NWX-FDA OC

Moderator: Gary Norris
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Coordinator: Welcome and thank you for standing by. At this time all lines are in listen-only mode until the question and answer session. If you'd like to ask a question at that time you may do so by pressing Star then 1 and recording your first and last name. Today's call is being recorded, if you have any objections you may disconnect at this time. I would now like to introduce your host for today's call Mr. Gary Norris. You may begin.

Gary Norris: Good afternoon everyone and thank you for joining us for this afternoon's 50 state conference call. My name is Gary Norris, I am the Federal State Health Communications Program Manager with the FDA's Office of Regulatory Affairs and I'll be serving as the moderator for today's call.

The purpose of today's call is to provide an overview of the agency's recommendations for mitigating the risk of non-tuberculosis mycobacterium infections associated with heater-cooler devices.

Today's conference call is scheduled for one hour and will be recorded with the first portion of the call dedicated to opening remarks and a presentation. Following the presentation we'll give you an opportunity to ask questions or

provide comments during a question and answer session. At this time I'd like to turn the call over to Irene Aihie with FDA's Center for Devices and Radiological Health for opening remarks.

Irene Aihie: Thank you Gary. On October 15, 2016 the FDA issued a safety communication on non-tuberculosis mycobacteria infections associated with heater-cooler devices to heighten awareness about infections associated with heater-cooler devices and set healthcare providers and health facilities to mitigate risk to patients.

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

On June 2nd through the 3rd 2015 the FDA will hold an advisory committee meeting to seek expert scientific and clinical opinions related to heater-cooler device contamination associated patient infection and potential mitigation strategy. The advisory committee's opinion on these issues will assist the FDA in providing recommendations to further minimize patient exposure to infections. The focus of today's Webinar is to review CDRH's and CDC's recommendations to help mitigate the risk of infection. Your presenters will be Dr. Suzanne Schwartz from CDRH's Office of the Center Director and Dr. Kiran Perkins from the Centers for Disease Control and Prevention. Following the presentation we will open the lines for your questions related to this topic

only. Additionally there are other sister subject matter experts available to assist with the Q&A portion of our Webinar. Now I give you Suzanne.

Dr. Suzanne Schwartz: Thank you Irene and good afternoon. My name is Suzanne Schwartz and I'm the Associate Director for Science and Strategic Partnerships at FDA's Center for Devices and Radiological Health. We're pleased to inform you that today's briefing will be co-presented by FDA and the CDC and so as Irene mentioned I am joined by Dr. Kiran Perkins from CDC's Prevention and Response Branch in the Division of Healthcare Quality Promotion.

The objective of today's call is threefold. Number one, to heighten awareness across states departments of health and local tribal and territorial organizations of the recent associations of NTM infections with heater-cooler devices in patients who have undergone open chest cardiac procedures. Number two, to inform stakeholders of ongoing and upcoming efforts by FDA and CDC to address this public health issue and finally number three, to provide recommendations and resources to you that can aid in risk reduction.

We are eager to foster collaboration with you, our state and local partners in addressing this emerging challenge of healthcare associated infections. And upon completing this formal presentation today, we'd like to hear from you as to what questions you may have. The road map we'll cover for today's talk will start with what is the public health issue we're facing today? We'll then describe what heater-cooler devices are; we'll talk very briefly about non-tuberculosis mycobacteria or NTM - all of this as background to contextualize for you the different elements of CDC's investigation and its recommendations, as well as FDA's multipronged response spanning our investigation, our objectives for patient protection, near-term, midterm, and long-term, our outreach for engagement, what we've communicated thus far,

our compliance -related activities and our communication efforts as we go forward and finally a few words about our upcoming advisory committee meeting.

