LivaNova

Health innovation that matters

December 2016 – Valid only for 3T Heater-Cooler users in the European Union

Frequently Asked Questions (FAQs) Regarding the FIELD SAFETY NOTICE UPDATE - ''Cardiac Surgery Mycobacterium Risks - Disinfection and Cleaning of Sorin Heater Cooler Devices''

Q1: Why did LivaNova[1] issue a Field Safety Notice Update?

Q2: What do customers need to do in response to the Field Safety Notice Update?

Q3: What is the difference between this FSN Update and the FSN issued in June 2015?

Q4: What is the deep-disinfection (DD) service?

Q5: How long does it take for a DD service?

Q6: Under which conditions can confirmed M. chimaera contaminated units access DD service?

Q7: Is there a timeline to submit requests for DD and when will units be processed?

Q8: Will LivaNova provide a loaner for all M. chimaera units undergoing a DD?

Q9: In cases where additional units are contaminated with M. chimaera at the same facility, will LivaNova provide multiple loaners?

Q10: Can contaminated units not confirmed for M. chimaera access the DD service?

Q11: How can I submit to LivaNova a request for DD and for a loaner?

Q12: How long does it take to perform a test for M. chimaera?

Q13: Is LivaNova providing a protocol for testing for M. chimaera?

Q14: What are the limitations for devices suitable for DD Service?

Q15: Why does LivaNova not provide DD service on devices produced before 2007?

Q16: How do I know when my 3T heater-coolers were manufactured?

Q17: Is there a serious risk to continuing to use 3T heater-coolers?

Q18: What information is known about the potential risk of NTM transmission at this time?

Q19: What further investigation has LivaNova done to understand this issue?

Q20: What has LivaNova done up to now to respond to this potential risk of infection?

Q21: What other recommendations does LivaNova have regarding use or maintenance of the device?

Q22: 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?

---

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. In this document, we refer to all entities using the brand name LivaNova.

Q1: Why did LivaNova issue a Field Safety Notice Update?

A1: On October 13, 2016, the United States Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) issued several communications related to nontuberculous mycobacterial (NTM) infections associated with the use of heater-cooler devices. The CDC Morbidity and Mortality Weekly Report ("MMWR") article describes the results of a genomic analysis of samples obtained from patients with NTM infections caused by Mycobacterium chimaera (M. chimaera). As the MWWR article acknowledges, the data presented therein is not new data; rather it appears to corroborate the conclusions previously presented in an April 2016 EuroSurveillance article by Haller, et. al. However, based on the data presented in this publication, LivaNova wished to proactively convey its recommended actions in all the countries of the European Union, in which there are options that are unavailable in the United States.

Q2: What do customers need to do in response to the Field Safety Notice Update?

A2: The Field Safety Notice Update is being distributed to all LivaNova Heater-Cooler customers of record in the European Union. Customers should carefully review this FSN Update and consider the benefits and risks of continued use of certain groups of devices. Updated recommendations are as follows:

1. Heater-cooler devices known or suspected to be contaminated with M. chimaera, based on the facility's testing program or other information known to the hospital, should be removed from the operating room or, if feasible, from service as soon as is practicable. We recommend contacting your LivaNova representative to arrange to have a deep-disinfection service performed prior to further use.

2. For facilities who have devices that are not known to be contaminated with M. chimaera, we recommend the following actions:

    a. Following the Operating Instructions for heater-cooler devices and specifically those relating to cleaning and disinfecting. We continue to believe that following these operating instructions is essential to mitigating the potential risk posed by using these non-sterile devices.

    b. If appropriate for your operating room, direct or channel the heater-cooler exhaust away from the patient, e.g., to the operating room exhaust vent per the Field Safety Notice "Cardiac Surgery Mycobacterium Risks issued in June 2015.

    c. Conducting water quality monitoring per the Field Safety Notice "Cardiac Surgery Mycobacterium Risks issued in June 2015.

    d. Using new accessories, tubing, and connectors to prevent recontamination when using a different heater-cooler device. Be aware that device contamination also may occur from other sources such as environmental contamination or device contact with contaminated accessories

Q3: What is the difference between this FSN Update and the FSN issued in June 2015?

A3: There is not a significant difference between this and prior FSNs. The primary difference is that LivaNova is advising to have units known or suspected to be contaminated with M. chimaera taken out of the OR or, if feasible, out of service as soon as is practicable and subjected to deep-disinfection prior to further use. This focus on M. chimaera is consistent with the CDC publication and the potential linkages between patient infections and heater-cooler devices by genotyping (DNA test). LivaNova's updated recommendations define a

different level of risk for units confirmed with M. chimaera contamination vs. other NTM or bacteria contaminations.

