

FDA Executive Summary

Prepared for the
June 2 -3, 2016 meeting of the
Circulatory Devices Panel of the
Medical Devices Advisory Committee

***Nontuberculous Mycobacterium (NTM) Infections Associated with
Heater-Cooler Devices (HCD) during Cardiothoracic Surgery***

Contents

1. Introduction and Purpose of the Advisory Committee Meeting	4
2. Incidence of Cardiothoracic Procedures in US.	6
3. Timeline of Investigations into Infections and Actions	6
4. Background on Non-tuberculous Mycobacteria (NTM).....	10
5. Infection Reports submitted to FDA.....	12
5.1 Overview of MDR Database.....	12
5.1.1 Strengths and Limitations of MDR Data	12
5.1.2 Methodology	13
5.1.3 Results.....	14
5.2 Overview of MDRs.....	14
6. Heater Cooler Devices (HCD)	20
6.1 Pre-market Evaluation of HCDs	22
6.2 Device-Related Challenges Contributing to Contamination.....	23
6.2.1 Design Challenges.....	24
6.2.2 Labeling Challenges.....	26
6.2.3 Point Source Contamination Challenges.....	27
7. Environmental Contributors to HCD-Related Infections.....	28
7.1 Transfer of NTM from the HCD into the Operating Room air.....	28
8. Considerations for Cleaning/Disinfection of HCDs	29
8.1 Acceptable levels of microbial contamination in water	30

8.2 Regulatory Approach for validation of decontamination, cleaning and disinfecting of non-HCD water circuits	31
8.2.1 Disinfectants	31
8.2.2 Water Purification Systems (WPS) and Dialysate Delivery Systems (DDS) Disinfectants	31
8.3 Proposed Adapted Regulatory Approach for HCDs	33
8.3.1 Manufacturer Decontamination, Cleaning, and Disinfection Validation.....	34
8.3.2 End User In-Use / Actual-Use Decontamination, Cleaning, and Disinfection Validation .	35
8.4 Endpoints for disinfection.....	36
8.4.1 Low and intermediate level disinfection:	36
8.4.2 High level disinfection:	37
8.4.3 Disinfection of HCD water circuit:	37
9. Ethical Aspects.....	38
9.1 Potential Patient Factors.....	38
9.2 Patient Notification	38
10. Summary	39
11. Appendices.....	40
12. Glossary	40
13. Literature References	41

1. Introduction and Purpose of the Advisory Committee Meeting

Recently, nontuberculous mycobacteria (NTM) infections have been identified in patients in Europe and the US that previously underwent cardiothoracic surgeriesⁱ. Epidemiologic analysis and laboratory investigations have now described an association among patients who manifest deep seeded, valvular and bloodstream infections (sepsis) with NTM and prior exposure to a device known as a heater-cooler device (HCD), utilized for body temperature regulation during cardiopulmonary bypass (CPB)^{ii iii iv}. While the heart–lung machine during CPB takes over the work normally performed by the heart and lungs to assure oxygenated blood is being continuously distributed to all organs, the perfusion of oxygenated blood to end organs must also be accompanied by temperature control of the extracorporeal circuit. Currently, heart-lung machines and HCDs are essential equipment in cardiothoracic surgical suites.

Heater-cooler devices, used in conjunction with heart-lung machines during CPB, allow for circulating blood to be maintained at specific temperatures. During cardiothoracic operations such as, but not limited to, valve replacements and coronary artery bypass graft (CABG) procedures, cooling is used to stop the heart – known as inducing cardioplegia - which enables the surgeon to perform the operation, mitigating damage to myocardial tissue.

The cooling effect on the heart is achieved by simple heat convection. When warm blood passes through the heart-lung machine to be oxygenated, heat is also transferred through a heat exchanger where chilled water flows on one side of a non-porous barrier and the warmer blood on the other side of the barrier. The cooled blood now lowers body temperature when it circulates systemically to all organs and tissues. The same process takes place again with warm water when normo-thermia (i.e., warming the blood back up to normal body temperature) is required at the end of the surgery. The temperature controlled water being fed to the heat exchanger is part of a cardiopulmonary bypass temperature controller, otherwise known as the heater cooler device (HCD).

It is important to note that the HCD is a closed, non-sterile circuit whereby no contact with patient's blood or body fluids takes place at any time. It sits outside of the sterile field inside the operating room. However, analyses have now demonstrated that although the water in the HCD circuits does not come into direct contact with the patient's blood or body fluids, there is potential for NTM contaminated water contained in the HCD tanks to transfer from the device into the operating room environment and ultimately into the patient via the open chest^{ii, iii, iv}.

This concern raises several key questions regarding the adequacy of cleaning and disinfection of this reusable device as well as how to best remediate the mode of NTM aerosolized transmission from HCD to the sterile field and to the patient's open chest.

Challenges in Epidemiologic Investigation.

Although reported cases across the US and internationally of NTM infections associated with prior cardiothoracic procedures are rare, there may be under-reporting due to the challenges inherent to identifying patients and consequently, in pursuing a comprehensive diagnostic workup. To date, a case definition has not been established on a global level. The NTM infections that have been reported in the US and Europe linked to prior cardiothoracic procedures have caused serious illness and death.

Because of a latency period, patients may not manifest symptoms for months to years after initial exposure. This is especially the case with respect to certain types of NTM known as “slow-growers”, such as *Mycobacterium chimaera* (*M. chimaera*). Even in the presence of fevers of unknown origin, NTM sepsis and other manifestations of systemic nontuberculous mycobacterial disease, the healthcare provider may not associate the infection with cardiothoracic surgery that may have occurred four or more years prior. Moreover, cardiothoracic surgery may have taken place at a healthcare facility remote from the locale and the community where a symptomatic patient currently resides and is under a different provider’s care, making the potential link between the two events even more challenging and leading to delay in workup and diagnosis. A timely diagnosis therefore becomes dependent upon how well-informed the patient’s provider is regarding these emerging and life-threatening infections as well as the capabilities of the clinical laboratory in undertaking NTM testing.

FDA is therefore convening its Circulatory Devices Advisory Committee to address questions regarding: (1) The effectiveness of cleaning and disinfection methods for heater-cooler devices; (2) The amount and type of premarket data and information needed to demonstrate validation of cleaning and disinfection of heater-cooler devices in support of labeling claims and technical instructions; (3) The appropriate risk mitigations to be implemented by manufacturers of heater-cooler devices and/or hospital facilities to ensure patient safety during surgical procedures where these devices are used; and (4) The appropriate guidelines and/or criteria based on a risk stratification schema for notifying patients who may have already been exposed to NTM during prior cardiac surgeries.

FDA believes that, in keeping with its public health mission, it is appropriate to have an open and transparent dialogue with all stakeholders to review and discuss available data regarding the benefits and risks associated with the use of HCDs during cardiothoracic surgeries and generate evidence-based recommendations on how to best care for patients undergoing these life-saving procedures.

2. Incidence of Cardiothoracic Procedures in US.

Each year, thousands of cardiothoracic surgeries are performed in the United States. The majority of these cases are performed with cardiopulmonary bypass (heart-lung machines and HCDs). According to the Society of Thoracic Surgery, in 2014 approximately 170,000 coronary bypass procedures were performed. Also performed in that year were more than 108,250 other cardiothoracic procedures including: aortic valve replacements, mitral valve replacements, mitral valve repair aneurysms, transplants, aortic procedures, pulmonary and tricuspid valve procedures, cardiac tumors, trauma and other miscellaneous procedures on the heart or great vessels^v.

With uncertainty as to the magnitude of patients potentially exposed to NTM during prior cardiothoracic surgery, FDA has already taken multiple measures to heighten awareness. These efforts have included: issuing safety communications; establishing an informational webpage; convening a 50 States call; presenting at the March 2016 Healthcare Infection Control Practices Advisory Committee (HICPAC) meeting, partnering with The Centers for Disease Control and Prevention (CDC); engaging with professional societies; directly reaching out to healthcare facilities and collaborating with regulatory entities outside the US under established information-sharing mechanisms.

Yet, additional work is necessary to address the challenges in identifying patients at increased risk and establishing a diagnosis of NTM infection. FDA believes that further amplifying awareness is important, as is working with federal and state partners who can formulate discrete guidelines for all stakeholders across the continuum of care for those patients who have already undergone cardiothoracic procedures, as well as recommendations for prospective patients.

The committee will be asked to identify an appropriate case definition for patient identification and stratification for communication with patients, as well as methods for tracking patients and appropriate time period for healthcare providers to communicate with their potentially affected patients.

3. Timeline of Investigations into Infections and Actions

The following summarizes key activities in FDA's investigation of NTM infections associated with HCDs. It is not intended to be an exhaustive list of FDA activities or actions, but rather a general overview. In addition, actions taken by other agencies and health departments within and outside the United States are chronologically summarized as well.

Summer-Fall 2014

FDA receives medical device reports (MDRs) from a single user facility (UF) reporting postoperative patient infections including four deaths related to an atypical species of NTM known to be ‘fast growing’ (*M. abscessus*). Of the patients infected, not all cases were cardiothoracic and a definitive link to the HCD as the vector of NTM transmission was not established at the conclusion of the investigation by state, local and hospital authorities. Nevertheless, this *M. abscessus* outbreak prompted FDA to initiate an investigation into the adequacy of cleaning and disinfection instructions for the specific HCD that was in use at this UF, the Livanova/Sorin Stockert 3T.

Winter-Summer 2015

FDA begins to receive MDRs related to reports of NTM infections in post-cardiothoracic patients from across healthcare facilities in Europe followed by several inside the US which associate the infections to several manufacturers’ HCDs.

FDA initiates inspections of Livanova/Sorin’s HCD production facilities in Europe as well as its US domestic facility during this time period.