By the end of today's call the key takeaways will include a better understanding of this emerging concern, what current countermeasures are recommended to protect patients from infection prospectively as well as CDC's interim guide to assist in identifying patients with NTM infections associated with exposure to heater-cooler devices in order to help ensure timely diagnosis and treatment of infection. A year ago, in May-June 2015, CDC and its European counterparts reached out to us regarding a potential association between heater-cooler devices and NTM infections in patients who had undergone cardiac surgery based on early signals observed in Europe. What you see here is a representation of reports filed with the FDA for heater-cooler devices from 2009 extending to February of this year for patient infections and for device contamination. This graph represents all comers. In other words it's not specific to anyone manufacturer nor to any one specific organism. It also represents a compilation of user facility reports, voluntary reports and manufacturer submitted reports.

What is notable and not surprising - in fact it's characteristic of reporting trends whenever a safety notice is issued by FDA as well as our regulatory partners outside the US - is a spike in reporting due to increased awareness generated by the communication. It's recognized also that there is a delay or latency between exposure to NTM organisms and development of symptoms in those patients who have developed invasive infection. It's therefore important to note that the dates indicated on this bar graph reflect when the MDRs were reported to FDA. However the initial exposure to NTM, the seeding with the organism and the development of what are here non-pulmonary invasive infections could have occurred several years prior. The

same holds true for device contamination. This is extremely important because without heightened awareness across states and within the healthcare provider community, we at FDA are handicapped with limited information. And this impacts our ability to ascertain the breadth of the issue in order to conduct a timely investigation and affect a timely response.

One key point I'd like to underscore here and it will be a running theme throughout our presentation is FDA's approach to this investigation being broad across all heater-cooler devices and not focused solely on a single product and a single manufacturer. While this is an ongoing investigation we believe that it's necessary to take a close look at all of the heater-cooler devices under our regulatory authority that are used for cardiac surgeries and we are currently doing so.

So what are heater-cooler devices? Well they're used primarily during cardiothoracic surgeries as well as other medical procedures to warm or cool a patient. These devices include water tanks that provide temperature controlled water through closed-circuits to external heat exchangers or warming cooling blankets. It's very important to note that water in the circuits does not come into direct contact with the patient. Yet because these devices are not airtight or water sealed there is a potential for contaminated water to enter other parts of the device or transmit bacteria through the air, aerosolized in other words, through the device's exhaust vent into the environment into the patient. So what is non-tuberculous mycobacteria?

This diagram is a simplified schematic showing where this relatively new species can be found under the general term mycobacteria. In this slide we break down mycobacteria into non-tuberculous as well as into M. TB, *Mycobacteria tuberculosis*. The device contamination and patient infections that have been observed with heater-cooler units has fallen within the NTM

the non-tuberculous mycobacteria branch. Many of them have been identified as *M.* c*himaera* which was separated out from a group called the *Mycobacteria intracellulare* in 2004. Please do note though that while *M.* c*himaera* isolates have been identified in many of the cardiac surgical patients' infections to date, clusters of infections have also been attributed to *M. abscessus*, another non-tuberculous mycobacteria as well as others.

NTM can further be categorized into rapid growers and slow growers. All of these waterborne bacteria have the ability to form biofilm. And this is important from a contamination standpoint because once biofilm has formed inside the tank or a circuit, cleaning and disinfection of the device becomes extremely difficult if not impossible at the present time. Now that we know what NTM is, where does it reside and how are patients infected? Well NTM is widespread in nature as it's found in natural and tap water, in the soil and even in some surgical solutions. NTM is likely to be spread through an aerosolization route. Historically NTM infections mainly occurred in individuals with predisposing factors including an altered or local systemic immunity, a history of prior pulmonary disease such as COPD and cystic fibrosis. However -- and this is an important distinguishing factor -- the NTM infections that have occurred in patients who have undergone cardiothoracic procedures associated with heater-cooler devices appears to represent a different profile. These patients do not have underlying disease or known predisposing factors to the best of our awareness and these represent a much more invasive type of infection. Thus far the commonality among these patients is direct exposure through an open chest cavity wherein the NTM is able to invade to see the tissue and to invade.

