Frequently Asked Questions (FAQs) Regarding Potential Risk of Non-Tuberculous Mycobacteria Infection in Response to New EuroSurveillance Article

Q1: What information is provided in the EuroSurveillance article?

A1: On April 28, 2016, EuroSurveillance published a Surveillance and Outbreak Report ("the Report") with the results of the authors' investigation regarding *Mycobacteria chimaera* ("*M. chimaera*") infections involving heater/cooler devices. 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 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/cooler units ("HCUs") that were contaminated with non-tuberculous mycobacterium ("NTM") from more than one manufacturer. Included in the report were surveillance results from certain clinical cases of contaminated HCUs as well as details of environmental investigations in Germany. In addition to *M. chimaera,* a specific type of NTM found in heater/cooler units from a certain manufacturing site, other types of NTM were reported to be found in various cardiac surgery centers in Europe. Furthermore, NTM was also found in HCUs produced by other manufacturers at other sites.

The Report stated that *M. chimaera* was found in samples taken: (1) from five (5) infected patients in Germany who had undergone open chest surgery; (2) from used heater/cooler units from various sites; and (3) from new heater/cooler devices and the environment at a certain manufacturing site. The Report suggested that there may be a link between the infected patients and the *M. chimaera* found at one manufacturing site in Germany. The Report noted that preliminary genotype results appear to indicate that the strains of *M. chimaera* found in infected patients, used HCUs, and the manufacturing site appear to be almost identical.

M. chimaera-positive samples were obtained from environmental investigations at the manufacturing site during the July 2014 to June 2015 time frame. The manufacturing

site referred to in the Report is a Sorin Group Deutschland GmbH[1] manufacturing site. Samples from the manufacturing facility in 2014 were taken prior to implementation of the disinfection process adopted at the manufacturing facility in August 2014, under which new machines are disinfected prior to shipment. The sample from June 2015 was taken in the pump assembly area at the manufacturing site which is upstream of the disinfection process. Samples were also taken in 2014 and 2015 from two used HCUs 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.

As noted above, in August 2014, a disinfection process was adopted by LivaNova at the manufacturing site. The company also implemented monitoring for NTM presence at the manufacturing site. In June 2015, LivaNova issued a Field Safety Notice to users of the 3T System which included recommendations for environmental monitoring, as well as instructions for handling devices that were suspected of being contaminated.

To date, LivaNova has received very limited access to the data that is referenced in this article. However, in the course of the company's own investigation regarding the potential link between NTM found at the manufacturing site and potentially related patient infections, LivaNova recently received information suggesting a link between the bacteria found at device's contract manufacturer site (prior to the manufacturer adopting a disinfection process) and at least one patient infection. The company is actively attempting to obtain more information about the possible link between the specific NTM found at the manufacturing site and potentially related patient infections.

The Report recommended that users continue to adhere to the Operating Instructions and Field Safety Notices issued by manufacturers of heater/coolers when using HCUs. LivaNova also encourages users to adhere to the provided Operating Instructions and issued Field Safety Notice.

Q2: What information is known about the potential risk of NTM transmission at this time?

A2: 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:

[1] 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. For this document, we will refer to all entities using the brand name LivaNova.

- 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 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 device ("3T System") is cleared by FDA as a non-sterile device. Like other equipment used outside of the surgical field during open-heart procedures (such as heart-lung machines), heater/cooler devices 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 device is operated and maintained in non-sterile environments. Furthermore, since the 3T System 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 as described in the device's Operating Instructions is intended to control biofilm formation and bacterial growth.

Q3: What further investigation has the company done to understand this issue?

A3: 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 described airborne NTM, a phenomenon that had not been previously known to either the company or the scientific 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 2 above.

Q4: What has the company done to respond to this potential risk of infection?

A4: LivaNova has taken the following actions, among others, in its investigation and response:

- **Device Manufacturing and Design Changes**
    - The company implemented a disinfection and drying 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 (e.g., disinfection of production equipment, use of sterile filtered water).
    - The company is implementing design changes for devices in production (e.g., replacing device tubing, plugging unused overflow outlet).
- **Device Labeling**
    - The company communicated to customers the newly identified potential risk and importance of continuing to adhere to the cleaning and disinfection process.
    - The company 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.

Q5: Is there a serious risk to continuing to use heater/cooler devices?

A5: Heater/Cooler devices have become essential in the open-heart surgery environment and generally, there are no reasonable alternatives to use of such products. While the literature is evolving, post-surgical infection due to airborne NTM appears to be exceedingly uncommon. For example, in an October 2015 publication, Public Health England stated: "This new risk is extremely small. Approximately 1 in 10,000 patients having this type of surgery might be affected. This level of risk is so small that surgery should not be delayed, as the risks of delaying surgery are greater than proceeding". The publication went on to state that "[t]his risk identified above is extremely small compared to the background risk of infection recognized following this type of surgery." *Infections Associated with Heater Cooler Units Used in Cardiopulmonary Bypass and ECMO: Information for Healthcare Providers in England*, PUBLIC HEALTH ENGLAND (Oct. 2015), https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/474218/Infections_associated_with_heater_cooler_units_version_1.pdf. 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.

The potential risk of airborne NTM transmission from heater/cooler devices has only recently been recognized, and the understanding of this potential risk is continuing to evolve. At this time, the company believes that a properly maintained device poses minimal risk of NTM transmission. LivaNova continues to actively seek appropriate solutions to mitigate any potential risk even further.

Q6: Does this article mean that all heater/cooler devices that were manufactured before August 2014 (the time when a disinfection process was adopted at the manufacturing site) are contaminated with NTM?

A6: No, the data in the article and the company's own data do not support the conclusion that all heater/cooler devices that were manufactured before August 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 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.

In addition to following the Operating Instructions, users should also follow the instructions provided in the June 2015 Field Safety Notice ("FSN") and the August 2015 update to the FSN issued to 3T System users. The FSN outlines steps to be taken when a device is suspected of contamination, including frequent cleaning and disinfection of the device and sampling the air and water from the 3T System. Copies of these communications are available on the 3T System website: http://www.livanova.sorin.com/ 3t.

Q7: What other recommendations does LivaNova have regarding maintenance of the device?

A7: LivaNova believes that patient safety requires a shared partnership between LivaNova and users of the 3T System. LivaNova takes care in manufacturing the 3T System and in providing comprehensive Operating Instructions for the System to customers. To help ensure correct functionality, safety and cleanliness of the 3T System 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 heater/cooler device and as indicated by the Operating Instructions, as well as regular maintenance checks.

In addition to following 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 described in the Answer to Question 6 above. Copies of these communications are available on the 3T System website: http://www.livanova.sorin.com/ 3t.

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 Field Service Representatives. The company encourages reporting of complete information, so field experiences can be adequately evaluated and investigated.

If you have additional questions, please email LivaNova 3T Support at 3T.US@LivaNova.com or call the Technical Services Hotline at 1-800-221-7943, extension 6355.