Q4: What is the deep-disinfection (DD) service?

A4: The deep-disinfection (DD) service is a special service implemented by LivaNova in 2015 that allows facilities to return heater-cooler units for a full cleaning, disinfection and replacement of connectors and tubing. The DD service is currently implemented at LivaNova facilities in Munich and is available within the European Union. Since its availability, the DD service has been frequently used by European facilities that knew or suspected contamination of their heater-cooler devices.

Q5: How long does it take for a DD service?

A5: The complete DD process requires a minimum of 10 weeks starting from when the unit is returned to LivaNova to when the unit is back to the hospital.

Q6: Under which conditions can a confirmed M. chimaera contaminated unit access DD service?

A6: As global leader in the heater cooler market, LivaNova is committed to both helping clinicians and institutions implement this updated FSN and supporting the continued use of our heater cooler devices, which are recognized as playing a critical role in the cardiac surgery OR around the world. Therefore, in line with the recommendations included in the updated FSN, the deep disinfection service will be made available in priority and free of charge to all facilities requesting it who will demonstrate to have a confirmed M. chimaera contaminated unit. While submitting your request for a DD service at LivaNova, you will be requested to file an official complaint to LivaNova and provide documentation to confirm the M. chimaera contamination according to your facility's testing protocol.

Q7: Is there a timeline to submit requests for DD and when will units be processed?

A7: All DD requests will have to be submitted before February 28th, at the latest. The HC units that have documented M. chimaera contamination can undergo prioritization immediately. At the moment, we have a good DD monthly capacity in place in Munich, which has allowed us to process many units that have requested DD in the past year. Therefore, we encourage facilities to request as soon as possible a DD service for a unit that is already known to be contaminated, in order to take advantage of any service slots currently available. For all units that will still have tests results pending when submitting a request, final documentation for M. chimaera contamination will be accepted until February 28th at the latest. To ensure the best possible service and to satisfy potential incremental requests moving forward, further DD capacity will be in place from January 2017 in Munich. If demand exceeds capacity, slots will be allocated according to a priority process in relation to the level of risk (M. chimaera being the first priority).

Q8: Will LivaNova provide a loaner for all M. chimaera units undergoing a DD?

A8: At the moment, both our global supply of 3T systems and our loaner availability are extremely limited. We are actively working to increase our supply and availability of loaners is expected to increase in the next few months. A loaner request can be submitted together with a DD request, and must arrive before February 28th, 2017. Once we have received all requests, LivaNova will consider them for prioritization by an internal, cross-functional committee, consistent with the updated FSN and aiming to ensure we can support as many institutions as possible at the same time. Absolute priority for the DD service as well as for a potential loaner will be given to units with a confirmed for M. chimaera contamination. There will be no charge for the approved 3T loaner device, shipping, installation or service, when related to units with confirmed M. chimaera contamination.

Q9: In cases where additional units are contaminated with M. chimaera at the same facility, will LivaNova provide multiple loaners?

A9: To ensure we can maximize the number of hospitals we can serve at the same time, we will allocate a maximum of one loaner device per institution. In case an institution has more than one device contaminated with M. chimaera, a rotation mechanism should be implemented. Once the first device is returned to the hospital after DD, a second device can be shipped to LivaNova for DD. When all devices will have completed DD and the last will be returned to the hospital, the loaner will have to be returned immediately to LivaNova.

Q10: Can contaminated units not confirmed for M. chimaera access the DD service?

A10: It is our goal to guarantee access to the DD service to all our customers, and therefore facilities who have contaminated units, but not confirmed to be M. chimaera contaminated, can certainly request a DD service. These units will be charged a fixed minimum fee. While submitting your request for a DD service at LivaNova, you will be requested to file an official complaint to LivaNova and provide documentation to confirm the contamination, according to your facility's testing protocol. In line with the risk level determined by this updated FSN, in the event loaner demand exceeds availability, confirmed M. chimaera contaminated units will be given the highest priority in the loaner allocation process.

Q11: How can I submit to LivaNova a request for DD and for a loaner?

A11: You may submit your DD request one of two ways:

1. Complete the deep-disinfection service request form available for download at http://www.livanova.sorin.com/products/cardiac-surgery/perfusion/hlm/3t-out-us and email them to sorin.fsn@stericycle.com
2. Call Stericycle and they will assist you in completing the necessary forms (please refer to A22 for more details on Stericycle)

Q12: How long does it take to perform a test for M. chimaera?