Medical literature on emerging infectious diseases draws attention to the issue of NTM infections in patients with open heart surgeries and epidemiological evidence for the airborne transmission of NTM from contaminated heater-cooler device water tanks^{i, ii, iii}.

In parallel, CDC notifies the FDA of newly identified patient infections in the US and OUS who had undergone cardiac surgery years prior.

The FDA and CDC build a collaborative effort to investigate the NTM outbreaks, including establishing communication with the European Centre for Disease Prevention and Control (ECDC) and other European health agencies as well as regulatory bodies in order to learn more about the potential links between NTM outbreaks and HCDs.

Fall 2015-Winter 2016

FDA issues a safety communication further amplified by CDC interim practical guidance to inform healthcare facilities about the association between HCDs and NTM infections in patients who have undergone cardiothoracic procedures, and to recommend mitigation measures hospitals should take to reduce risk of HCD contamination and NTM aerosolization during use in the operating suite.

Consequently, some healthcare facilities identify and notify prior cardiothoracic surgical patients who may be at risk of developing an NTM infection due to the use of a HCD during their surgery.

FDA sends Information Request (IR) letters to all water-based HCD manufacturers focusing on specific areas of HCD design – accessibility to tank, water agitation, ice/refrigerant, fans/speeds, vents/location and pumps/location, etc., cleaning/disinfection validation, and labeling.

Inspection findings at LivaNova/Sorin prompts FDA to issue a Warning Letter and Import Alert for violations related to the Quality Systems Regulation, 21 CFR Part 820.

Winter-Spring 2016

FDA review of the responses from the IR letters from each of the manufacturers leads to the conclusion that all HCDs have design features that could lead to aerosol formation.

FDA reaches out to multiple professional societies to ensure that stakeholders are aware of the Agency's safety communications and the steps that healthcare facilities should consider to reduce risk of patient infection.

FDA delivers a presentation on NTM device-related infections at the CDC HICPAC Meeting.

Throughout the entire span of investigation, FDA proactively reaches out to multiple healthcare facilities across the US, including pediatric specialized cardiac centers to hear directly about the challenges faced in cleaning and disinfection of HCDs, to encourage voluntary reporting of contaminated devices despite adhering to manufacturers' instructions for cleaning and disinfection, and to discuss FDA's recommendations.

As stated in the timeline above, FDA has issued frequent public communications during the course of this investigation, including:

- October 15, 2015: FDA released a Safety Communication to heighten awareness about infections associated with HCDs and steps healthcare providers and health facilities can take to mitigate risks to patients. The communication is provided at: <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm466963.htm> and is also available in Appendix A of this document.

- December 22, 2015: A Warning Letter was sent to LivaNova/Sorin with an Import Alert after inspections conducted at facilities in Munchen, Germany and Arvada, Colorado revealed violations to the Quality Systems Regulation, 21 CFR Part 820.
- March 28, 2016: FDA released a new webpage to provide further information about its work towards addressing the challenges of NTM infections with HCDs. The webpage can be found at:
<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CardiovascularDevices/Heater-CoolerDevices/>.

This is also available in Appendix B of this document.

In addition to FDA’s public communications, other regulatory agencies and public health authorities also released information on these investigations:

- April 30, 2015: The European Centre for Disease Prevention and Control (ECDC) released a Medical Device Alert entitled “Invasive cardiovascular infection by Mycobacterium chimaera potentially associated with heater-cooler units used during cardiac surgery”. The Alert can be found at:
<http://ecdc.europa.eu/en/publications/Publications/mycobacterium-chimaera-infection-associated-with-heater-cooler-units-rapid-risk-assessment-30-April-2015.pdf>
- June 11, 2015: Both the Medicines and Healthcare products Regulatory Agency (MHRA) and Public Health England (PHE) in the United Kingdom released communications related to risk of infection with Mycobacterium species with HCDs used in cardiac surgery. MHRA’s Alert can be found at:

This is also available in Appendix C of this document.

<https://www.gov.uk/drug-device-alerts/heater-cooler-devices-used-in-cardiac-surgery-risk-of-infection-with-mycobacterium-species>

https://assets.digital.cabinet-office.gov.uk/media/557958c640f0b615b8000025/MDA-2015-022_Heater-coolers.pdf

PHE’s note recommended microbiological testing, enhanced decontamination, and the removal from service of some machines, and also provided additional information on the scientific evidence of bacterial aerosolization occurrence common to all HCDs.

<https://www.gov.uk/government/publications/health-protection-report-volume-9-2015/hpr-volume-9-issue-15-news-30-april>

Both communication documents are also available in Appendix D in this document.

- October 27, 2015: The CDC updated its Interim Practical guidance on NTM Infections and Heater-Cooler Devices. The document can be found at: <http://www.cdc.gov/HAI/pdfs/outbreaks/CDC-Notice-Heater-Cooler-Units-final-clean.pdf>

This is also available in Appendix E of this document.
- December 11, 2015: The Pennsylvania Department of Health released a guidance regarding NTM infections among patients undergoing open heart surgeries on cardiopulmonary bypass. The Guidance can be found at: http://www.health.pa.gov/Your-Department-of-Health/Offices%20and%20Bureaus/epidemiology/Documents/PA%20HAN/2015/2015-PAHAN-322-12-10-NTM%20guidance_final_S.pdf

This is also available in Appendix F of this document.
- May 13th, 2016: CDC releases Interim Guide for the Identification of Possible Cases of Nontuberculous Mycobacterium Infections Associated with Exposure to Heater- Cooler Units. This guide can be found at: <http://www.cdc.gov/hai/pdfs/outbreaks/Guide-for-Case-Finding.pdf>

This is also available in Appendix G of this document.

4. Background on Non-tuberculous Mycobacteria (NTM)

The nontuberculous mycobacteria (NTM) are a heterogeneous group composed of 169 different species^{vi} in the family of mycobacteria that have the potential to cause human disease, but do not cause tuberculosis (TB). NTM are free-living mycobacteria normally found in the soil, natural water, drinking water distribution systems, and household and building plumbing, especially in recirculating hot water systems in hospitals, apartment buildings, etc.

Due to a hydrophobic permeability barrier, these organisms are able to survive for weeks to months on inanimate surfaces if protected from sunlight. The NTM can be killed by heat (e.g. >60°C) and are more resistant to acids, alkali, and some chemical disinfectants than other non-spore-forming bacteria.

Reports from literature provide information on why NTM is likely to survive and grow in HCDs. The optimum temperatures for growth vary widely among NTM species and range from <20 to 50°C. *M. avium*, for example, is also very resistant to higher temperatures and it has been shown that 90% of these bacteria survive exposure to 50 °C for 60 min^{vii}. NTM also have the ability to grow inside protozoa such as amoeba, at low organic carbon concentrations and also under conditions of stagnation^{viii}.

Mycobacteria like other bacteria also form biofilm which serves as a successful survival strategy for these ubiquitous organisms. Biofilm assembly includes reversible attachment, irreversible attachment, mature biofilm formation and dispersion^v. NTM, organized in biofilms, are difficult to eradicate with common decontamination practices and are relatively resistant to standard disinfectants, such as chlorine, organomercurials, and alkaline glutaraldehydes^v.

Biofilm formation has been a notable challenge in HCDs used clinically. Once established within the device, routine cleaning and disinfection as described in a manufacturer's instructions for use is insufficient for its removal.

The committee will be asked to discuss what factors would have the most impact on the minimization of biofilm formation.

NTM Present Unique Laboratory Testing Challenges.

Compared to the growth of other bacteria, most NTM species grow slowly with generation times of up to 20 hours on commonly used media. But there is even further delineation between slowly and rapidly growing species of NTM, which impacts, in turn, on laboratory testing capabilities and consequently, on correct diagnosis of a patient's clinical sample. The slow growers require more than 7 days to form colonies on solid media from a dilute inoculum under ideal culture conditions (e.g., *M. avium*). By contrast, rapid growers require less than 7 days when sub-cultured on Lowenstein-Jensen (e.g., *M. abscessus*).

The committee will be asked to discuss monitoring of HCD water in the clinical environment, with consideration for the following: monitoring being routine or situational; frequency of testing; entities to perform the testing; protocol for testing; and other indicators that healthcare facilities could use in their monitoring or in their identification of units that should be removed from service.

Pulmonary NTM Disease.

NTM infection has been classically studied in patients with pre-existing conditions such as cystic fibrosis, bronchiectasis, Lady Windermere syndrome, chronic granulomatous disease (CGD), and acquired immunodeficiency syndrome (AIDS). In these susceptible populations, transmission occurs via inhalation of NTM-laden aerosols leading to pulmonary disease^{ix}. The clinical presentation in these cases is very similar to that of pulmonary tuberculosis with lymphadenopathies, chronic or recurring cough, fever, fatigue and loss of energy, lack of

appetite, hemoptysis (blood in sputum), and night sweats. Other means of transmission of NTM is through exposure to the gastrointestinal tract (e.g., drinking water, showers, etc). The most common slow growing NTM found in clinical practice are the *Mycobacterium avium complex* (MAC) and include *M. avium*, *M. intracellulare*, and *M. chimaera*.

NTM Infections Associated with Cardiac Surgery.

Yet, the more recently described cases of disseminated *M. chimaera* have occurred in patients with a prior history of open cardiothoracic surgeryⁱ. These cases represent a very different epidemiological phenomenon. For example, transmission route is not inhalational, nor have there been any reports of underlying chronic pulmonary conditions or of pre-existing immune compromise among infected patients. These *M. chimaera* infections also demonstrate a more aggressive pathological profile. The infections are non-pulmonary; they are invasive, deep seeded within the heart at times of heart valve replacements^{i, ii, iii}.

