speakers, the manufacturers, our partners in -- among the other federal agencies and state agencies as well as the subject matter experts, for the information and the insights and expertise that was shared and for really adding to the robust discussion that we had today. I think that it gives us a better sense of clarity around this issue, which continues to evolve and for which we continue to learn more and for which we intend -- we're committed to sharing more information with you and with the public. And once more, really a very, very big thank you. A lot of appreciation for all of your input.

I don't know if you'd like to add anything, Aguel.

MR. AGUEL: This is Fernando Aguel. I would just add that I think we got a lot of really good information, and that's information that we're planning on taking back, and we have a bit of a charge for some work to do, and we look forward to incorporating all of this information into that. And I think it's forward looking, so we're hopeful that we can improve the situation as we move.

DR. LANGE: The presentations were outstanding. The FDA, excellent presentation. Our industry representatives, very balanced and even, very informative. Our guest speakers and those that traveled across the Atlantic to get here as well, really appreciative of them. Our epidemiologists and the Panel, I want to say thank you very much for the attention. This was one of the harder panels because we really don't have all the information; we're doing the best we can. The nice thing is this will be an ongoing process as we get more information. And the last thing is I'm reminded of my children. We have three boys that are all grown now, but further -- for almost a couple decades, they showered infrequently and never made their bed, and I had no idea they had more insight into NTM than I did.

(Laughter.)

DR. LANGE: So with that, I'll close the Panel, and thank you all very much.

(Whereupon, at 3:04 p.m., the meeting was adjourned.)

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This is to certify that the attached proceedings in the matter of:

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