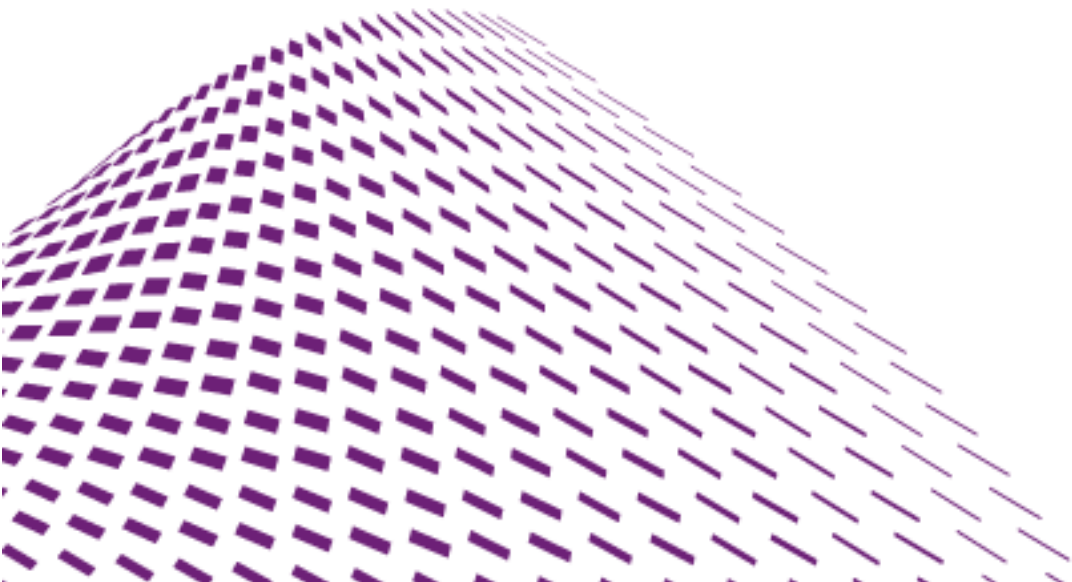




Circulatory System Devices
Panel of the Medical
Devices Advisory
Committee
June 2-3, 2016



Meeting Attendees Representing LivaNova

- **Brian Duncan, MD** – Vice President, Medical Affairs, Cardiac Surgery Business Unit, Arvada, Colorado
- **Thierry Dupoux** – Vice President, Quality and Regulatory Affairs, Cardiac Surgery Business Unit, Mirandola, Italy
- **Christian Peis** – Quality Director, Sorin Group Deutschland, Cardiac Surgery Business Unit, Munich, Germany
- **Paul Talbot, MS** – Quality Laboratory Services Manager, Cardiac Surgery Business Unit, Vancouver, Canada

Presentation Outline

- I. Introduction
- II. Overview
- III. NTM Background
- IV. Initial Report and Response
- V. Stakeholder Partnership
- VI. Medical Device Reporting
- VII. Cleaning and Disinfection
- VIII. Servicing
- IX. Ongoing Actions

LivaNova*: Our Commitment

- U.S. market leader in heater-cooler space
- Committed to patient safety
- Continued dialogue and collaboration with FDA
- Proactively engaged

- Issue:
 - Unusual and unexpected public health challenge posed by non-tuberculous mycobacteria (“NTM”)
 - Developing new knowledge to understand the potential risk to public health
 - Applying this understanding to develop best practices

*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 presentation, we will refer to all entities using the brand name LivaNova.

Heater-Cooler Overview

- Critical component of cardiac surgery procedures
 - Essential to achieve precise control of patient temperature during cardiac surgery
 - No reasonable alternatives to heater-cooler devices
- Not sold sterile and is not in the sterile surgical field
 - Heater-cooler devices are not sterile and cannot practically be used in a sterile fashion, much like other equipment used outside of the surgical field (such as heart-lung machines)
 - Periodic cleaning and disinfection described in the Instructions for Use (IFU) to control biofilm formation and bacterial growth

Indispensable Component of Cardiac Surgery

Heater-Cooler Overview (continued)

