DE NOVO CLASSIFICATION REQUEST FOR BIOHEALX ANAL FISTULA DEVICE

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Anal fistula closure device**. An anal fistula closure device is a surgical implant for anal fistula repair and is intended for closure of the anal fistula. The device may be manually applied or delivered with a delivery device.

NEW REGULATION NUMBER: 21 CFR 878.4835

CLASSIFICATION: Class II

PRODUCT CODE: QML

BACKGROUND

DEVICE NAME: BioHealx Anal Fistula Device

SUBMISSION NUMBER: DEN240007

DATE DE NOVO RECEIVED: February 2, 2024

SPONSOR INFORMATION:

Signum Surgical Limited
Galway Harbour Enterprise Park, New Docks, The Docks
Galway H91 NNY6 Ireland

INDICATIONS FOR USE

The BioHealx Anal Fistula Device is indicated as follows:

> The Signum Surgical BioHealx Anal Fistula Device is indicated for closure of the internal opening of mature, cryptogenic, transsphincteric, non-branching fistulas in ano via tissue apposition.

LIMITATIONS

The sale, distribution, and use of the BioHealx Anal Fistula Device are restricted to prescription use in accordance with 21 CFR 801.109.

Contraindications

- The BioHealx Anal Fistula Device should only be used for the repair of anal fistulas.
- This device should not be used in tissues that have a direct anatomic relationship to major vascular structures.

Key Limitations

- The BioHealx Anal Fistula Device should be used only by physicians having adequate training and familiarity with the implant technique.
- The BioHealx implant is suitable only for use in fistulas of any length greater than 2cm.
- The BioHealx device has not been evaluated in patients with Crohn's disease.
- The device should not be used in pregnant women.
- The device should not be used in patients with a known allergy to poly (lactic-co-glycolic acid), (PLGA).
- Do not attempt anterior delivery in females, to prevent implant penetration through the vaginal wall.
- Do not deliver at external opening of fistula tract.
- Remove implant if not completely delivered.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The BioHealx Anal Fistula Device comprises the BioHealx Implant and the Delivery System.

The BioHealx implant is designed as a sterile, single use helical, barbed bioabsorbable implant intended to promote healing by primary intention. The BioHealx delivery device is a sterile single-use, disposable delivery device that rotates the implant into the soft tissue surrounding the internal opening of the fistula tract.

The BioHealx implant apposes the internal opening of the fistula channel and is held in position by its design geometry. The implant is fully enclosed in the anal sphincter muscle tissue and is not exposed to the ano-rectal canal. The implant retains adequate strength to compress the tissue of the internal opening of a fistula for 4 - 6 weeks and is absorbed within 6 - 12 months.

BioHealx Implant

The BioHealx implant is designed as a coil, with a tapered inner surface. The coil design facilitates insertion around the fistula tract lumen at the internal opening. The sphincter muscle tissue surrounding the fistula internal opening is gathered and compressed by the implant's internal taper geometry during implant delivery, effecting closure of the internal opening by direct tissue apposition.

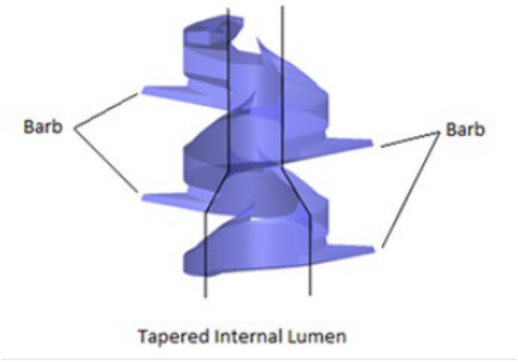

Figure 1 Signum Surgical BioHealx™ Anal Fistula implant.

The anti-rewind features ("barbs") (Figure 1) at the outer perimeter of the implant serve as retention features to prevent the device migration/extrusion once implanted. The implant is centered around the fistula tract at the internal opening in the sphincter muscle complex, causing the fistula to close within the tapered internal lumen of the implant.

