Field Safety Notice

(1) No-React® BioConduit (NRAC),
(2) No-React® BioPulmonic Conduit (NRPC),
(3) No-React® Injectable BioPulmonic (NRIP),
(4) No-React® BioMitral (NRM),
(5) No-React® BioAortic (NRA)
FSCA-003-22

Date: 2022-11-25

Devices: bioprosthetic heart valves (1) No-React® BioConduit (NRAC), (2) No-React® BioPulmonic Conduit (NRPC), (3) No-React® Injectable BioPulmonic (NRIP), (4) No-React® BioMitral (NRM), (5) No-React® BioAortic (NRA)

Advise on action to be taken by the user: a lifting of any holds / restrictions on any of the aforementioned products within the UK.

Summary update: *This Field Safety Notice is an update from the one distributed April 2022 introducing a voluntary hold on products after some mycobacterial DNA was identified on some valves by a lab in the EU. While some results from one lab in the EU indicated the presence of mycobacterial DNA, all bacterial growth studies were negative. After a months-long investigation, the precautionary product hold or restrictions related to a mycobacterial investigation are being lifted in the United Kingdom. The DNA findings by third parties could relate to other sources, as mycobacteria are most commonly found in non-sterile water sources and skin. Given the most widely-used BioIntegral valve in the UK is exclusively indicated for infection and other highest-risk cases, the benefits of use of the products continue to outweigh the risks.*

Based on months of consistent evidence that its devices have remained sterile, BioIntegral Surgical has decided to lift the voluntary hold which was placed on the devices in April 2022. This removes any manufacturer-suggested restrictions on the sale, distribution, or use of BioIntegral's adult and pediatric valve lines in the UK.

The product hold has already been lifted in 100+ countries globally.

No mycobacteria were found using an array of validated test methods. While concerns were raised by a lab in early 2022 that viable *Mycobacteria chelonae* could be present in devices, the multi-laboratory EU/Canadian investigation to date has not shown any positive growth in culture on dozens of sterilized devices tested, of any type of organism[1]. Canadian labs have yet not been able to initiate PCR testing, complicated by the fact that no growth was observed in several labs (i.e., no growth indicates an

[1] Based on dozens of samples tested in four labs in the EU and Canada. Manufacturing data also unequivocally supports the sterility of the products.

inadequate amount of DNA to test using PCR), and reliable PCR test data are notoriously difficult to obtain on fixed tissue, with or without growth, given well-known glutaraldehyde interference/DNA destruction. Lastly, to date, the PCR labs which identified the DNA have not shared their detailed methodology with the manufacturer.

All xenografts and homografts contain DNA fragments, and there is no evidence in the literature or otherwise that they lead to clinical issues. It is typical to find DNA fragments in biological tissue. The gold standard of biological heart valve replacement in infected cases, the human cadaver homograft, contains whole human DNA. Glutaraldehyde fixation both denatures DNA strands as well as mummifies any cellular or bacterial components into the collagen tissue, making DNA analysis likely less useful in analyzing risks to patients.

BioIntegral Surgical adult heart valves are indicated for infected and other high-risk cases. Sterility testing data, a lack of suitable homografts and the unchanged benefit/risk ratio for patients favor continued use of the devices. Due to a general lack of suitable homografts, the most widely used BioIntegral Surgical valve in the United Kingdom is the valved aortic conduit. Given its indications include infection and other high-risk indications, the benefits of use of the product continue to outweigh the risks. The benefit-risk ratio has been established by decades of clinical data, suggesting the device is as effective in reducing infection as homografts, and better than homografts in reducing overall adverse event rates[2]. In a critically-ill population, the devices can continue to be useful additions to a consultant's armamentarium.

While CE marked valve inventories are available, like many other smaller manufacturers, BioIntegral Surgical has demurred from continuing to serve the EU market moving into the MDR era and hence will not be manufacturing new devices for the EU market. That said, BioIntegral Surgical is cooperating with local distributors to make existing inventories available.

Transmission of this Field Safety Notice. This notice needs to be passed on to all those who need to be aware within your organization (distributors) or to any organization where the potentially affected devices may have been transferred within the UK.

The MHRA and various other UK agencies have been informed of this Field Safety Notice.

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[2] Clinical Evaluation Reports, 2022.