Non-Sterile Equipment



OR Lights



Anesthesia Machine



Heart-Lung Machine

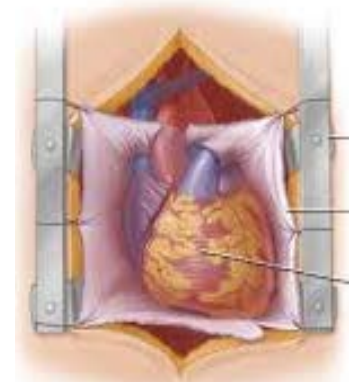


Heater-Cooler

Sterile Field



Valves and Other Implants



Incision

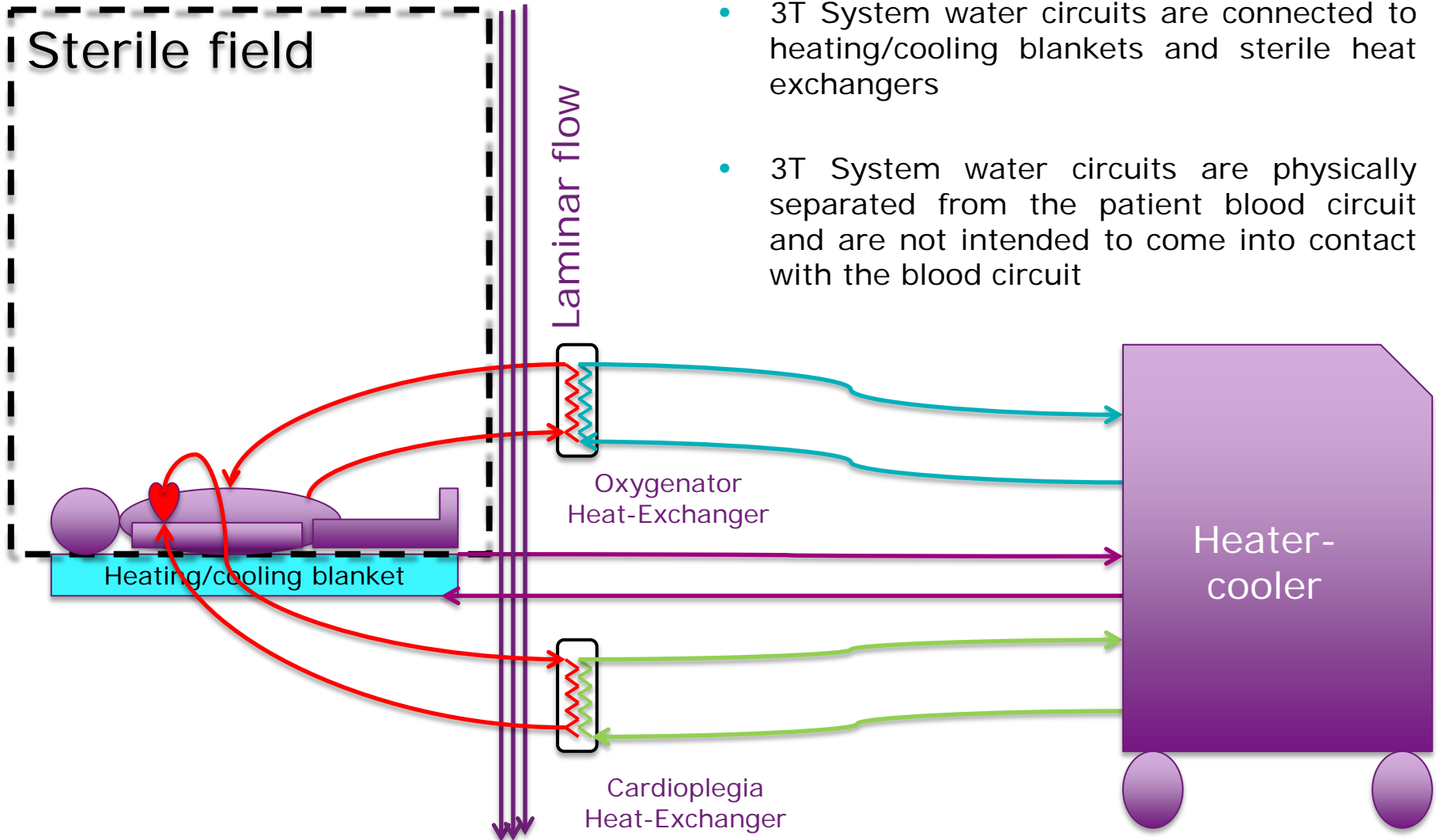


Surgical Instruments



Sterile Bypass Equipment and Disposables

3T System Overview



- 3T System water circuits are connected to heating/cooling blankets and sterile heat exchangers
- 3T System water circuits are physically separated from the patient blood circuit and are not intended to come into contact with the blood circuit

3T Heater-Cooler System (K052601)



Indications for Use:

The Stockert Heater-Cooler System is used with a Stockert S3 heart-lung machine and/or any other heart lung machine featuring a separate temperature control for extracorporeal perfusion of durations of up to 6 hours.

