KEYSTONE
Rev 1: May 2020

Keystone Heart

FSN Ref: FCN-RR-2022-001

FSCA Ref: FSCA-RR-2022-001

Date: 2022.05.10

Field Safety Notice
TRIGUARD 3

For Attention of*:Distributors and users

Contact details of local representative (name, e-mail, telephone, address etc.)*
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Keystone Heart

FSCA Ref: FSCA-RR-2022-001

Field Safety Notice (FSN)
TRIGUARD 3
Regulatory Recall

1. Information on Affected Devices*	
1.	1. Device Type(s)*
	TriGUARD 3™ Cerebral Embolic Protection Device, Model: FG00005, Lot:3.0HS20211007/ 3.0HS20210904 / 3.0HS20210924.
1.	2. Commercial name(s)*
	TriGUARD 3™ Cerebral Embolic Protection Device
1.	3. Unique Device Identifier(s) (UDI-DI)
	072900115 95205 7
1.	4. Primary clinical purpose of device(s)*
	Cerebral embolic protection
1.	5. Device Model/Catalogue/part number(s)*
	FG00005
1.	6. Software version
	N/A
1.	7. Affected serial or lot number range
	3.0HS20210904 3.0HS20211007 3.0HS20210924
1.	8. Associated devices
	N/A

2. Reason for Field Safety Corrective Action (FSCA)*	
2.	1. Description of the product problem*
	Keystone Heart has become aware of a manufacturing error relating to a 3rd party supplier, which has resulted in a planned regulatory recall of the TriGUARD 3™, a cerebral embolic protective device. Nonconforming product was identified during the manufacturer of a recent lot of TriGUARD 3™ due to the use of 2.6U heparin manufactured by Bioiberica, instead of the approved supplier Smithfield Bioscience (formally known as Celsus Laboratories). Bioiberica is not a TriGUARD 3™ approved supplier. Therefore, the use of raw material supplied by Bioiberica do not meet Keystone Heart requirement listed in TriGUARD 3™ heparin coating specification.
2.	2. Hazard giving rise to the FSCA*
	Keystone Heart has completed a safety and performance assessment and has concluded that there is no inherent impact to product safety or performance, and no new or increased clinical risks are introduced as a result of this TriGUARD 3™ manufacturing error. An independent third-party expert impact assessment has been completed concluding that no new risks are introduced as a result of TriGUARD 3™ devices having been coated with Bioiberica heparin. These assessments included a review of heparin quality and performance, coating safety and performance lot release testing results, final lot release results, and animal origin considerations. It is concluded there was no clinical (safety or performance) risks introduced as a result of this manufacturing error, however there was a regulatory compliance breach. A field safety

	corrective action is not required to prevent or reduce the risk of a serious incidents in relation to the devices made available on the market, however all impacted devices were recalled for regulatory compliance reasons.
2.	3. Probability of problem arising
	There is no clinical (safety or performance) risks introduced as a result of this manufacturing error, however there was a regulatory compliance breach. A field safety corrective action is not required to prevent or reduce the risk of a serious incidents in relation to the devices made available on the market, however all impacted devices were recalled for regulatory compliance reasons.
2.	4. Predicted risk to patient/users
	There is no clinical (safety or performance) risks introduced as a result of this manufacturing error
2.	5. Further information to help characterise the problem
	As the device is not approved for commercialization, this regulatory action is initiated.
2.	6. Background on Issue
	Nonconforming product was identified during the manufacturer of a recent lot of TriGUARD 3™ due to the use of 2.6U heparin manufactured by Bioiberica, instead of the approved supplier Smithfield Bioscience (formally known as Celsus Laboratories). Bioiberica is not a TriGUARD 3™ approved supplier. Therefore, the use of raw material supplied by Bioiberica do not meet Keystone Heart requirement listed in TriGUARD 3™ heparin coating specification.
2.	7. Other information relevant to FSCA
	The resulting nonconforming product investigation included a full review of all previously released lots. Three previously released lots were identified through batch records as using Bioiberica heparin sodium raw material in the coating. All incoming, in-process, and final other function testing requirements were met for the impacted lots. Heparin manufactured by Bioiberica was used in the previous generation of TriGUARD 3™, TriGuard HDH. As part of the CE certification process under the MDD for the TriGuard HDH, a scientific opinion of the quality, safety and usefulness of the heparin manufactured by Bioiberica was provided by the MHRA, and CE certification (581463) was issued by BSI. The safety of the TriGUARD 3™ device coated with HP01 was demonstrated in Keystone Heart's REFLECT Phase II clinical study (CIR-09, Clinical Study Report). In the REFLECT Phase II study, the safety of the TriGUARD 3™ device was evaluated in 157 subjects (116 treated as part of the Phase II Randomized trial; 41 additional Roll-In subjects). Of particular note, 40 of the TriGUARD 3™ devices were coated with Bioiberica heparin. This large, multi-center, randomized, controlled study demonstrated that the profile of the TriGUARD 3™ was sufficient to prove the safety of the device in clinical use. The HP01 Photo-Heparin coating used on TriGUARD 3™, was developed by 3rd party provider, Surmodics, and utilizes its core PhotoLink coating technology, a UV-based chemistry that allows the coating to be covalently bonded to the device surface. SurModics Drug Master File (DMF)-MFD-16994-2-10225-0010 [3.2.S.2.3 Control of Materials (HP01)] specify two approved sources of heparin with distinct geographical locations (Smithfield-USA, Bioiberica-Spain) to provide supply chain flexibility for Surmodics. Based on technical information provided, Surmodics regards the Smithfield and Bioiberica sourced heparin as equivalent and can use them interchangeably if permitted by a client. Bioiberica sourced raw material is approved and supported by results of batches analysis-material qualification (3.2.S.4.4) Table 1-3. The test results have met the acceptance criteria. Heparin sodium manufacture by Bioiberica complies with specification in the monographs of the European Pharmacopoeia (monograph No. 0333), current edition (HP007-M3-01 DMF document Module 3.2.S.4.5). The batch analysis of heparin sodium (HP007-M3-01 DMF document Module 3.2.S.4.4T) used for coating of TriGUARD 3™ devices (19/0001), is in compliance with Ph. EU. monograph 0333, current edition. Both Smithfield BioScience and Bioiberica manufacture heparin from an ISO 22442-2 certified porcine intestinal tissue raw

