

## October 2016

### **Frequently Asked Questions (FAQs) Regarding Potential Risk of Non-Tuberculous Mycobacteria (“NTM”) Infection in Response to CDC’s Health Alert Network Communication and Publication in Morbidity and Mortality Weekly Report, and Related FDA Safety Communication**

- Q1: What new information regarding LivaNova’s 3T heater-coolers is provided in the CDC’s Health Alert Network Communication and Morbidity and Mortality Weekly Report released on October 13, 2016?*
- Q2: We understand the FDA issued a new Safety Communication in response to the CDC’s Health Alert Network Communication and MMWR publication. What does the FDA say about this issue?*
- Q3: Why did LivaNova issue a Field Safety Notice Update?*
- Q4: What do we need to do in response to the Field Safety Notice Update?*
- Q5: How does this new information relate to the EuroSurveillance article published earlier this year?*
- Q6: Why are the CDC and FDA focused on 3T heater-coolers manufactured prior to September 2014?*
- Q7: How do I know when my 3T heater-coolers were manufactured?*
- Q8: Do the EuroSurveillance, CDC or FDA publications mean that all 3T heater-coolers manufactured before September 2014 (the date a post- production disinfection process was adopted at the manufacturing site) are contaminated with NTM?*
- Q9. Is there a serious risk to continuing to use 3T heater-coolers?*
- Q10: The FDA stated in the new Safety Communication that the agency is aware of some 3T devices manufactured after September 2014 which have tested positive for M. chimaera. What is the company’s position on this?*
- Q11: What information is known about the potential risk of NTM transmission at this time?*
- Q12: What further investigation has LivaNova done to understand this issue?*

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<sup>1</sup> LivaNova PLC is a U.K. holding company with a number of wholly-owned subsidiaries, including Sorin Group Deutschland GmbH and Sorin Group USA, Inc. In this document, we refer to all entities using the brand name LivaNova.

Q13: *What has LivaNova done up to now to respond to this potential risk of infection?*

Q14: *What other recommendations does LivaNova have regarding maintenance of the device?*

Q15: *Who do we contact if we want to report a complaint or have questions about the Field Safety Notice Update or the 3T heater-cooler generally?*

**Q1: What new information regarding LivaNova’s 3T heater-cooler devices is provided in the CDC’s Health Alert Network Communication and Morbidity and Mortality Weekly Report released on October 13, 2016?**

**A1:** On October 13, 2016, the Centers for Disease Control and Prevention (“CDC”) released a publication in the Morbidity and Mortality Weekly Report (“MMWR”) describing the results of tests conducted by CDC and National Jewish Health in Denver, Colorado. According to the CDC’s report, these tests indicate that there appears to be genetic similarity between both patient and heater-cooler strains of the NTM bacteria *M. chimaera* isolated in Iowa and Pennsylvania. Given the geographic separation between the two hospitals performing the investigation, there may be a shared point source for the isolated NTM. The company is continuing to analyze the data referenced in the CDC MMWR. In conjunction with the MMWR report, CDC has also issued a Health Advisory on its Health Alert Network (“HAN”) that assesses certain risks associated with heater-cooler devices and provides guidance for providers and patients. These two communications can be found on the CDC’s website at:

- CDC MMWR publication:  
[https://www.cdc.gov/mmwr/volumes/65/wr/mm6540a6.htm?s\\_cid=mm6540a6\\_w](https://www.cdc.gov/mmwr/volumes/65/wr/mm6540a6.htm?s_cid=mm6540a6_w)
- CDC Health Advisory Number 397:<https://emergency.cdc.gov/han/han00397.asp>

**Q2: The FDA has issued a new Safety Communication in response to the CDC’s MMWR publication. What does the FDA say about this issue?**

**A2:** On October 13, 2016, the United States Food and Drug Administration (“FDA”) released a Safety Communication concerning issues raised regarding 3T heater-coolers in the CDC’s Morbidity and Mortality Weekly Report. In its Safety Communication, which can be found on the FDA’s website at <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm520191.htm> FDA provides the following guidance to users of the 3T heater-coolers:

- Heater-cooler devices known or suspected to be contaminated with NTM should be removed from service.