As I mentioned at the very beginning of this briefing, over the past ten months we've received an increasing number of reports of NTM infections identified by healthcare facilities through retrospective reviews of their patients who

were exposed to contaminated heater-cooler devices during cardiac surgery going back in some cases for years. We also continue to receive reports of device contamination in spite of adherence to manufacturer's instructions for cleaning and disinfection of these devices. And therefore our approach has been one of looking at this very challenging complex issue from A to-Z and from all different angles: from FDA research including examining and evaluating device design itself, the environment in which it resides and the usability aspects of cleaning and disinfecting what we call human factors so several different activities and outreach to various organizations agencies and experts.

Our cross-cutting activities have including broad stakeholder outreach, basic communication, and compliance activities. As mentioned earlier, we've posted a new Web page on heater-cooler devices and lastly the medical device advisory committee public meeting which we will be convening in early June. FDA's ultimate objective is to protect patients from infection. Based upon the investigation, the data, the theories, the suppositions, we've identified some short term, midterm and longer term goals which we're acting on in parallel in order to reach this objective.

The first line of defense are things that have to be done now in order to reduce the possibility of infection without compromising the device's performance, it's structural integrity and for patient safety and these included the location of the heater-cooler device in relation to the sterile field and patient; the location of the heater-cooler vent in relation to the patient in the sterile field; directing the exhaust from the device away from the patient in the sterile field; performing an evaluation of the OR environment with respect to airflow; and reviewing hospital infection control procedures for any improvements that can be made.

Our midterm goals include mitigation of aerosols from the heater-cooler device into the OR. We're currently working with manufacturers on design aspects of their heater-cooler devices in order to mitigate this aerosolization of NTM into the OR. Another area of study includes whether airflow in the operating room can be manipulated to reduce the possibility of aerosols reaching the sterile field. And further down the road our longer term goals include identifying cleaning and disinfection methods that will prevent biofilm formation and maintain contamination levels in the tank and water circuit at acceptable levels. I'm going to now turn the slides over to Dr. Perkins who will discuss CDC's role in investigation, public health response and guidance.

Dr. Kiran Perkins: Thank you Suzanne.

Dr. Suzanne Schwartz: Sure.

Dr. Kiran Perkins: So I want to briefly share CDC's perspective on our role during this ongoing public health investigation and also to provide some guidance for identifying patients at risk as Suzanne mentioned. Next slide please. So recent CDC active involvement with the current ongoing investigation actually started with a field investigation in Pennsylvania during the summer of 2015 last year when CDC worked alongside the Pennsylvania Department of Health to identify some strong evidence associating a cluster of invasive NTM infection among cardiac surgical patients to exposure to heater-cooler devices. In October we received preliminary results of extensive laboratory testing. And when this became available this really strengthened the association that we had found during our field investigation. And as a result CDC issued interim practical guidance to identify clinical cases that may be associated with heater-cooler devices in that month.

At that time CDC also held several calls with multiple professional societies as well as other stakeholders to alert them to the guidance and to recommend increased vigilance. Since October CDC has continued an active engagement with FDA, our partners in the European Union such as the European CDC as well as state and local health departments, healthcare facilities and other clinical and laboratory partners both domestic and abroad in trying to characterize the aspects of these infections and bacterium. Now given the increasing number of reports from across the US of facilities dealing with this issue, CDC has drafted some additional guidance to assist healthcare facilities in identifying patients with NTM infections that may be associated with exposure to heater-cooler devices in order to help ensure timely diagnosis and treatment of patients which is otherwise often delayed. Next slide please.