These *M. chimaera* infections have been traced to the presence of the organism in the water reservoirs of heater-cooler devices; and through aerosolization, the NTM contaminated water is dispersed outside of the device into the ambient air of the operating room, and comes into direct contact with the patient through the open chest^{i, iv}.

Recent evidence of airborne transmission of NTM^{i, ii, iii} indicates a forceful rush of escaping gas from the HCDs creating fine droplets carrying NTMs that then burst and are aerosolized. Increased turbulence in the HCDs water tanks can create more bubbles thus potential for greater contaminated aerosol formation^x.

5. Infection Reports submitted to FDA

5.1 Overview of MDR Database

5.1.1 Strengths and Limitations of MDR Data

Each year, the FDA receives several hundred thousand medical device reports (MDRs) of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type

- Detect actual or potential device problems used in a “real world” setting/environment, including:
 - rare, serious, or unexpected adverse events;
 - adverse events that occur during long-term device use;
 - adverse events associated with vulnerable populations;
 - off-label use; and
 - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important post-market surveillance data sources. Other limitations of MDRs include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subject to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

5.1.2 Methodology

The Agency conducted queries of the MDR database for reports of all patient infections and/or device contamination associated with the use of heater-cooler devices entered between January 1, 2010 and February 29, 2016. The searches resulted in 180 MDRs. All reports were reviewed for factors such as incidence of patient infections and device contamination, event type, report source, patient age, patient gender, reporting country and the time to event occurrence (TTEO) for reported patient infections. The TTEO is determined based on the date of patient infection relative to the surgical procedure as specified in the narrative text of the MDR. These report details are characterized in the results summary.

5.1.3 Results

Of the 180 MDRs, 146 MDRs were submitted by manufacturers, 33 originated from user facilities (UF) and 1 was submitted by a patient. In some cases, multiple reports were submitted for the same event, particularly in instances where both the UF and the manufacturer submitted MDRs. 61 MDRs mentioned patient infections.

The reporting country was identified in all 180 MDRs and included the United States (US), 62 MDRs) and foreign countries (OUS, 118 MDRs). OUS Countries included the United Kingdom (48 MDRs), Germany (44 MDRs), Netherlands (9 MDRs), Denmark (7 MDRs), Switzerland (5 MDRs), France (4 MDRs) and China (1 MDR).

5.2 Overview of MDRs

A total of 4 heater-cooler device manufacturers and 55 unique UFs are represented across the 180 MDRs with reported patient infections and/or contamination of the heater-cooler device. Table 1 categorizes the MDRs by the reported device manufacturer, brand name and the origin of the report as either US or OUS. Of the 55 UFs involved, there were 3 UFs reporting two different manufacturers of heater-cooler devices.

Table 1. MDRs by Manufacturer, Brand Name and User Facility (US vs. OUS)

MDRs by Manufacturer and UF				
Manufacturer and Brand Name	Total # of MDRs	Number of User Facilities Represented in the MDRs		
		US	OUS	Total*
LivaNova/Sorin Stockert 3T	160	15	35	50
Maquet HCU20, HCU30 & HCU40	9	0	5*	5*
Cincinnati Sub-Zero 333W and Hemotherm	3	2*	0	2*
Terumo HX2	8	1*	0	1*
Total	180	16 (2*)	39 (1*)	55 (3*)

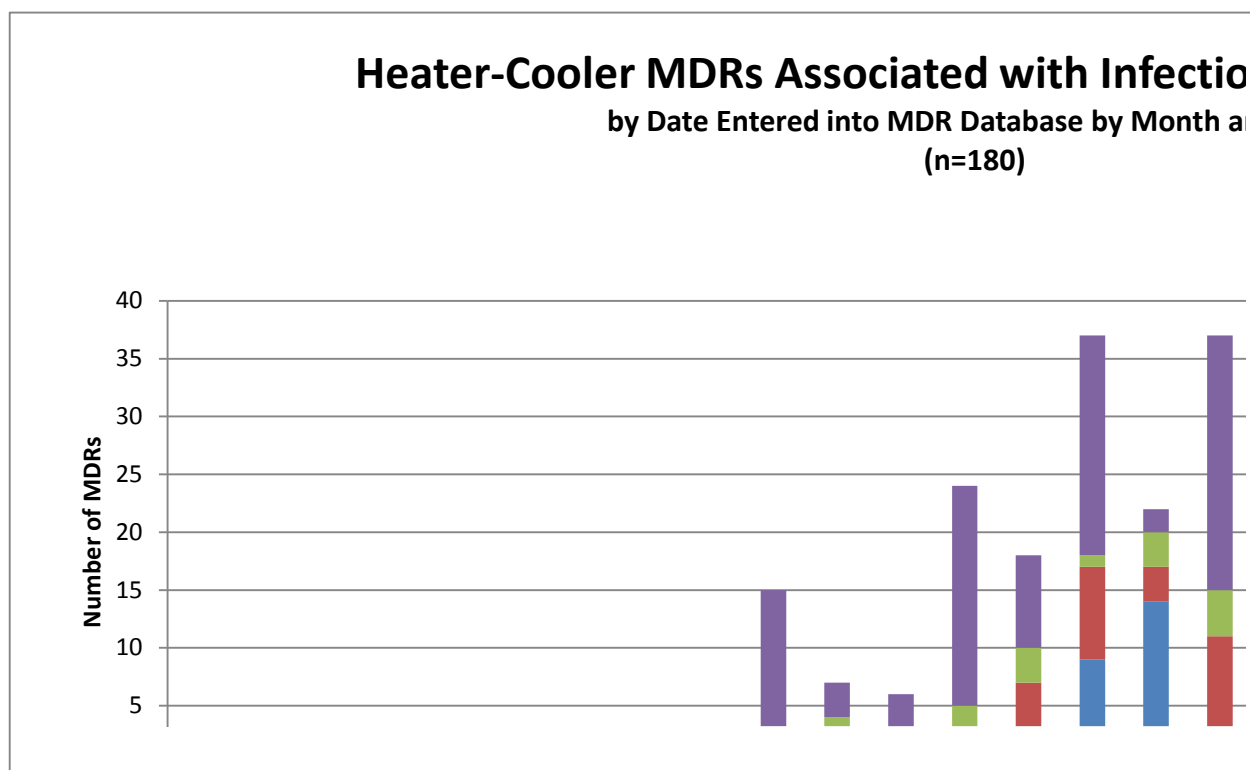
*Note that 3 UF reported devices from 2 different manufacturers

LivaNova/Sorin devices have approximately 60% of the US marketshare for this type of device. In Europe, the market share is higher.

Reported Problems

The MDRs were individually reviewed for adverse events reported as patient infection potentially related to use of a HCD or device contamination where there was no mention of a patient infection. There were 61 MDRs which identify patient infections and 119 MDRs which identify device contamination without mention of a patient infection. Note that there may be multiple MDRs on the same event in cases where both the manufacturer and the UF submit MDRs. The MDRs were further stratified by UF in their geographical origin (US and OUS). Figure 1 illustrates the 180 MDRs entered into the MDR database over time by month and year categorized by patient infection or device contamination both within the US or OUS.

Figure 1. MDRs entered into MDR database over time categorized by patient infection or device contamination



Each MDR was also reviewed for outcomes such as the number of infected patients, the number of patient deaths where an infection was reported, and the number of devices reported as being contaminated and further categorized by UF to identify unique events. These are not mutually exclusive as one MDR may report patient infections, deaths and contaminated devices. In some cases, an MDR may include a cluster of patients; therefore, the number of deaths and patient infections include the number of known patients involved and may not match the total number of MDRs. Table 2 identifies the number of involved patients and devices reported in the MDRs by manufacturer and brand name. Some MDRs imply more than one patient or one device without

determination of a specific number of cases. This is characterized by the “+” sign as likely being more than the number listed.

Table 2. Patient and Device Counts reported in MDRs by Manufacturer and Brand Name

Manufacturer and Brand Name	Total Number of MDRs	Patient Infections ¹		Patient Deaths ²		Device Contamination ³	
		US	OUS	US	OUS	US	OUS
LivaNova/Sorin Stockert 3T	160	40+	21+	7+	5	33+	111+
Maquet HCU20, HCU30 & HCU40	9	0	0	0	0	0	9
Cincinnati Sub-Zero 333W and Hemotherm	3	1	0	0	0	6	0
Terumo HX2	8	4	0	2	0	0	0
Total	180	45+	21+	9+	5	39+	120+

Note that MDRs may include information on more than one patient and/or device.

¹Patient infection identifies the total number of patients reported in the MDRs as having an infection.