Background: Non-Tuberculous Mycobacteria (NTM)

- Common water-borne environmental contaminant
- FDA has recognized that “NTM organisms are widespread in nature and can be found in soil and water, including tap water sources. They are typically not harmful, but in rare cases may cause infections in very ill patients and/or in individuals with compromised immune systems.”
- NTM presence can result in post-surgical infection only if directly transmitted to the patient
 - Rare transmission by aerosolization only recently appreciated
- NTM post-surgical infection 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.”
 - “This risk identified above is extremely small compared to the background risk of infection recognised following this type of surgery.”

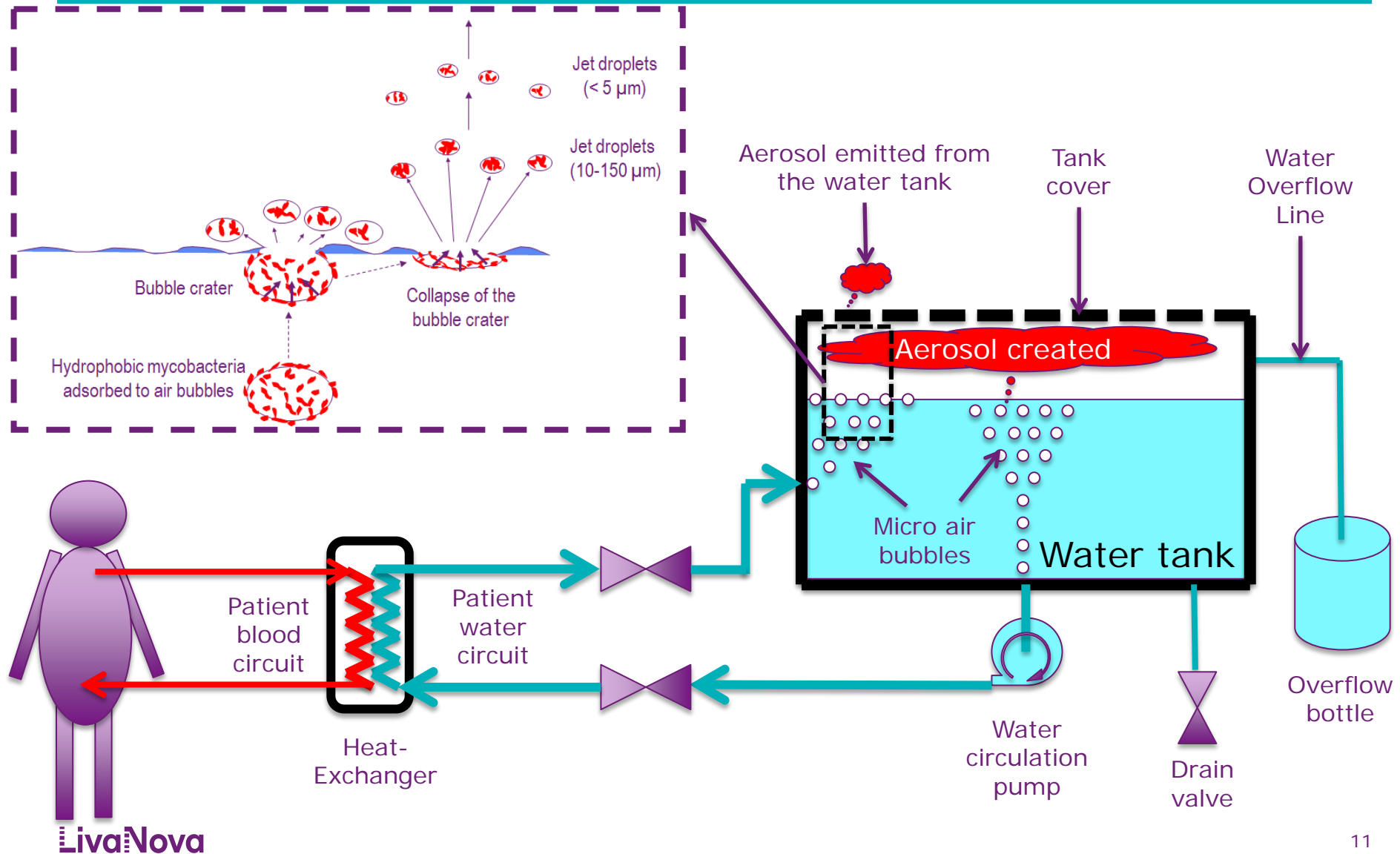
Clinical Need for Heater-Cooler Devices

- “For most patients, the benefit of undergoing a surgical procedure recommended by their doctor outweighs the risk of infection.” (FDA website, Heater-Cooler Devices, Information for Patients)
- “In most cases the risk from delaying cardiothoracic surgery, including valve replacement or repair, is likely to outweigh the infection risk. The [agency] advises that the risk of dying or suffering other adverse events due to delay in valve replacement is likely to be significantly greater than the risk of acquiring mycobacterial infection in this context.” (Public Health England, June 2015)
- “This level of risk is so small that surgery should not be delayed, as the risks of delaying surgery are greater than proceeding.” (Public Health England, October 2015)

Initial Report and Response

- Report of possible airborne infection in January 2014 from Swissmedic (Authority)
 - The initial report described airborne NTM, a phenomenon that had not been previously known to either the company or the scientific community
 - At the time of the report, no firm evidence tied the 3T System to the reported infections
- LivaNova undertook an intensive investigation into how this type of infection might occur, essentially creating new knowledge to understand the phenomenon
 - Investigation included how aerosols may be generated, emitted, and dispersed

Initial Report and Response (continued) – Current Thinking Regarding Potential Aerosolization of NTM



Initial Report and Response (continued) – Factors that Could Potentially Impact Infection Risk

- Condition and maintenance of heater-cooler device
- Level of bacterial growth in the water tank
- Extent of aerosolization within the tank
- Airflow generated inside and outside of the tank
- Machine placement
- Potential airflow within the room
- Extent to which contaminated aerosols exit the tank, pass through laminar flow, and land in surgical field
- Exposure time of implant to environment
- Length of procedure