So healthcare facilities that perform cardiac surgeries that require cardiopulmonary bypass should probably consider taking the following steps to help identify patients at risk. First you would want to consider a laboratory assessment and by this I mean trying to identify all NTM positive cultures that came from an invasive sample such as blood, tissue biopsy or for example implanted prosthetic material. And you can do this using the micro biologic database at your institution. Your institution should decide how far back to pull records and that will vary. Some of you used a four-year time period to look back but others have opted for a longer time frame.

Next slide please. Next we would recommend doing a clinical assessment by cross-referencing the NTM positive cultures with medical and surgical records to try to identify patients who meet at least one of the clinical criteria. These clinical criteria would include things such as prosthetic valve endocarditis, prosthetic valve vascular graft infection, sternotomy wound infection, ileus tinnitus, bloodstream infections or disseminated infections would include -

which would include embolic and immunologic manifestations for example spinal megaly, arthritis cytopenia, nephritis, et cetera. Next slide please.

Finally taking the patients that are identified using the above criteria, you would want to assess for exposure by looking for a history of surgery that has required cardiopulmonary bypass that occurred prior to the diagnosis of NTM infection. Next slide please. Finally as the CDC guidance in October highlighted, we again stressed the importance of maintaining the high index of suspicion for NTM infection in patients who have been exposed to cardiopulmonary bypass moving forward. So NTM infections are not generally diagnosed using routine microbiologic testing and oftentimes require cultures for acid fast bacilli or ASB. So in any patient who has a history of surgery that's required cardiopulmonary bypass and presents with any of the clinical criteria that I had mentioned on the prior slides you would want to consider ordering these ASB cultures.

Additionally, NTM infections often present with very vague symptoms and this is likely contributing to the delayed diagnoses. So therefore I would consider ordering ASB cultures in any patient who presents with some of these vague symptoms which would include recurrence for persistent fever of unknown ideology, night sweats, joint or muscle pain, weight loss or fatigue.

Now if you have an ASB culture that returns positive and is identified as a mycobacterium avium complex commonly known as MAC you should consider sending these cultures to an NTM reference laboratory for further speciation to identify the type of mycobacterium as this may be important for treatment decisions. Next slide please. The guidance that I just reviewed is posted on our Web site at cdc.gov/hia/outbreaks under our Safety Alerts. And please feel free to contact us at 1-800-CDC-INFO for any questions that may

come up during your review. I'm going to go ahead and turn it back to Suzanne. Thank you.

Dr. Suzanne Schwartz: Thanks Kiran. So again once more the activities that we have been involved with at FDA have included broad outreach communicating through safety communications as well as an update to the Web page which really allows us to remain somewhat nimble with new information and to provide or distribute that information to the public as it becomes available. And again the announcement of the medical device advisory committee meeting that will be taking place June 2nd and 3rd. So I'd like to just spend a few moments highlighting some of the key recommendations that we had released that we had issued in our safety communication. And these bullets actually appear within the communication and on the Web site as well. But it's important to underscore the necessity to adhere to the cleaning and disinfection instructions that are provided in the manufacturers' device labeling and to also make certain that you are working off the most current version of the manufacturer's instructions and that those are readily available to staff.

With respect to the water that's utilized in order to fill, rinse, refill these heater-cooler water tanks, tap water should not be utilized because this may introduce NTM organisms. One should only use sterile water or water that has been passed through a filter of less than or equal to .22 microns. As I mentioned before the importance of directing the heater-coolers exhaust vent away from the surgical field away from the patient and towards an operating room exhaust vent, this is one of the ways that we can reduce the risk of the potential for aerosolization of NTM that exists in devices that are presently distributed in the field and importantly to establish regular cleaning disinfection and maintenance schedules for heater-cooler devices.