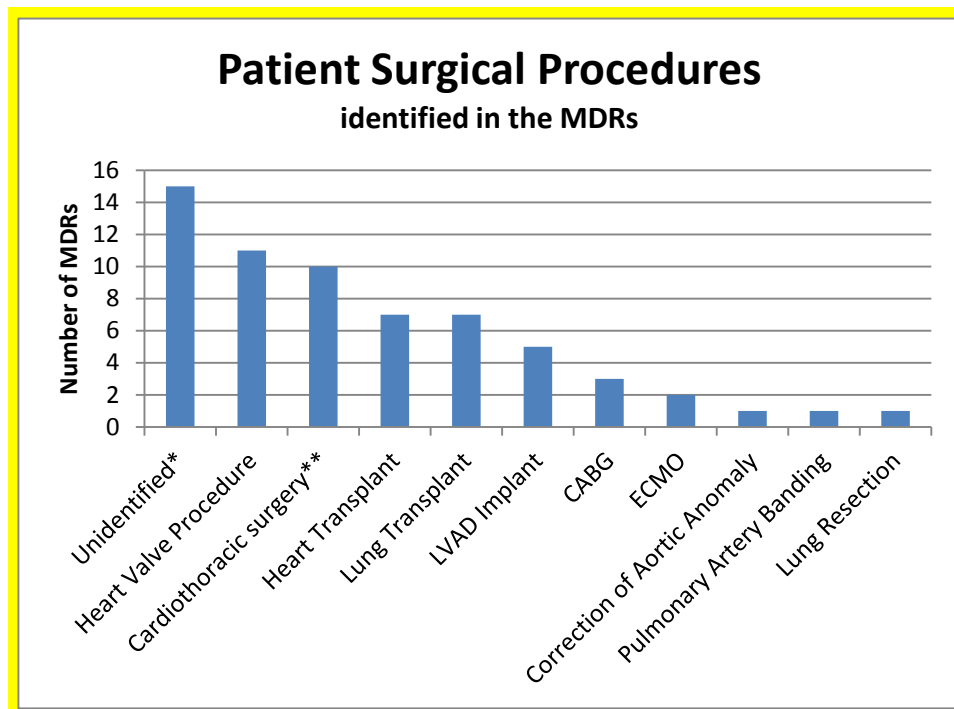
²Patient death identifies the number of patient deaths reported in the MDRs from the number of infected patients.

³Device contamination identifies the total number of devices as reported as being contaminated with or without known patient infection.

Reports of Patient Infections

Forty six of the 61 MDRs mentioning patient infections identified the patient's surgical procedure performed where the heater-cooler unit was used. The MDR counts identifying the types of procedures are depicted in Figure 2.

Figure 2. Patient Surgical Procedures mentioned in the MDRs



Note that one MDR may include multiple procedures during the surgical intervention.

* Surgical procedure was unknown or not identified

**Unspecified Cardiac/Cardiothoracic Procedure

LVAD (Left Ventricular Assist Device Implant)

CABG (Coronary Artery Bypass Grafts)

ECMO (Extracorporeal Membrane Oxygenation)

Among the 61 MDRs reporting patient infection, there were 48 reports which identified the diagnosis and/or location of infection. The time to event occurrence (TTEO) information was obtained in 33 MDRs based on the reported date of patient's infection diagnosis relative to the date of the surgical procedure, as specified in the narrative text of the MDR. Table 3 identifies the types of patient infections identified in the MDRs with the TTEO when this information was available.

Table 3. Types of Patient infections reported in the MDRs with TTEO

Diagnosis/Location of Infection	MDR counts	TTEO* Range (months)	TTEO* Mean (months)
Surgical wound infections	15	2.5 - 60	46
Unspecified	13	0 - 21	11
Endocarditis	12	2.5 - 51	26
Blood stream infection	11	0 - 60	19
Aortic root abscess	3	10 - 51	31
Empyema	2	4	4
Abdominal abscess	2	31	31
Disseminated infection	2	48	48
Driveline infection	2	31	31
Muscle Flap	2	3	3
Mycotic Aortic arch Pseudoaneurysm	2	10	10
Myocutaneous Thoracotomy Flap infection	2	10	10
Pericardial Abscess	2	31	31
Gastroenteritis	1	UNK	UNK
Mitral Valve ring infection	1	9	9
Septic Shock	1	0 - 39	20

*TTEO is time to the event occurrence when reported in the MDR narrative text

Note that one MDR may contain multiple infection diagnoses.

Type of Organisms identified in the MDRs

The MDRs were further classified by the type of organism identified in the patient infection and/or device contamination. Table 4 depicts the number of MDRs by the type of organism categorized by manufacturer and brand name.

Table 4. Type of Organism by Manufacturer and Brand Name as mentioned in MDRs

Type of Organism	LivaNova/Sorin Stockert 3T	Cincinnati Sub-Zero 333W and Hemotherm	Maquet HCU20, HCU30 & HCU40	Terumo HX2
Bacteria (unidentified)	25	0	2	0
Coliform/HPC*	2	1	0	0
<i>Cupriavidus pauculus</i>	0	2	0	0
<i>Legionella sp.</i>	1	0	0	0
<i>M. abscessus</i>	8	0	0	8
<i>M. avium</i>	5	0	0	0
<i>M. avium intracellulare</i>	1	0	0	2
<i>M. chimaera</i>	30	0	4	0
<i>M. fortuitum</i>	1	0	0	0
<i>M. intracellulare</i>	2	0	0	0
Mycobacterium (unspecified)	53	0	1	0
NTM/Atypical Mycobacteria	21	0	0	0
<i>Pseudomona aeruginosa</i>	1	0	2	0
Unidentified organism	12	0	0	0
Totals	162	3	9	10

*HPC- Heterotrophic Plate Count

Note that the counts do not equal the number of MDRs as there are cases where multiple organisms may be identified in one MDR.

Of note, a recently published European epidemiologic study describes a link between *M. chimaera* clinical isolates from infected cardiothoracic patients with samples from the HCDs used during these patient's procedures, and with environmental samples from the manufacturer's production line including samples from devices in the manufacturer's production and servicing facility. The paper suggests a point source for the *M. chimaera* infections among the European patients exposed during open chest cardiac surgery, deriving from one specific heater-cooler device – the Livanova/Sorin Stockert 3T^{xi}.

Further evaluation via whole genome sequencing is presently being conducted on clinical isolates from *M. chimaera* infections that have been identified among US patients exposed during open chest cardiothoracic surgery as well as on samples from the HCDs in operation during their surgeries to determine if the US *M. chimaera* infections associated with the Livanova/Sorin Stockert 3T also originate from the same point source as the European cases.

6. Heater Cooler Devices (HCD)

Heater cooler devices (HCDs) are devices that provide temperature controlled water to 1) oxygenator heat exchangers, 2) cardioplegia heat exchangers, and/or 3) warming/cooling blankets to effect thermal exchange. These heater cooler devices include water tanks, pumps and tubing that provide the temperature-controlled water to the external heat exchangers or warming/cooling blankets through closed water circuits (i.e., not intended to come into contact with the patient or the circulating blood, or bodily fluids).

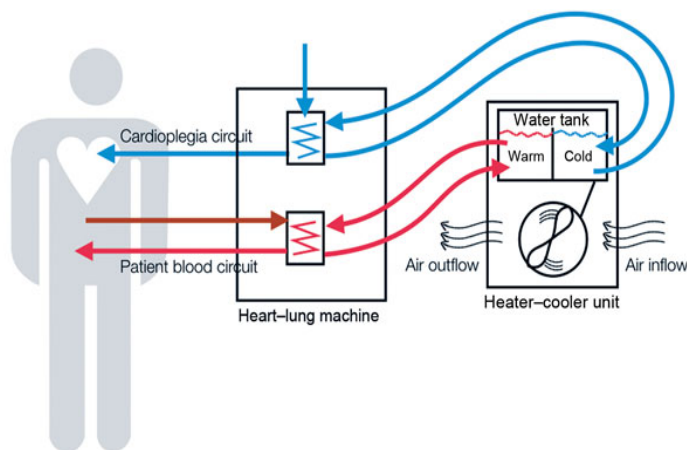




Figure 3: HCD Pathwaysⁱⁱⁱ

Heater-cooler devices are intended to be used during cardiothoracic surgeries for up to 6 hours, as well as other medical and surgical procedures to warm or cool a patient to optimize medical care and improve patient outcomes.

In the U.S., there are five manufacturers of HCDs. Of those companies, LivaNova/Sorin holds the U.S. largest market share; approximately 60% of HCD units. Table 5 below identifies a sampling of HCDs that are currently in use in the U.S. from these five manufacturers:

Table 5: HCD Manufacturers and Models

Manufacturer/ Distributor	Model(s)	Image*
LivaNova/Sorin	Stockert 3T	
Maquet	HCU30	
CardioQuip	MCH 1000(i)	
Terumo	TCM II	

Cincinnati Sub Zero	Hemotherm 400CE		
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* All images used with permission of manufacturers

6.1 Pre-market Evaluation of HCDs

HCDs are Class II devices. Manufacturers of HCDs must submit 510(k) premarket notifications for new devices to FDA for review and clearance prior to marketing in the US. HCDs are cleared under one of two regulations:

- 870.4250 Cardiopulmonary Bypass (CPB) Temperature Controller (product code DWC)
- 870.5900 Thermal Regulating System (product code DWJ)

21 CFR 870.4250 (product code DWC) defines CPB temperature controller as a device used to control the temperature of the fluid entering and leaving a heat exchanger. These devices are generally used in patients undergoing cardiothoracic/cardiovascular surgeries requiring an extracorporeal circuit and an open-chest procedure (e.g. full sternotomy, mini thoracotomy). The thermal regulating systems (product code DWJ) are labeled for use with warming/cooling blankets and may use other mechanisms besides water-based technology (i.e. forced air, electrical, etc.) to heat or cool the patient.

This panel will focus on Cardiopulmonary Bypass Temperature Controllers (DWC), which utilize water and are primarily used in the operating room. It should be noted that recommendations made for Cardiopulmonary Bypass Temperature Controllers can be applied to the water-based thermal regulating systems (DWJ) as applicable.

HCDs used for cardiopulmonary bypass have been in use in the US since the 1960s - that is before FDA regulations of medical devices existed (often referred to as pre-1976 or pre-amendment devices).

In general, FDA's premarket review of HCDs includes an evaluation of the following:

- Device technology
- Electrical Safety/ Electromagnetic compatibility
- Mechanical testing of the hardware

- Performance testing regarding heating/cooling capability
- Software testing
- Labeling

The labeling includes the cleaning/disinfection procedure to be followed for the heater-cooler device. Since the temperature controlled water circuit is a closed circuit, with no intended patient or blood contact, and the device is non-sterile, the health risk to the patient was considered very low. As such, FDA has not historically required the submission and premarket review of the cleaning/disinfection protocols for these devices. However, under the quality system regulations (21 CFR Part 820), manufacturers are required to have testing protocols and validation data supporting their cleaning/disinfection procedures within their own files.