- Heater-cooler devices manufactured before September 2014 should only be used as directed by the FDA Safety Communication.
- Heater-cooler devices manufactured during or after September 2014 should be used in strict accordance with the Operating Instructions and facilities should take into account additional precautions specified in the FDA Safety Communication.

The company continues to believe that following the device's Operating Instructions is essential to mitigating the potential risk posed by using these non-sterile devices. The FDA Safety Communication confirms the importance of following the Operating Instructions.

**Q3: Why did LivaNova issue a Field Safety Notice Update?**

**A3:** LivaNova is committed to working closely with both FDA and CDC to address their concerns about this industry issue and to ensure continued clinician access to this important medical device. Therefore, LivaNova and its representatives are proactively and voluntarily contacting 3T heater-cooler users to inform them of the new information in CDC's HAN and MMWR communications, and the FDA's Safety Communication, and to help facilitate implementation of the agency recommendations outlined in those publications.

**Q4: What do we need to do in response to the Field Safety Notice Update?**

**A4:** The Field Safety Notice Update is being distributed to all U.S. customers of record of the 3T heater-coolers. Customers should carefully review CDC and FDA communications and consider the benefits and risks of continued use of the specified devices. All 3T heater-cooler customers of record will be contacted by LivaNova representatives to help facilitate implementation of FDA's and CDC's recommendations. LivaNova will also seek to understand users' cleaning and disinfection practices and to obtain results of water quality monitoring where available.

**Q5: How does this new information relate to the EuroSurveillance article published earlier this year?**

**A5:** In April 2016, EuroSurveillance published a Surveillance and Outbreak Report ("the EuroSurveillance Report") with the results of the authors' investigation regarding *Mycobacteria chimaera* ("*M. chimaera*") infections involving heater-coolers.<sup>2</sup>

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<sup>2</sup> S. Haller et al., *Surveillance and Outbreak Report: Contamination during Production of Heater/Cooler Units by Mycobacterium Chimaera Potential Cause for Invasive Cardiovascular Infections: Results of an Outbreak Investigation in Germany, April 2015 to February 2016*, EURO SURVEILL. (April 28, 2016), <http://www.eurosurveillance.org/images/dynamic/EE/V21N17/art22461.pdf>

The EuroSurveillance Report stated that the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, "BfArM"), a German regulatory agency, had received incident reports of heater-coolers from various manufacturers that were contaminated with NTM. Included in the EuroSurveillance Report were surveillance results from certain clinical cases of contaminated heater-coolers as well as details of environmental investigations in Germany. In addition to *M. chimaera*, other types of NTM were reported to be found in various cardiac surgery centers in Europe.

The EuroSurveillance Report suggested that there may be a link between the infected patients and the *M. chimaera* found in samples obtained in 2014 and 2015 from environmental investigations at the 3T heater-cooler manufacturing site. The EuroSurveillance Report noted that preliminary genotype results appeared to indicate that the strains of *M. chimaera* found in infected patients, used heater-coolers, and the manufacturing site appeared to be almost identical.

All 3T heater-coolers undergo functional testing at the manufacturing site to ensure the devices are in good working order prior to shipment. Heater-coolers are non-sterile devices, and the 3T heater-cooler Operating Instructions have always instructed customers to perform an initial disinfection of the device upon installation and before first use. However, in August 2014, as knowledge of this issue increased, LivaNova implemented a post-production/pre-shipment disinfection process at the 3T heater-cooler manufacturing site to help further mitigate the risk of bacterial contamination of the devices. The company also implemented monitoring for NTM presence at the manufacturing site. Thus, the 2014 samples referenced in the EuroSurveillance article were taken *prior to* implementation of the disinfection process adopted at the manufacturing facility under which new machines are disinfected after manufacturing but prior to shipment. The sample from June 2015 was obtained in the pump assembly area at the manufacturing site which is upstream of the pre-shipment disinfection process. Samples were also taken in 2014 and 2015 from two used heater-coolers that had been returned to LivaNova for investigation. Both of these units were produced prior to implementation of the disinfection process adopted at the manufacturing facility in August 2014.