	material. Bioiberica has provided animal origin (AO) safety information in their HP-007-M3-01 DMF document, "Module 3.2S – 3.2A, Heparin Sodium EP" and other correspondences with Keystone Heart. Animal species, tissues and cells of animal origin have originated from animals that have been subjected to veterinary controls, and information on the geographical origin of the animals in accordance with EN ISO 22442-1 and -2:2020. Information on sourcing, processing, preservation, testing, and handling of tissues, cells, and substances of animal origin to provide safety for patients, users, and other persons in accordance with EN ISO 22442-1 and -2:2020. Recent literature demonstrates that the TriGUARD 3™/Heparin Inactivation Methods are considered "state-of-the-art" in accordance with ISO 22442-3. There is a very low risk due to transmission of non-viral adventitious agents (TSE, bacteria, and fungi) and viral safety is achieved by validated methods of viral inactivation treatments during production and sourcing controls in accordance with EN ISO 22442-1:2020 and EN ISO 22442-3:2007. A detailed summary of the biocompatibility testing on the final, finished TriGUARD 3™ devices-coated with heparin sodium manufactured by Bioiberica has concluded that TriGUARD 3™ devices are non-cytotoxic, non-sensitizer, no-imitant, non -toxic, non-pyrogenic, non-hemolytic and non-activator. TriGUARD 3™ device coated with Bioiberica heparin passed all biocompatibility endpoints, providing additional assurance that Bioiberica does not pose a safety risk.

3. Type of Action to mitigate the risk*		
3.	**1. Action To Be Taken by the User***	
	☒ Identify Device ☒ Quarantine Device ☐ Return Device ☐ Destroy Device ☐ On-site device modification / inspection ☐ Follow patient management recommendations ☐ Take note of amendment / reinforcement of Instructions For Use (IFU) ☐ Other ☐ None Keystone representative will pick up the non conforming devices	
3.	2. By when should the action be completed?	Specify where critical to patient/end user safety. 15 May 2022
3.	3. Particular considerations for: Choose an item. Is follow-up of patients or review of patients' previous results recommended? No Provide further details of patient-level follow-up if required or a justification why none is required.	
3.	4. Is customer Reply Required? * (If yes, form attached specifying deadline for return)	No
3.	**5. Action Being Taken by the Manufacturer***	
	☒ Product Removal ☐ On-site device modification/inspection ☐ Software upgrade ☐ IFU or labelling change ☐ Other ☐ None	

	Provide further details of the action(s) identified.	
3.	6. By when should the action be completed?	May 30 2022
3.	7. Is the FSN required to be communicated to the patient /lay user?	No
	8.	

4. General Information*		
4.	1. FSN Type*	New
4.	2. For updated FSN, reference number and date of previous FSN	N/A
4.	3. For Updated FSN, key new information as follows:	
	N/A	
4.	4. Further advice or information already expected in follow-up FSN? *	No
4.	5. If follow-up FSN expected, what is the further advice expected to relate to:	
	N/A	
4.	6. Anticipated timescale for follow-up FSN	N/A
4.	7. Manufacturer information (For contact details of local representative refer to page 1 of this FSN)	
	a. Company Name	**Keystone Heart**
	b. Address	15 Halamish St., POB. 3170, IL 3088900
	c. Website address	www.keystoneheart.com
4.	8. The Competent (Regulatory) Authority of your country has been informed about this communication to customers. *	
4.	9. List of attachments/appendices:	
4.	10. Name/Signature	xxx

	Transmission of this Field Safety Notice
	This notice needs to be passed on all those who need to be aware within your organisation or to any organisation where the potentially affected devices have been transferred. (As appropriate) Please transfer this notice to other organisations on which this action has an impact. (As appropriate) Please maintain awareness on this notice and resulting action for an appropriate period to ensure effectiveness of the corrective action. Please report all device-related incidents to the manufacturer, distributor or local representative, and the national Competent Authority if appropriate, as this provides important feedback.*

Note: Fields indicated by * are considered necessary for all FSNs. Others are optional.