Notwithstanding the recent published European epidemiologic investigation that link *M. chimaera* clinical samples from infected cardiothoracic patients, with samples from the HCDs and from the manufacturer's production line suggesting an *M. chimaera* point source from one specific heater-cooler device, other heater-cooler devices (as described in the previous section on 'Infections reported to FDA') have also been associated with *M. chimaera* (and/or other NTM) infections and/or device contamination.

Since heater-cooler device contamination appears to be a recurring challenge, not limited to a single manufacturer's device, FDA has taken a holistic approach. The Agency is actively working with each of the manufacturers to appropriately validate their cleaning and/or disinfection procedures. Human factors testing is incorporated to demonstrate that the labeled procedures result in an acceptably disinfected product (i.e., will minimize water contamination and inhibit biofilm formation), and to assure that the instructions can be effectively followed by the anticipated end user. It is important to note that cleaning and/or disinfecting the heater-cooler devices outside or in excess of the manufacturer's labeled procedures may result in a damaged device.

6.2 Device-Related Challenges Contributing to Contamination

As described in Section 4, NTM is widespread in nature, and can be found in the water in hospital plumbing and the water found on manufacturing lines. Below we discuss several pathways regarding how NTM may be introduced into the heater cooler devices and/or water circuits, and how/why contamination/re-contamination seems to be a recurring problem. Heater cooler devices are not sterile medical devices, nor are they intended to be sterilized for their labeled intended use.

6.2.1 Design Challenges

Water Tank and Other Circuit Component Access

While some HCDs allow the end user access to the tank by lifting a lid, other HCDs do not have practical access to the inside of the water tank to permit cleaning. Access to the heater-cooler device water tank and the ability to mechanically clean the tanks (i.e., scrubbing with detergents) prior to disinfecting may be necessary to keep these water tanks and circuits at an acceptable level of contamination. However, once a biofilm has formed, it is extremely difficult, if not impossible, to remove even with mechanical scrubbing. (Please refer to Section 4 above). Additionally, even when access to the tanks is feasible, other components, such as metal coils (used for heating or cooling the water) and pumps are found inside the tanks, and may hinder the ability to effectively clean the tanks prior to disinfection. Since disinfection procedures alone will not remove a biofilm, consideration should be given to the inclusion of a cleaning process (e.g., with detergents) prior to each disinfection as part of regular system maintenance. However, there are some components (e.g. tubing, connectors, etc.) that are unable to be reached via a cleaning procedure using mechanical scrubbing. Therefore, manufacturers should not only consider device designs that allow for effective cleaning, but also consider providing specific time intervals or time of use of the device at which reusable components should be replaced.

Connection to Other Circuit Components

The heater cooler device is connected to several extracorporeal circuit components – e.g., the oxygenator heat exchanger, the cardioplegia heat exchanger, and in some cases a patient warming/cooling blanket. These external devices may contain reusable components that are not part of the heater cooler device disinfection process (e.g., tubing, connectors, blankets, etc.). Therefore, if NTM was originally introduced into the circuit, and the reusable circuit components are not part of the heater cooler device’s disinfection process, then reconnection of a disinfected (or new) heater cooler device to the contaminated external reusable components would readily contaminate or re-contaminate the heater cooler device.

Water Agitation within Tanks

Agitation inside water tanks, created by, for example, mixing components, pumps, and the return water circuit inlet, have the potential to produce air bubbles. These bubbles attract the hydrophobic NTM, and the amount of bubbles could influence the amount of aerosolized NTM within the tank. All of the HCD models have the capability to create water bubbles within their tanks; however the methods and amount of water agitation within the tank(s) vary by manufacturer due to device design differences (e.g., location of water recirculation inlet, water flow rate, speeds of mixing components/pumps, etc.).

Water/Air Filters

Some HCDs contain water and/or air filters (i.e., wire mesh); others do not. Water and air filters with the appropriate pore sizes should be able to remove most NTM from tap water and capture aerosolized NTM bacteria, respectively. However, not all currently used HCDs contain water and air filters that would be suitable for this need.

Fans/Vents

Fans are found on all units and are usually used to cool the electronics and/or aid in the cooling efficiency of a compressor. The fan speeds range from 20 cubic feet per minute (CFM) to over 700 CFM. The fan location varies with some of the units having fans on the front or back and others on the bottom. These fans may facilitate the movement of aerosolized NTM from the inside of the unit into the operating room, and possibly into the sterile surgical field (via laminar flow disruption).

Vents are found on all units, and, as with the fans, their locations vary with the different HCDs (i.e., some on the sides of the HCD, some on top, and some on the bottom). The location of the vent(s) and where the air from the fan is exhausted may play a role in disturbing airflow in the operating room.

HCD Operating Temperatures

The heating mechanism varies by unit, e.g., electronic resistance heating with coils to warm the water, inline heaters, etc. The temperature of the water may inhibit or facilitate NTM proliferation and the growth of biofilm. The typical temperature range of the water during operation of HCDs is well suited for NTM survival.

Future HCD Design Considerations

These HCD design features, and possibly others, may contribute to NTM biofilm formation within the water pathways and release of NTM into the environment. New or modified HCD design features can be considered for reducing or mitigating NTM growth and/or aerosolization. Evaluating the optimal designs of tank geometry, tank and circuit materials, internal tubing location, replacement schedule, temperature and/or flow rate of the circulating water, and disinfection/cleaning procedures/frequency are suggested considerations.

The committee will be asked to discuss device design features that could be improved in the future in order to mitigate aerosolization and minimize patient infection.

6.2.2 Labeling Challenges

Manufacturer's Water Recommendations

The heater cooler devices contain one or more water reservoirs (several liters in volume) within the unit. The various manufacturers recommend different types of water to be used to fill the water reservoirs in their units. These recommendations include tap water, distilled water, decalcified water, and filtered tap water. Most units remain filled with the same water between cases, until the recommended cleaning/disinfection schedule in the manufacturer's labeling indicates that the water in the circuit should be replaced (this varies among manufacturers and can be from 1 to 4 weeks). In between water changes, more water will be added to the tanks to account for volume changes within the circuit. Some heater cooler devices utilize ice to cool the circuit water while others use a compressor and refrigerant. During disinfection, the tanks are rinsed with water prior to refilling for the next use.

FDA's Safety Communication recommends the use of either filtered tap water with a 0.2 micron filter or sterile water to reduce the risk of the source water having NTM and introducing the bacteria into the tanks. It is also important to remember that filtered or sterile water needs to be considered for filling (including ice making), re-filling, topping-off and cleaning/rinsing of the HCDs, so as not to introduce NTM into the water circuit.

Inadequate Cleaning/Disinfection Procedures

Currently, the majority of heater cooler units recommend the use of chemical disinfectants to disinfect the water tank and circuits, while cleaning is conducted only on the exterior of the device. It is unclear if a cleaning regime should be included prior to disinfecting the tanks and circuits in order to improve the efficacy of the disinfection process by disrupting biofilm formation and/or NTM proliferation. It is also known that biofilms and microorganisms, including NTM are being found in heater-cooler devices, even after the health care facilities have followed the recommended disinfection procedures. It is apparent that the currently recommended procedures for disinfection may not be adequate. The effectiveness of cleaning and disinfection procedures should be supported by the following:

- 1) Validation of the cleaning and disinfecting procedure (by the manufacturer) to an acceptable endpoint/level (log reduction), before being recommended in the labeling. FDA's proposed validation procedures are detailed in Section 8.3 of this document;
- 2) The procedures in the labeling need to be strictly followed by the hospital staff; and
- 3) The procedures need to be written in a way that the end-users can follow them and obtain a disinfected product as demonstrated during the manufacturer's validation procedures.

Regular Maintenance/Serviceing

HCDs need regular preventative maintenance (i.e. change internal tubing, check fans, etc.), usually recommended at specified intervals (based on time or hours of use) to be performed by the manufacturer or trained representatives. Some manufacturers offer an optional training program on servicing the HCD for hospital staff; while others have service manuals and/or servicing contracts. Due to differences in device design, these servicing contracts and training programs differ among the manufacturers. It is unclear whether the servicing contracts and training programs currently available are adequate to mitigate NTM proliferation, biofilm generation and ultimately patient infections – e.g., are servicing periods appropriate? Are the maintenance procedures appropriate? Future contracts, programs and manuals should prioritize their schedules and procedures to keep mitigation of clinically relevant device contamination a priority.

6.2.3 Point Source Contamination Challenges

Manufacturing Line

NTM may be introduced at the manufacturing site since disinfection and validation of the HCD (using tap water) is conducted prior to release from the facility. FDA is currently conducting inspections of manufacturers of heater cooler devices and will be obtaining water samples from the manufacturing line as well as reviewing the manufacturing process to determine whether there is the possibility that NTM are introduced into the devices at the time of manufacture. It is hoped that advanced molecular diagnostics including whole genome sequencing (WGS) of NTM isolates, in particular *M. chimaera* but also *M. abscessus* may shed light on the question of a point source of contamination.

Locating the source(s) of NTM contamination remains elusive. There may be one point-source or many sources responsible for the introduction of NTM into the heater-cooler devices (e.g., tap water, ice machines, manufacturing line, etc.). The challenges we face with attempting to identify the source(s) include genotyping method limitations, a long latency period between initial infection and symptomatic disease, traceability back to a specific heater-cooler unit, mutation of the mycobacteria over the latency period, etc. In the case of many sources, it may be impossible to maintain a NTM-free HCD over time.