The EuroSurveillance report recommended that users continue to adhere to the Operating Instructions and Field Safety Notices issued by all manufacturers of heater-coolers. FDA released a Safety Communication on June 1, 2016 addressing the EuroSurveillance article; this Safety Communication is available on the FDA's website at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm504465.htm>.

**Q6: Why are the CDC and FDA focused on 3T heater-coolers manufactured prior to September 2014?**

**A6:** CDC is reporting that its testing indicates what appears to be a genetic similarity between both patient and heater-cooler strains of the NTM bacteria *M. chimaera* isolated in Iowa and Pennsylvania hospitals and the Sorin Group Deutschland GmbH manufacturing site. As described above, in order to help further mitigate the risk of bacterial contamination of the devices, LivaNova implemented a post-production/pre-shipment disinfection process at the 3T heater-cooler manufacturing site in mid-August 2014. As is the case with the testing reported in the EuroSurveillance article, the CDC report concerns samples taken from machines that were manufactured prior to the company's implementation of the post-production/pre-shipment disinfection process.

**Q7: How do I know when my 3T heater-coolers were manufactured?**

**A7:** All 3T heater-coolers have a label affixed to the back panel of the device showing the serial number (beginning with 16S-) and date of manufacture. Also, as noted above, all 3T heater-cooler customers of record will be contacted by LivaNova representatives to help facilitate implementation of the FDA's and CDC's recommendations. You will be asked for the serial number(s) of the 3T heater-cooler(s) at your facility, at which time LivaNova will be able to confirm the date of manufacture for each device if it is not readily apparent upon inspection.

**Q8: Do the CDC, FDA or EuroSurveillance publications mean that all 3T heater-coolers manufactured before September 2014 (the time when a post-production disinfection process was adopted at the manufacturing site) are contaminated with NTM?**

**A8:** No, the data in the CDC, FDA and EuroSurveillance publications, and the company's own data, do not support a conclusion that all heater-cooler devices manufactured before September 2014 were contaminated with NTM at the manufacturing site. Moreover, LivaNova's Operating Instructions for the 3T System have instructed the user to conduct cleaning and disinfection of the device before initial use for as long as the device has been commercially distributed in the United States. The company's documentation demonstrates that there is a scientific basis for the cleaning and disinfection process, and the company believes that a properly maintained device (one cleaned and disinfected prior to initial use and in accordance with the Operating Instructions), where all other aspects of the Operating Instructions are carefully followed, poses minimal risk of NTM transmission.

Nonetheless, as noted above, LivaNova is committed to working closely with both FDA and CDC to address their concerns about this industry issue and ensure continued clinician access to this important medical device. Therefore, LivaNova and its representatives are proactively and voluntarily contacting 3T heater-cooler users to

inform them of the new information in the MMWR and the FDA's Safety Communication, and to help facilitate implementation of the agency recommendations outlined in those publications.

**Q9: Is there a serious risk to continuing to use 3T heater-coolers?**

**A9:** Heater-cooler devices have become essential in the open-heart surgery environment and generally, there are no reasonable alternatives to use of such products. The potential risk of airborne NTM transmission from heater-cooler devices has only recently been recognized, and while the understanding of this potential risk continues to evolve, post-surgical infection due to airborne NTM appears to be exceedingly uncommon. As FDA currently states on its website, "[f]or most patients, the benefit of undergoing a surgical procedure recommended by their doctor outweighs the risk of infection." HEATER-COOLER DEVICES: INFORMATION FOR PATIENTS, FOOD AND DRUG ADMINISTRATION, <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/CardiovascularDevices/Heater-CoolerDevices/ucm492585.htm>.

However, consistent with FDA's and CDC's recommendations, LivaNova is recommending (i) that 3T heater-coolers known or suspected to be contaminated with NTM should be removed from service, (ii) that 3T heater-coolers manufactured before September 2014 should only be used as directed by the FDA Safety Communication, and (iii) that 3T heater-coolers manufactured during or after September 2014 should be used in accordance with the Operating Instructions and facilities should take into account additional precautions specified in the FDA Safety Communication, as more fully described in the Field Safety Notice Update and Question 2 above.