- Surgical procedure (including implant placement or not)
- Patient condition and immune function
- Type and extent of bacterial presence in the wound

Initial Report and Response (continued)

- Device Manufacturing and Design Changes
 - Implemented a disinfection and drying process at the production facility in August 2014 to supplement the existing cleaning and disinfection process in the field
 - Implemented additional manufacturing measures (e.g., disinfection of production equipment, use of sterile filtrated water)
 - Implementing design changes for devices in production (e.g., replacing device tubing, plugging unused overflow outlet)
- Device Labeling
 - Communicated to customers newly identified potential risk and importance of cleaning and disinfection process described in IFU
 - Communicated to customers information regarding how to handle devices suspected of contamination and environmental monitoring

Initial Report and Response (continued)

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

S Haller¹, C Höller², A Jacobshagen³, O Hamouda⁴, M Abu Sin⁴, DL Monnet⁴, D Plachouras⁴, T Eckmanns¹

1. Department for Infectious Disease Epidemiology, Robert Koch Institute (RKI), Berlin, Germany

2. Bavarian Health and Food Safety Authority (LGL), Oberschleißheim, Germany

3. Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany

4. European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden

- Suggests that some *M. chimaera* infections may be linked to manufacturing site
- LivaNova working with stakeholders
 - Shared non-patient genotyping data to facilitate understanding of NTM issue
 - Actively attempting to obtain the patient genotyping data cited in the article
- In August 2014, the company implemented a disinfection/drying process at production facility to supplement existing cleaning and disinfection process in the field
- Other important statements in the article:
 - Bacteria were also isolated from heater-coolers from other manufacturers
 - Heater-cooler contamination may have resulted from NTM contamination at healthcare facilities in some cases
 - Other manufacturers' heater-coolers may have been the source of exposure in some cases

Medical Device Reporting

- Company has a robust reporting process (which is applied to NTM)
 - Integrated with Service
 - Proactively recommended testing and reporting of potential contamination
 - Actively raised awareness among its users concerning the potential for NTM contamination
 - Filed MDRs for reports of potentially contaminated devices, regardless of patient involvement or outcome
- Comparing MDR data among manufacturers has recognized limitations
 - Especially difficult with large differences in market shares
- As FDA has emphasized, all heater-cooler devices may be affected by this phenomenon and the issue of potential airborne NTM contamination