The committee will be asked to comment on FDA's safety communication and provide additional, if any, suggestions for devices on the market that may help mitigate or minimize patient infections from aerosolized NTM.

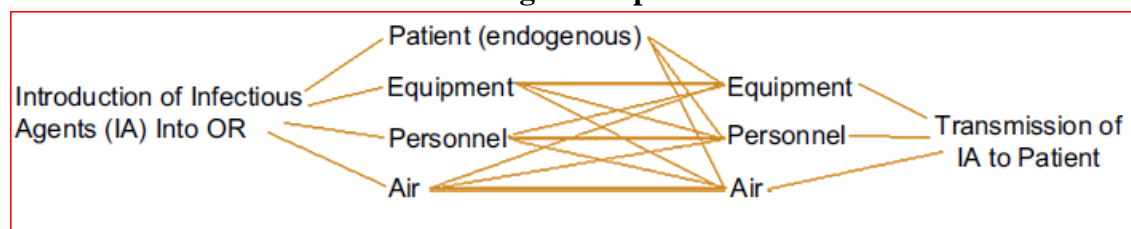
7. Environmental Contributors to HCD-Related Infections

Due to the complexity and global nature of the problem, our approach has included investigating this challenging issue from many different angles, in addition to device design. Published literature provides additional insight into NTM behaviors, NTM routes of transmission, and how the environment in which the heater cooler unit is used contributes to HCD-related NTM infections in patients. As noted in several papers, possible sources of NTM in the OR environment resulting in patient infections include the following elements^{xii, xiii}:

- Operating room personnel and their clothing
- Surgical instruments and equipment, and
- Operating room air

These elements are in constant interaction as noted in Figure 4:

Figure 4. Interactive permutations of factors that could end in transmission of infectious agents to patients^{xi}.



Our investigations have led us to believe that the most likely source of patient infection is through operating room (OR) air.

7.1 Transfer of NTM from the HCD into the Operating Room air

The transmission of NTM from contaminated water within the HCD to an airborne pathogen within the operating room environment requires two steps: aerosolization of the NTM within the HCD water tank(s), and transmission of this aerosolized NTM within the water tank into the operating room environment.

Aerosolization of NTM within the HCD

The pathway from an HCD water tank into the operating room environment necessitates the assumption that the NTM becomes airborne. An overview of how NTM can become aerosolized is provided in Section 8. The resulting NTM film droplets are very small in size, and can undergo desiccation which enhances their potential to remain airborne for prolonged periods of time and can be carried by Operating Room (OR) air currents over several meters. Moreover, the concentration of mycobacteria on the ejected water droplets can be 1,000 to 10,000-fold greater relative to the concentration of the mycobacteria in the contaminated water inside the HCD tanks.

As mentioned in the previous section, there are several different device design aspects that allow all heater cooler devices to have the capability of creating water bubbles within their tanks. If NTM are found in higher concentrations on the surface of air bubbles found in water, and all of the HCDs have the capability to create water bubbles within their tanks, then all of the heater cooler devices have the capacity to aerosolize NTM within their water tanks.

Transmission of Aerosolized NTM within the water tank(s) into the OR

The water tanks within the heater cooler devices are not air tight or water sealed. Areas of communication between the tank(s) and the inside of the unit (casing) and/or directly into the operating room include the tank lid, circulating water inlet/outlet locations, pump introduction location(s), temperature probe introduction location(s), etc. Once the aerosolized NTM escape into the HCD casing, any opening in the HCD casing (e.g., vents) will permit the NTM to enter the operating room environment. Additionally, most of the HCDs have a fan(s), which may facilitate movement of the aerosolized NTM laden water droplets into the OR through the exhaust vent(s).

Air Flow in the OR

The HCD is placed outside the sterile field, and the patient is under a protective laminar flow of air – laminar airflow is intended to provide unidirectional airflow over the patient to keep the sterile field contaminant-free. Turbulent airflow is undesirable in a surgical environment as it disrupts the unidirectional vertical air flow protection over the surgical field. It is therefore believed that when the protection provided by the laminar vertical airflow is disrupted, particles such as aerosolized NTM already suspended in the OR air as droplet nuclei may settle inside the open wound during cardiothoracic surgeries. It is hypothesized that once the aerosolized NTM are in the OR air environment, the NTM may remain suspended in the air, traveling on air currents, until reaching the surgical field. This possible route of transmission was studied by Sommerstein et al. The study suggests that disruption of the protective laminar air flow due to the heater cooler device exhaust fan, may create enough turbulence to permit a pathway for the aerosolized NTM to find its way into the sterile field and ultimately into the patient’s open chest cavity^{xi}.

Overall OR Infection Control Prevention

Established HVAC-related infection control measures, including proper air quality (filtration, humidity, temperature), air volume and maintaining positive pressure, proper air flow direction and UV-C lighting for germicidal irradiation may also help ensure a reduction in the transmission of airborne pathogens, including *M. chimaera*.

8. Considerations for Cleaning/Disinfection of HCDs

As noted above, the validation of the procedures for cleaning and disinfecting HCD water circuits have not been previously evaluated or considered by FDA. In addition, there are no

guidance documents or standards for validating the effectiveness of cleaning or disinfection processes for HCD water circuits.

FDA believes that validation of cleaning and disinfection processes for heater-cooler device (HCD) water circuits should demonstrate that soil and contaminants will be effectively removed and that the microbial load in the water system has been reduced to levels that will minimize biofilm formation and aerosolization of NTM. The validation testing would also ideally demonstrate that the manufacturer's recommended frequency for cleaning and disinfection processes maintains the quality of the water circuits over time with repeated use and periods of inactivity.

The committee will be asked to comment on the recommended routine maintenance by the manufacturer and an acceptable level of bacterial contamination in the water pathways upon release of a new or serviced HCD from the manufacturer.

8.1 Acceptable levels of microbial contamination in water

The EPA National Primary Drinking Water Regulations or primary standards are legally enforceable standards that apply to public water systems. Primary standards protect public health by limiting the levels of contaminants in drinking water. The Table of Regulated Drinking Water Contaminants includes microbial content, including limits for specific waterborne disease-causing organisms as well as a Heterotrophic Plate Count (HPC) of no more than 500 bacterial colonies per milliliter (<500 cfu/ml).

The FDA recognized standard, ANSI/AAMI 13959:2014 Water for hemodialysis and related therapies, sets limits for microbial counts in water used for hemodialysis. The standard indicates that total viable microbial counts in dialysis water shall be less than 100 cfu/ml or lower if required by national legislation or regulations. The limit is based on rates of pyrogenic reactions related directly to the number of bacteria in dialysis fluid.

The standard also indicates that an action level shall be set based on knowledge of the microbial dynamics of the system. Typically, the action level will be 50 % of the maximum allowable level or 50 cfu/ml. The action level was established to allow the user to initiate corrective action before levels exceed the maximum levels established by the standard.

The committee will be asked to comment on the appropriateness of existing standards or limits for microbial water quality for use as a surrogate when determining acceptable levels of NTM in the circulating water in the HCD water pathways.

8.2 Regulatory Approach for validation of decontamination, cleaning and disinfecting of non-HCD water circuits

FDA regulates disinfectants intended for reprocessing reusable medical devices, including high, intermediate, and low level disinfectants. These include Medical Washer Disinfectors (see Special control guidance document)^{xiv}.

8.2.1 Disinfectants

FDA regulates germicides used to disinfect medical devices. High level disinfectants are regulated as Class II medical devices under 21 CFR 880.6885 and undergo premarket review for substantial equivalence. The FDA guidance document, *Guidance for Industry and FDA Reviewers Content and Format of Premarket Notification [510(k)] Submissions for Liquid Chemical Sterilants/High Level Disinfectants – 2000*, describes the information, including performance validation testing, that should be provided in a 510(k) submission. High level disinfectants are most commonly used to reprocess semi-critical medical devices, such as endoscopes and ultrasound probes.

General purpose disinfectants, which includes low level disinfectants and intermediate level disinfectants, are regulated as Class I medical devices under 21 CFR 880.6890 and are exempted from premarket notification requirements. Low level disinfectants and intermediate level disinfectants also require registration as pesticides under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) by the Environmental Protection Agency (EPA). EPA specifies the information that must be submitted for registration and reviews the safety and effectiveness data for these disinfectants.

8.2.2 Water Purification Systems (WPS) and Dialysate Delivery Systems (DDS) Disinfectants

FDA has also reviewed and cleared products intended for disinfection of water distribution systems in dialysis facilities, water purification systems (WPS) for dialysis, and dialysate delivery systems (DDS), although no specific guidance document for these disinfectants exists. In addition, FDA recognizes standards that set limits for microbial levels in water used for hemodialysis (ANSI/AAMI 13959:2014 Water for hemodialysis and related therapies^{xv}) and describe the requirements for water treatment equipment, including disinfection equipment, used to produce water for hemodialysis^{xvi}. The disinfection equipment includes ultraviolet irradiators, hot water disinfection systems, and ozone disinfection systems.

FDA also regulates disinfectants that are intended for reprocessing dialysate delivery systems as Class II medical devices under 21 CFR 876.5860 which are subject to premarket review for substantial equivalence. Disinfectants intended for reprocessing water purification systems for

hemodialysis are regulated as Class II medical devices under 21 CFR 876.5665 and are exempted from premarket notification requirements. The FDA guidance document, *Regulatory Status of Disinfectants Used to Process Dialysate Delivery Systems and Water Purification Systems for Hemodialysis; Guidance for Industry and FDA*, released in 2002, explains the risks that patients are exposed to and clarifies the regulatory status of disinfectants as accessories to dialysate delivery systems and water purification systems used in hemodialysis.