**Q10: The FDA stated in the new Safety Communication that the agency is aware of some 3T devices manufactured after September 2014 which have tested positive for M. chimaera. What is the company's position on this?**

**A10:** In August 2014, the company implemented a validated post-production/pre-shipment disinfection process at the 3T heater-cooler manufacturing site to help further mitigate the risk of bacterial contamination of the devices. The company also conducted monitoring of the validated post-production/pre-shipment disinfection process. The presence of mycobacteria was not detected in the devices during the monitoring.

The company believes FDA's statement refers to two (2) user reports concerning 3T heater-cooler devices manufactured after September 2014 that were reported to be contaminated with Mycobacterium chimaera. LivaNova's investigation of these reports found that the devices were likely contaminated at the user facilities. The company is not aware of M. chimaera patient infections associated with 3T devices that were manufactured after September 2014. Similarly, FDA states in its Safety Communication

that, to date, the agency is also not aware of *M. chimaera* patient infections associated with 3T heater-cooler devices that were manufactured after September 2014

**Q11: What information is known about the potential risk of NTM transmission at this time?**

**A11:** LivaNova has previously conducted, and is continuing to conduct, extensive testing and data collection to understand how NTM transmission may be occurring during the use of heater-cooler devices. In this process, the company has consulted numerous experts to understand this phenomenon. The current thinking of the company is as follows:

- The failure to clean and disinfect a water circuit of a heater/cooler can allow biofilm formation. NTM is known to proliferate in biofilm and may lead to contamination of the heater/cooler water circuit.
- In operation of the device, air bubbles may be generated in the water tanks and then exit the device as aerosolized particles. The NTM present in the water may be carried by aerosolized particles out of the tank.
- Via air flow, the aerosolized particles may then be dispersed into the surrounding environment.
- The state of scientific knowledge provides no evidence that NTM can be transmitted via water evaporation because individual water molecules formed by evaporation are too small to carry the bacteria.

The literature currently available highlights that a key consideration with potential NTM transmission is the nature of the organism at issue. NTM is a ubiquitous environmental contaminant that is present in many water supplies, in the air, and in other non-sterile environments. NTM is also frequently identified in hospital environments. Consequently, in a non-sterile environment, such as outside of the sterile field of an operating room, NTM can certainly be present. NTM presence can result in post-surgical infection only if directly transmitted to the patient.

LivaNova's 3T heater-cooler is cleared by FDA as a non-sterile device. Like other equipment used outside of the surgical field during open-heart procedures (such as anesthesia machines and pharmacy carts, for example), heater-coolers are not sterile and cannot practically be used in a sterile fashion. Sterility of the water circuit during device operation is also not possible, as the devices are operated and maintained in non-sterile environments. Furthermore, since the 3T heater-cooler water circuits are physically separated from the blood circuit and are not intended to come into contact with this circuit, it is not necessary for the water circuit to remain sterile. The periodic

cleaning and disinfection procedures described in the device's Operating Instructions are intended to control biofilm formation and bacterial growth.

**Q12: What further investigation has LivaNova done to understand this issue?**

**A12:** Since the company became aware of this issue, the company has proactively conducted an investigation into the issue of potential NTM infection, and has had ongoing conversations with numerous government regulatory agencies. It is important to note that the initial report received by the company in 2014 described airborne NTM, a phenomenon that had not been previously known to either the company or the scientific or physician community. The company undertook an intensive investigation into how this might occur, essentially creating new knowledge to understand the phenomenon. This investigation has resulted in the company's current thinking about how NTM may become aerosolized and dispersed, as described in the answer to Question 10 above. Our investigation work continues in close collaboration with FDA.