Stakeholder Partnership

- LivaNova believes that patient safety requires partnership with users
- LivaNova provides the IFU, which includes detailed instructions on cleaning and disinfection
- The cleaning and disinfection routine performed by the user and regular maintenance checks help ensure correct functionality, safety, and cleanliness of 3T System
- LivaNova offers in-service training and provides additional instruction upon customer request
- LivaNova encourages customers to report complete information so that field experiences can be adequately evaluated and investigated

Cleaning and Disinfection

- LivaNova's IFU has always included instructions for cleaning and disinfection of the water circuit prior to initial use and periodically thereafter by using certain chemical disinfectant solutions
- The company believes that the 3T System instructions for cleaning and disinfection have always been adequate for maintaining a clean device
- Failure to perform adequate cleaning and disinfection per the IFU has the potential to lead to contamination, including NTM contamination
- The device's cleaning and disinfection regimen has been updated to reflect evolving information
- Validation for current cleaning and disinfection procedure includes simulated clinical condition testing and suspension testing
 - Company has committed to conducting confirmatory validation of the cleaning and disinfection procedure

Cleaning and Disinfection (continued)

- The current IFU instructs the user to conduct cleaning and disinfection using a solution of either Minncare Cold Sterilant or Clorox Regular Bleach:
 - Before initial use;
 - Every two weeks (previously conducted on a quarterly basis); and
 - Before placing the device into storage
- In addition to the more frequent disinfection of the water circuit, current device cleaning and disinfection regimen requires:
 - Weekly water changes; and
 - The addition of hydrogen peroxide solution to the water to act as a preservative and further prevent biofilm formation

Servicing

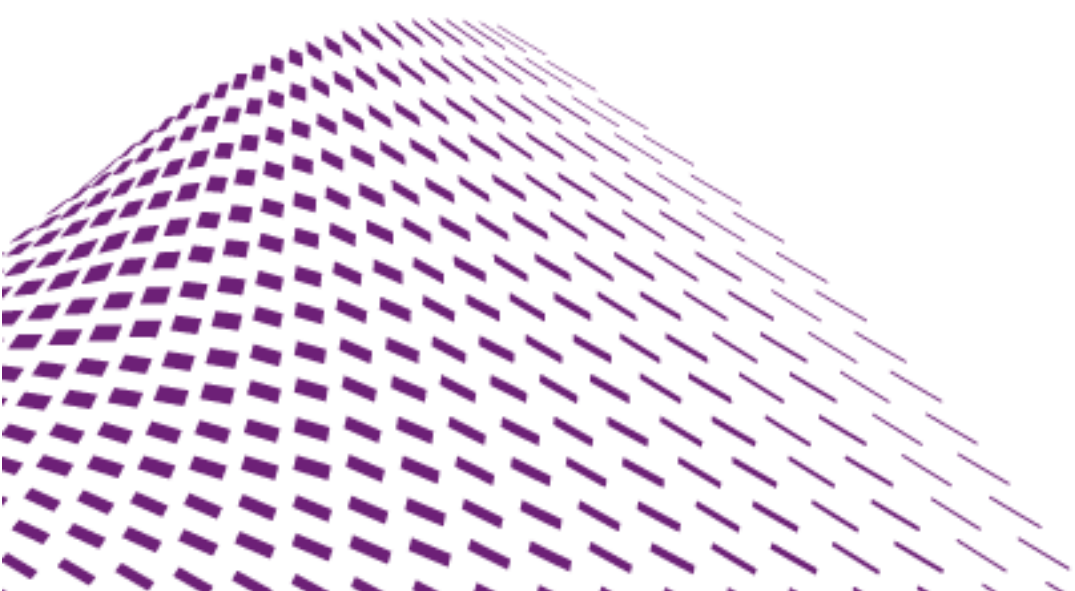
- LivaNova offers and makes available an annual preventive maintenance servicing plan
- LivaNova offers and provides servicing and maintenance on an as-needed basis
- Customers have the option of performing their own service and maintenance (certain activities require company training or certification)

Ongoing Actions

- LivaNova is conducting confirmatory testing and validation of cleaning and disinfection
- LivaNova is making the following changes to devices in production and/or in the field
 - Plugging unused overflow outlet on devices
 - Eliminating use of ice container
 - Replacing internal and external water circuit tubing with tubing more resistant to biofilm formation
- The company has instituted changes to the device's labeling, manufacturing and design, and will continue to evaluate potential further changes as our understanding and knowledge continue to develop
- LivaNova looks forward to continuing to work with FDA and other stakeholders to further address these potential issues

LivaNova

Health innovation that matters



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