Table 6: Disinfectant Regulatory Classifications

Disinfectant	Classification	510(k) Requirements?	Device Use
High level disinfectant	Class II 21 CFR 880.6885 Liquid chemical sterilants/high level disinfectants	Yes <ul style="list-style-type: none"> Guidance on the Content and Format of Premarket Notification [510(k)] Submissions for Liquid Chemical Sterilants and High Level Disinfectants; Final 	Semi-critical medical devices, such as endoscopes and ultrasound probes
Low and intermediate level disinfectants	Class I 21 CFR 880.6890 General purpose disinfectants EPA registration as a pesticide	Exempted	Non-critical medical devices and equipment surfaces
Dialysate delivery systems (DDS) disinfectant	Class II 21 CFR 876.5820 Hemodialysis system and accessories 21 CFR 876.5860 High permeability hemodialysis system and accessories	Yes	Dialysate delivery systems

Disinfectant	Classification	510(k) Requirements?	Device Use
Water purification subsystems disinfectant	Class II 21 CFR 876.5665 Water purification system for hemodialysis	Exempted	Water purification systems for hemodialysis
Dialyzer reprocessing system	Same as DDS	Yes	Disinfectants intended for reprocessing dialyzers

Although DDS and WPS do not make direct contact with the patient or the patient’s blood, the dialysate produced by the dialysate delivery system with water purified by the water purification system may pick up toxins or other contaminants from bacteria in these systems. These contaminants potentially can cross the semi-permeable membrane into the blood during dialysis.

Similarly, HCDs do not have direct contact with the patient or their blood during use. However, as described above, the water can become contaminated and may be aerosolized and cause patient infections. Therefore, the methods for validating the disinfection of the water purification systems for hemodialysis may be used as an example.

8.3 Proposed Adapted Regulatory Approach for HCDs

The following information is based on the validation testing of disinfectants used to decontaminate water purification and distribution systems. **FDA is proposing that this information be adapted to HCDs and used by manufacturers to validate their decontamination, cleaning and disinfecting processes.**

Qualification of Disinfectant

Potency tests are conducted to demonstrate the potential use of the products for decontamination and disinfection of medical devices by establishing a broad spectrum of microbicidal activity of the test germicide. Therefore, the recommended disinfectant should be either an EPA-registered disinfectant with tuberculocidal efficacy, or the following tests should be conducted to establish that the microbicidal activity of the test germicide. The recommended potency tests are standardized benchmark tests that allow products to be compared one to another. Manufacturers should conduct all potency testing under worst case conditions and according to the recommendations for the contact conditions specified in the germicide labeling.

- Tuberculocidal Activity of Disinfectants (AOAC 6.3.06:1995, Official Method 965.12) [AOAC 6.3.06:1995, Official Method 965.12] in which the carrier challenge is quantified or a quantified suspension test (Ascenzi, 1987) - You should use an appropriate nontuberculous waterborne mycobacterium (*Mycobacterium abscessus*, *Mycobacterium fortuitum*, or *Mycobacterium mucogenicum*).
- Fungicidal Activity of Disinfectants Using *Trichophyton mentagrophytes* (AOAC 6.3.02:1995, Official Method 955.17) [AOAC 6.3.02:1995, Official Method 955.17]
- AOAC Use-Dilution Method or AOAC Hard Surface Carrier Test Testing Disinfectants Against *Salmonella choleraesuis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, Use-Dilution Methods (AOAC 6.2.01:1995, Official Methods 955.14, 955.15, and 964.02)[AOAC 6.3.02:1995, Official Method 955.17]
- Virucidal Test previously recommended by the EPA for its germicide registration program (EPA DIS/TSS-7, November 12, 1981) [EPA DIS/TSS-7, November 12, 1981]

8.3.1 Manufacturer Decontamination, Cleaning, and Disinfection Validation

The HCD manufacturer should conduct simulated use testing to demonstrate the effectiveness of the recommended cleaning and disinfection processes. The testing should incorporate the following elements:

Test devices: The validation testing should consider the condition of the HCDs to be tested. A HCD that has been exposed to repeated cycles of use, cleaning and disinfection, and descaling represents a worst case situation for testing because the components may develop surface cracking or pitting which will make the surfaces more difficult to clean and disinfect.

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

Test organisms: The validation testing should include relevant waterborne test organisms, including *Pseudomonas aeruginosa* and *nontuberculous mycobacterium*, for example, *Mycobacterium abscesses*, *Mycobacterium fortuitum*, *Mycobacterium mucogenicum*, *Mycobacterium avium*, *Mycobacterium chimaera* and other relevant microorganisms.

Inoculation method: The most difficult areas of the device for the germicide to penetrate should be inoculated. The procedure for inoculating the test system should reflect the worst case use conditions that the system and germicide would experience in a hospital setting. The inoculum should be allowed to circulate and stand for a time period corresponding to the recommended interval between disinfection periods noted in the labeling. For example, if the machine labeling

recommends that the system be disinfected at the end of each week, then the inoculation method should reflect the same time period and use conditions.

Challenge quantification: The number of each organism recovered from one of the inoculated test devices or systems should be quantified. This procedure serves to estimate the actual microbial challenge to the germicide. All areas that could become colonized, such as water tanks, tubing, connections, and filters, should be microbiologically evaluated before and after the disinfection cycle.

Recovery method: The recovery method should be validated and the recovery conditions (media, temperature, and time) should be documented that they are adequate to detect low numbers of injured organisms. For example, the device should be inoculated with 10 cfus of the test organism or 100 cfus of injured test organism and then recovered to demonstrate that the method is capable of recovering the small number of organisms.

Sampling water: Water samples should be collected at specified sites along the circuit. A sufficient volume of water should be collected to allow for detection of low numbers of organisms and then membrane filtered and cultured on the appropriate media.

Sampling surfaces: Those areas of the test system identified as difficult for the germicide to penetrate, such as water tanks, tubing, and connections for the HCD and mated surfaces, joints, headers, and should be swabbed. The swab should be immersed in extraction fluid with neutralizer and sonicated to remove any viable bacteria. The extraction fluid should be membrane filtered and cultured on the appropriate media.

Internal surfaces: Culture the internal surfaces of the test system for viable organisms by culturing representative sections of the tubing. Direct culture of the tubing should be considered, whenever possible.

Treatment: Inoculated system should undergo label decontamination, cleaning/disinfection, process using minimal worst case conditions.

8.3.2 End User In-Use / Actual-Use Decontamination, Cleaning, and Disinfection Validation

The HCD manufacturer should conduct in-use testing of the cleaning and disinfection processes under actual use conditions in a clinical setting. In the testing, the cleaning and disinfection processes should be conducted by healthcare personnel that are responsible for using, implementing the cleaning and disinfection processes and maintaining the circuits and have been instructed to clean and disinfect the device according to the device label or the hospital protocol. No extraordinary methods of device preparation should be employed prior to exposure to the germicide. The device should be filled, operated, and maintained according to the label

instructions over an extended period of time under conditions that replicate worst case use conditions for the HCD water circuits including periods of inactivity. Water, surface swab samples, and internal surface samples should be collected over the test period to demonstrate that the cleaning and disinfection / maintenance process is sufficient to control microbial levels and contamination of unit at specified acceptable levels. The microbial load (bioburden) in representative control devices should be quantified before and after the cleaning and disinfection steps. In a recent publication by Garvey, et al^{xvii}, three different decontamination regimens were evaluated for reducing the microbial load in a HCD. The authors concluded that a decontamination cycle, including an initial replacement of internal tubing with weekly microbiological water samples is required to maintain the water quality within HCDs at an acceptable level.

The chemical germicides used to decontaminate, clean, and disinfect the HCD water circuits may damage these devices or lead to deterioration of the materials in these devices, including surface cracking or pitting that may lead to leaks in the system and will make the surfaces more difficult to clean and disinfect. FDA would like to recommend testing be conducted to demonstrate the compatibility of the germicide with the water system materials and components following repeated cleaning and disinfection processes. The testing would address the effects on the functionality, material compatibility, and specifications of the HCD water circuits.

8.4 Endpoints for disinfection

8.4.1 Low and intermediate level disinfection:

- a. Low level disinfection is a lethal process utilizing an agent that kills vegetative forms of bacteria, some fungi, and lipid viruses. Intermediate level disinfection is a lethal process utilizing an agent that kills viruses, mycobacteria, fungi and vegetative bacteria, but no bacterial spores.
- b. In the Class II Special Controls Guidance Document: Medical Washers and Medical Washer-Disinfectors, dated 3/7/02, FDA describes validation testing of low and intermediate level disinfection by medical washer-disinfectors and recommends the following endpoints during simulated use testing:
 - i. Low level disinfection: a 6-log reduction of a mixed suspension of typical vegetative organisms, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and representatives of the *Klebsiella*-*Enterobacter* group.
 - ii. Intermediate level disinfection: the 6-log reduction of the mixed suspension of vegetative organisms and a 3-log reduction of an appropriate mycobacterium

species. For thermal disinfection processes, FDA recommends the use of a thermophilic mycobacterium species.

8.4.2 High level disinfection:

- a. High level disinfection kills all forms of microbial life except for large numbers of bacterial spores. High level disinfection is indicated for disinfection of semi-critical medical devices that do not permit sterilization. These devices contact intact mucous membranes or non-intact skin.
- b. In the Class II Special Controls Guidance Document: *Medical Washers and Medical Washer-Disinfectors*, dated 3/7/02, FDA describes validation testing of high level disinfection by medical washer-disinfectors and recommends the following endpoints during simulated use testing:

6-log reduction of a mixed suspension of vegetative organisms, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, and representatives of the *Klebsiella*-*Enterobacter* group and a 6-log reduction of an appropriate mycobacterium species

- c. The recommended endpoints for simulated use testing to qualify a germicide as a hemodialyzer high level disinfectant and/or sterilant are as follows:

The germicide should show a minimum 6-log kill (microbicidal) of an appropriate nontuberculous mycobacterium (*M. abscessus*, *M. fortuitum*, or *M. mucogenicum*) species under the label contact and storage conditions.