Continuing onwards, developing and following the quality control program for maintenance cleaning and disinfection of devices and when heater-cooler devices have discoloration or cloudiness in the fluid lines or circuits that should be a sign to end-users to remove that device from use as it may indicate bacterial growth and to discuss and consult with your hospital, with the hospital's infection control officials so that the appropriate follow-up can be performed. We at FDA are encouraging healthcare facilities to submit reports both to manufacturers as well as to us via MedWatch even when suspecting bacterial contamination of heater-cooler devices that may have led to patient infection. Now because of the many challenges and complexities regarding heater-cooler devices that are associated with these invasive NTM infections in cardiothoracic surgical patients, FDA is convening this advisory committee meeting in order to address questions that we have regarding, number one: the effectiveness of cleaning and disinfection methods for those heater-cooler devices which are out in distribution and present use.

Also, regarding pre-market data and information that continue to demonstrate validation of cleaning and disinfection that will support labeling and instructions for use. We want to have a better understanding as well of aerosolization - how aerosolization occurs and how it can be mitigated with respect to these devices. And that leads also to protective measures and risk mitigation to ensure patient safety during procedures where these devices are used. We'll also be speaking with the panel with respect to what additional risk stratification guidelines may be developed in order to aid and assist in notification of patients who may have already been exposed to NTM during prior cardiothoracic procedures.

So the panel meeting is really an opportunity for healthcare facilities and other stakeholders to present data information or views and perspectives on this issue whether done orally or in writing. And while the deadline for oral

presentation has actually passed, written submission will be accepted until this Thursday, May 19 and you may use the link below in order to submit comments to the public docket which will then be provided to the committee members. And with that we want to be able to open this up for questions. Also the email address for submitting questions beyond - this particular session is available and showing on the screen. And as was mentioned the slide presentation, transcript and Webinar will - recording will be available at that link in several days' time. Thank you.

Gary Norris: Thank you Dr. Schwartz and Dr. Perkins. This is Gary Norris here, conference call moderator. We're now at a point in the call where we'd like to open the call for questions. So I'm going to ask the operator to open the lines and provide instructions to our callers who have questions. And just as a reminder for our callers please speak clearly and identify yourself by name and your organization.

Coordinator: At this time we'd like to begin the formal question and answer session of the call. If you'd like to ask a question please press Star then 1. You must record your first and last name to ask a question and to withdraw your question you may press Star then 2. Once again to ask a question at this time please press Star then 1 and record your first and last name. One moment for the first question please. At this time I'm showing no questions.

Gary Norris: Okay. We have no questions. We'll go ahead and turn it over - back over to Irene Aihie with the Center for Devices and Radiological Health for our closing remarks. Irene.

Irene Aihie: I believe we have a question in the queue.

Gary Norris: Very good.

Coordinator: First question comes from Kelley Garner. You may ask your question.

Kelley Garner: Hi. This is Kelley Garner with the Arkansas Department of Health and it's a great presentation. If you could go over one more time what the expectations are for state health departments regarding this issue? You know, we are trying to reach out and link with the other various areas that would get these kinds of reports. But just was hoping you could cover that one more time including TB programs.

Dr. Suzanne Schwartz: So this is Suzanne Schwartz in FDA. I'll answer on behalf of FDA's perspective and then I'll let Dr. Perkins or Dr. Perz as well speak from CDC's perspective. For us at FDA really where we would look towards the State Departments of Public Health is to help by increasing awareness across the healthcare facilities that are within your jurisdiction so that there is information about this issue, what can be done with respect to mitigation and really to simply socialize and make sure that healthcare facilities do have adequate awareness of this matter.

Dr. Kiran Perkins: This is Kiran Perkins. Was that Joe?

Dr. Joseph Perz: Yes Kiran would you like to go first?

Dr. Kiran Perkins: Sure. I just wanted to echo Suzanne's recommendations. What we're at least from our experience here at CDC is a lot of times we're hearing from the state and local health departments who are hearing from their facilities. So I think just being aware of the issue in general and being able to offer guidance and resources to facilities is a critical role that the health departments are playing in this investigation going forward.