**Q13: What has LivaNova done up to now to respond to this potential risk of infection?**

**A13:** LivaNova has taken the following actions, among others, in its investigation and response:

- **Device Manufacturing and Design Changes**

- The company implemented a post-production/pre-shipment disinfection process at the production facility in mid-August 2014 to supplement the pre-existing cleaning and disinfection process in the field.
- The company implemented additional manufacturing measures to mitigate the risk of NTM (e.g., drying process, disinfection of production equipment, use of PALL-filtered water, monitoring for NTM presence at certain points of the manufacturing process, and hot disinfection of water basin of pump assembly area).
- The company implemented design changes for devices in production (e.g., replacing device tubing, plugging unused overflow outlet).

- **Device Labeling**

- The company previously communicated to customers the newly identified potential risk and importance of continuing to adhere to the cleaning and disinfection process.

- The company has also provided information to customers regarding how to handle devices suspected of contamination and how to conduct environmental monitoring.
- LivaNova's Operating Instructions for the 3T System have included instructions for cleaning and disinfection as long as the device has been commercially distributed. Failure to perform adequate cleaning and disinfection per the Operating Instructions has the potential to lead to contamination, including NTM contamination. As more information has become available and while our investigation is ongoing, the device's cleaning and disinfection regimen has been revised to require: more frequent disinfection of the water circuit (e.g., disinfection every two weeks rather than quarterly) with specified disinfectant solutions; weekly water changes; and the addition of hydrogen peroxide solution to the water to act as a preservative and to further prevent biofilm formation. You can find the most current Operating Instructions at <http://www.livanova.sorin.com/products/cardiac-surgery/perfusion/hlm/3t>.

We are currently working with regulators to develop a solution to further mitigate the already low risk of NTM transmission, and ensure continued clinician access to this important device which enables lifesaving cardiac surgery.

**Q14: What other recommendations does LivaNova have regarding use or maintenance of the device?**

**A14:** LivaNova believes that patient safety requires a shared partnership between LivaNova and users of the 3T heater-cooler. LivaNova takes care in manufacturing the 3T heater-cooler and in providing comprehensive Operating Instructions to customers. To help ensure correct functionality, safety and cleanliness of the 3T heater-cooler and to further minimize risk to patients, the user must also perform the specified routinely required tasks – these include cleaning and disinfection of the device before initial use of the 3T heater-cooler device and thereafter as indicated by the Operating Instructions, as well as regular maintenance checks. Depending on the nature of the service, these maintenance checks can be performed by LivaNova technicians or trained hospital personnel.

In addition to following the most current revision of the Operating Instructions, users should also follow the instructions provided in the June 2015 FSN and the August 2015 update to the FSN issued to 3T System users, as well as the October 2016 Field Safety

Notice Update. The 2015 FSN includes recommendations for environmental monitoring, as well as instructions for handling devices that were suspected of being contaminated.

Copies of these communications are available on the 3T System website: <http://www.livanova.sorin.com/products/cardiac-surgery/perfusion/hlm/3t>. As noted above, LivaNova and its representatives will be contacting 3T heater-cooler users to inform them of the new information in the MMWR and FDA's Safety Communication, and to help facilitate implementation of the agency recommendations outlined in those publications.

**Q15: Who do we contact if we want to report a complaint or have questions about the Field Safety Notice Update or the 3T heater-cooler generally?**

**A15:** LivaNova has an established system for receiving and processing any relevant information regarding complaints and evaluating any potential adverse events. Customer complaints can be received by LivaNova's Customer Service group or by any LivaNova Field Service Representative. LivaNova encourages reporting of complete information, so field experiences can be adequately evaluated and investigated.

LivaNova will be partnering with Stericycle to contact 3T heater-cooler users to inform them of the CDC's MMWR and FDA's Safety Communication, and to help facilitate implementation of the agency recommendations outlined in those publications. Stericycle will also field questions related to the Field Safety Notice Update through a dedicated email box [sorin6564@stericycle.com](mailto:sorin6564@stericycle.com) and toll-free hotline at 1-888-570-1653.

For general technical or service questions related to the 3T heater-cooler, please continue to call the LivaNova Technical Services Hotline at 1-800-221-7943, extension 6355.

For all other questions related to the 3T heater-cooler, please email [3T.US@LivaNova.com](mailto:3T.US@LivaNova.com).