8.4.3 Disinfection of HCD water circuit:

Based on the above recommended endpoints and similarities to disinfection of water purification systems for hemodialysis, FDA asks the committee to consider the following two endpoints for validation testing of HCD disinfection during simulated use testing:

- a. The germicide should show a minimum of a 3-log kill (microbicidal) of an appropriate nontuberculous mycobacterium (*M. abscesses*, *M. fortuitum*, or *M. mucogenicum*) species and a minimum of a 6-log kill (microbicidal) of the vegetative bacteria (*P. aeruginosa*, etc.) from the HCD water pathways under the label contact conditions.
- b. The germicide should show a minimum of a 6-log kill of an appropriate nontuberculous mycobacterium (*M. abscesses*, *M. fortuitum*, or *M. mucogenicum*) species and a minimum of a 6-log kill (microbicidal) of the vegetative bacteria (*P. aeruginosa*, etc.) from the HCD water pathways under the label contact conditions.

The committee will be asked to discuss how manufacturers should develop validated disinfection processes that properly challenge HCDs in a laboratory environment that would replicate real-world use.

9. Ethical Aspects

9.1 Potential Patient Factors

Patient factors that may also play a role in the susceptibility of contracting an NTM infection include the type of surgery and whether the patient has received an implant (e.g., heart valve, left-ventricular assist device [LVAD]). As mentioned earlier, most of the reported infections are in patients undergoing an open-chest procedure requiring the use of an extracorporeal circuit. As a matter of comparison, FDA has not received any reports of infection while having the HCD running in robotic surgeries. Many of the patients identified with NTM infections are linked or presumably linked to a surgery that implanted a sterile device (e.g., a heart valve, LVAD, a vascular prosthetic graft).

9.2 Patient Notification

As described in the introductory section, patients infected with NTM during an open chest cardiac procedure may not manifest symptoms for months to years after initial exposure. Identifying risk factors that correlate with an increased susceptibility of NTM infection is therefore an important public health matter, so that healthcare providers can be alerted and patients at increased risk notified to present for follow-up and potential monitoring.

Some healthcare facilities have already issued broad communications to all patients previously exposed to contaminated HCDs during the prior 4 year period.

Efforts are also underway to create patient risk stratification criteria or tiered guidelines for notification based on an accepted case definition. For example, criteria that could be utilized might include:

- Type of surgery
- Whether the surgery involved placement of a prosthetic valve, vascular graft, or other implanted device
- When the surgery occurred
- Whether the facility had contaminated devices with or without NTM aerosolization
- Whether the facility has identified patient infections vs. device-only contaminations

Recently, CDC issued guidance to assist facilities in identifying patients with NTM infections associated with exposure to heater-cooler units in order to help ensure timely diagnosis and treatment of patients (<http://www.cdc.gov/hai/pdfs/outbreaks/Guide-for-Case-Finding.pdf>).

The committee will be asked to discuss what methods could be implemented for identification and tracking of potentially infected patients (e.g., registries, electronic health records etc.)

With respect to notification, what would be the best approach and appropriate time periods for healthcare providers to communicate with potentially infected patients without creating undue alarm?

10. Summary

Heater-cooler devices serve a critical function in often life-saving or life-sustaining cardiothoracic procedures. These Class 2 devices are not sterile and are not patient contacting. Specifically, they are closed circuits which do not interface with patient's blood, body fluids or mucous membranes. Traditionally, the risk of infection from these reusable devices was therefore considered very low. Validation of cleaning and disinfection procedures, while required under the quality system regulation, has not been subject to premarket review requirements.

FDA believes that the benefits of open chest cardiac surgery with cardiopulmonary bypass outweigh the risks in appropriately selected patients. Yet, the recently demonstrated potential for NTM transmission from the HCD to a patient via aerosolization in the OR, although uncommon, remains a serious public health concern. The NTM infections that have been reported in the US and Europe linked to prior cardiothoracic procedures have caused serious illness and death.

Several strategies have already been implemented to mitigate the risk of HCD contamination with NTM as well as to reduce potential for its airborne transmission by directing the device vents away from the patient and the sterile field. FDA is presently working with each of the HCD manufacturers to develop more robust cleaning and disinfection test methods and validated instructions for use. Questions, however, persist as to how clean is clean enough to enhance the safety margin of these devices, and what standards should be employed for microbial water contamination.

The recognized challenges of cleaning and disinfection of the heater-cooler device have been attributed to its design features. Innovation and modifications to device design that could

potentially overcome the inherent difficulties in attaining the necessary cleaning and disinfection and that can reduce or eliminate propensity for aerosolization are also key strategies to consider.

FDA's Circulatory Devices Advisory Committee is therefore being asked to discuss: (1) The effectiveness of cleaning and disinfection methods for heater-cooler devices; (2) The amount and type of premarket data and information needed to demonstrate validation of cleaning and disinfection of heater-cooler devices in support of labeling claims and technical instructions; (3) The appropriate risk mitigations to be implemented by manufacturers of heater-cooler devices and/or hospital facilities to ensure patient safety during surgical procedures where these devices are used; and (4) The appropriate guidelines and/or criteria based on a risk stratification schema for notifying patients who may have already been exposed to NTM during prior cardiac surgeries.

11. Appendices

Appendix A: October 2015 FDA Safety Communication

Appendix B: FDA Heater-Cooler Webpage

Appendix C: ECDC Risk Assessment

Appendix D: MHRA Medical Device Alert and Public Health England Safety Alert

Appendix E: CDC Interim Practical Guidance

Appendix F: Pennsylvania Dept. of Health Advisory

Appendix G: CDC Interim Guide for the Identification of Possible Cases of Nontuberculous Mycobacterium Infections Associated with Exposure to Heater- Cooler Unit Devices

12. Glossary

- Aerosolization: is the process or act of converting some physical substance into the form of particles small and light enough to be carried on the air i.e. into an aerosol.
- Cardioplegia: is the intentional and temporary cessation of cardiac activity, primarily for cardiac surgery
- Circuit: Path through which water travels through multiple devices including the oxygenator, heat exchanger, warming/cooling blanket, the heater-cooler device, etc.
- CFU: A colony forming unit refers to individual colonies of bacteria, yeast or mold. Colony forming units are used as a measure of the number of microorganisms present in or on surface of a sample.
- FIFRA : The Federal Insecticide, Fungicide, and Rodenticide Act (**FIFRA**) is a United States federal law that set up the basic U.S. system of pesticide regulation to protect applicators, consumers, and the environment.

- HPC: Heterotrophic plate count is an analytic method that measures colony formation on culture media to measure the variety of heterotrophic bacteria that are common in water.
- Water pathways: the route through which water travels within the heater cooler device and components – e.g., those components included with the disinfection procedures.

13. Literature References

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- ⁱ Sax, H. et al. Prolonged Outbreak of Mycobacterium chimaera Infection After Open-Chest Heart Surgery. *Clin Infect Dis* 2015;61:67-75
- ⁱⁱ Kohler, P. et al. Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated Mycobacterium chimaera infections subsequent to open heart surgery. [Eur Heart J.](#) 2015;36:2745-2753
- ⁱⁱⁱ Achermann, Y. et al. Prosthetic Valve Endocarditis and Bloodstream Infection Due to Mycobacterium chimaera. *J. Clin. Microbiol.* 2013;51:1769-1773
- ^{iv} Sommerstein, R. et al. Transmission of Mycobacterium chimaera from Heater-Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System. *Emerg Infect Dis.* 2016 Jun
- ^v Information provided by The Society of Thoracic Surgeons (STS)
- ^{vi} Sousa, S. et al. Nontuberculous mycobacteria pathogenesis and biofilm assembly. *Int J Mycobacteriol.* 2015;4:36-43
- ^{vii} Schulze-Robbeke, R. And Buchholtz, K. Heat Susceptibility of Aquatic Mycobacteria. *Appl. Environ. Microbiol* 1992; 58:1869-1873
- ^{viii} Falkinham, III. Common Features of Opportunistic Premise Plumbing Pathogens. *Int. J. Environ. Res. Public Health* 2015, 12, 4533-4545
- ^{ix} Tortoli, E. Clinical manifestations of nontuberculous mycobacteria infections, *Clin. Microbiol. Infect.* 15 (2009) 906–910.
- ^x Blanchard, D.C. and Syzdek, L. (1970) Mechanism for the water-to-air transfer and concentration of bacteria. *Science* 170, 626–628
- ^{xi} <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22461>
- ^{xii} Thiele, R.H. Et al. The "six sigma approach" to the operating room environment and infection. [Best Pract Res Clin Anaesthesiol.](#) 2008;22:537-52

^{xiii} Fencel, <http://www.healthcarefacilities.today.com/posts/Hospital-infection-control-reducing-airborne-pathogens--5523>, 2014

^{xiv} <http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/gastroenterology-urologydevicespanel/ucm445599.pdf>

^{xv} http://my.aami.org/store/sitecontent/previewfiles/13959_1409_preview.pdf

^{xvi} ISO 26722:2009, Water Treatment Equipment for Hemodialysis Applications and Related Therapies

^{xvii} Garvey, M. et al. Decontamination of heater-cooler units associated with contamination by atypical mycobacteria. *J Hosp Infect.* 2016 Mar 28. pii: S0195-6701(16)00127-4. doi: 10.1016/j.jhin.2016.02.007. [Epub ahead of print]