A12: It may take a maximum of 8 weeks

Q13: Is LivaNova providing a protocol for testing for M. chimaera?

A13: LivaNova will not provide a specific protocol for testing for M. chimaera. As indicated in the updated FSN, each institution is free to apply their own testing protocol.

Q14: What are the limitations for devices suitable for DD Service?

A14: The production date and age of the device is important for successful deep-disinfection service. Heater coolers produced before 2007 will not be suitable for the deep-disinfection process.

Q15: Why does LivaNova not provide DD service on devices produced before 2007?

A15:

a. Typical average useful lifetime of medical devices is ~10 years
b. Overall condition of older devices generally requiring additional repair work which is not included in the deep-disinfection service and would be subject to additional charges
c. Design changes during product lifecycle

We are currently working with regulators to develop a broad-scale 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.

Q16: How do I know when my 3T heater-coolers were manufactured?

A16: 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. In the Customer Response Form which is attached to the FSN Update, you will be asked to report the serial number(s) of all heater-cooler(s) in use at your facility.

Q17: Is there a serious risk to continuing to use 3T heater-coolers?

A17: 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 M. chimaera 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.

Q18: What information is known about the potential risk of NTM transmission at this time?

A18: 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 heater-coolers are cleared by Regulatory Bodies 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 LivaNova heater-cooler's 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.

Q19: What further investigation has LivaNova done to understand this issue?

A19: 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 18 above. Our investigation work continues in close collaboration with Competent Authorities.

Q20: What has LivaNova done up to now to respond to this potential risk of infection?

A20: 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**
  - In June 2015, LivaNova initiated a Field Safety Correcting Action, informing all customers on world basis about a newly identified risk associated with NTM infections in cardiac surgery and importance of continuing to adhere to the cleaning and disinfection process. LivaNova contacted all its HC customers globally to remind users the importance of following the company's disinfection and maintenance procedures, inform customers that bacteria may become aerosolized during H/C operation, serving as a source for contamination, provide customers with updated operating instructions regarding disinfection and maintenance procedures.

  - 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. The most updated operating instructions have been distributed in June 2015 as part of a FSN issued to all 3T System users globally.

- **Device services**
  - In 2015, LivaNova implemented a deep-disinfection service available within the European Union by which facilities can return the HCU for a full cleaning, disinfection and replacement of connectors and tubing. This service has been frequently used by facilities that observed or suspected contamination of their devices.

We are currently working with regulators to develop a broad-scale 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.

Q21: What other recommendations does LivaNova have regarding use or maintenance of the device?

A21: 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 issued to 3T System users, as well as the December 2016 Field 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-out-us. As noted above, LivaNova and its representatives will be contacting 3T heater-cooler users to help facilitate implementation of this updated FSN.

Q22: 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?

A22: 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 Representatives, 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.

For general technical or service questions related to the LivaNova heater-coolers, please continue to call your LivaNova Sales or Field Service or Technical Services representatives.

LivaNova will be partnering with a specialized company, Stericycle, to help facilitate implementation in the European Union of the recommendations outlined in this communication. Stericycle will also field questions related to the Field Safety Notice Update through a dedicated email box sorin.fsn@stericycle.com and toll-free hotline. The complete list of numbers for each individual country of reference is attached here following.

Contact Centre Toll-Free Lines

Country	CC Number	Notes / Language Support
Fax Number	+44 - 2080806540	Can be used internationally.
Italy	800-189-966	Italian
UK	0-800-014-8366	English
France	0800-914510	French
Belgium	0800-266-28	English, French
Netherlands	0-800-022-0441	English
Germany	0800-181-3333	German
Austria	0800-802705	German
Switzerland	0800-321-018	German, French, Italian
Spain	900-839248	Spanish
Portugal	800-180-405	English
Sweden	020-888-509	English
Denmark	8082-6009	English
Finland	0800-07-639	English
Norway	800-24-862	English
Ireland	1-800-904-112	English
Poland	0-0-800-141-0113	English
Czech Republic	800-880-909	English
Greece	800-848-1268	English
Cyprus	8009-4598	English
Bulgaria	+359 249 17435	**Toll Number - Mobile Enabled** - English
Romania	0-800-360-137	English
Hungary	**06-800-20470**	**Not mobile enabled -** English
Lithuania	**8-800-31544**	**Not mobile enabled -** English
Slovakia	**0-800-606-953**	**Not mobile enabled -** English
Latvia	8000-4535	English
Malta	+356 277 82028	**Toll Number - Mobile Enabled** - English
Luxembourg	800-2-8844	English, German, French
Estonia	**+372 8807982**	**Not a toll free number -** English