Dr. Joseph Perz: Yes. And this is Joe Perz also from the CDC. I guess I'll echo those comments and add on that CDC's guidance from October did recommend active outreach to facilities that perform cardiac surgeries that would involve bypass. So to be helpful, you know, on the receiving end if reports are received to assist with any investigation if necessary and to help ensure submission of an MDR to FDA or what we would like health departments to do on the receiving end so to speak but also to consider being proactive in reaching out to facilities to reassure the public health authority that the facility is aware of the issue, has reviewed current manufacturer instructions and maintenance requirements and so on and that they have considered the need for raising awareness among their providers and patients.

Kelley Garner: Thank you all. Those were wonderful answers and it definitely helps with the to do list. Just wanted to make sure that we're doing what we need to do here in Arkansas.

Coordinator: Thank you. I'm showing no further questions.

Gary Norris: And I see - this is Gary Norris the call moderator. I see no other calls in the queue. So with that I'll go ahead and turn the call back over to Irene Aihie with the Center for Devices and Radiological Health for closing remarks.

Irene Aihie: I believe we have another call, another question in the queue.

Coordinator: Next question comes from Eileen McHale. You may ask your question.

Eileen McHale: Hi. This is Eileen McHale from the Massachusetts Department of Public Health. I'm just wondering is there, you know, there have been - do you have any idea of the number of reports of this instance? And since, you know, there

was guidance issued in October has much changed from October to now that your - it seems to be there's increasing awareness on FDA's and CDC's part?

((Crosstalk))

Dr. Suzanne Schwartz: We're going to have our FDA subject matter experts from the Office of Surveillance and Biometrics respond to that.

Eileen McHale: Thank you.

(Kelly Bauer): Hi. This is (Kelly Bauer). I'm a Nurse Consultant in the Center for Devices and Radiological Health in the Office of Surveillance and Biometrics. Since we have received (unintelligible) 72 MDRs from multiple manufacturers…

Gary Norris: Could you speak up? I'm sorry this is the call moderator. We can't hear you.

(Kelly Bauer): I'm sorry. This is (Kelly Bauer). We have received a total of 172 MDRs from multiple manufacturers and user facilities related to this heater-cooler issue between January 2010 and February of 2016. We have received since the time of the original communication in October there were 140 additional reports that we have received likely due to the highlighted, you know, communication as well as the - a recall.

Eileen McHale: Thank you.

Dr. Kiran Perkins: Yes this is Dr. Kiran Perkins. From CDC's perspective we obviously don't have any - we don't have an official reporting mechanism. We are here as consultants for local and state health departments as questions arise regarding this issue. Anecdotally from the reports that we've had, I would definitely say that since October, since the guidance has gone out, we have had an

increasing number of states reaching out to us because institutions have contacted them regarding questions around identifying patients.

Dr. Joseph Perz: And Kiran this is Joe Perz. I will add on that in the course of having additional consultations with health departments and facilities, you know, we do have concerns that, you know, patients have had symptoms but have not had in all instances, you know, a timely diagnosis. So it's, you know, reason to continue to get the word out as far as raising awareness in the provider community especially that this risk exists or existed in the past and was unrecognized. So the need for raising awareness is something that I think we're very much aware of.

Coordinator: Again if you'd like to ask a question please press Star then 1. I'm showing no further questions.

Gary Norris: Okay Irene we'd like to do closing remarks. I see no more in the queue.

Irene Aihie: Thank you Gary. This is Irene Aihie. I hope that you found this - we hope that you found this Webinar informative and productive. We would like to thank all of our speakers and subject matter experts for providing this important information and to also thank all of our participants for joining us on today's call. If you have additional questions about our recommendations to mitigate the risk of infection please use the contact information provided at the end of the slide presentation. Also as a reminder today's presentation and transcript will be made available on the FDA's Heater-cooler Device Web page on Monday, May 23. Again thank you for participating and this concludes today's Webinar.

Coordinator: This concludes today's conference. Thank you for your participation. You may disconnect at this time.

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