Degradation

The constituent implant material is poly (lactic-co-glycolic acid), (PLGA). Poly (lactic-co-glycolic acid), (PLGA) is a material that degrades by hydrolysis (i.e., degradation takes place in the presence of water).

The progression of the absorption process proceeds from loss of mechanical strength followed by loss of physical structural integrity marked by fragmentation followed by breakdown to microscopic residue and ultimate elimination from the body. Non-clinical bench testing (in-vitro) found that the loss of physical structural integrity has occurred by week 26 (6 months). Biocompatibility testing (26-week implantation study) found that only test article fragments (i.e., mostly degraded) could be identified.

BioHealx Delivery System

The BioHealx implant is delivered to the operative site by means of a single-use disposable delivery device (**Figure 2**) that is preloaded with the implant (**Figure 3**). The BioHealx delivery system controls the positioning and depth of delivery of the implant, standardizing the procedure and reducing operator variability.

Figure 2 Signum Surgical BioHealx Anal Fistula delivery system.

(a) Photographic Image of Implant loaded on Driver Coil

(b) 3-Dimensional Model of Implant detached from Driver Coil

Figure 3 BioHealx implant preloaded to BioHealx delivery system.

A stainless-steel wire suture attachment loop extends 3mm to 5mm beyond the distal end of the device (see **Figure 4**). The suture attachment loop provides an easy access point allowing the user to attach a commercially available USP size 2-0, braided, coated synthetic absorbable suture for delivery device guidance prior to implant delivery. The suture attachment loop is attached internally to the lock component at the proximal end of the delivery device and is retracted with the lock retraction prior to implant delivery.

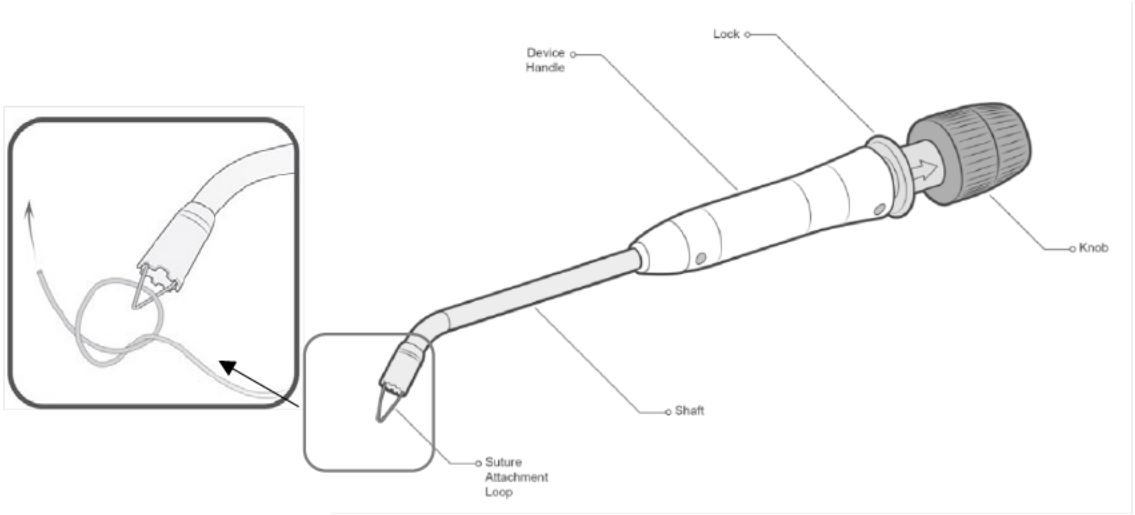

Figure 4 BioHealx Delivery System with Suture Attachment Wire Loop

Turning the delivery system knob clockwise (three full turns) rotates the implant driver coil clockwise to deliver the helical implant circumferentially to surround the internal opening of the fistula to the predefined depth controlled by the driver coil. The internal drive mechanism has a one-way ratchet to ensure the user deploys the device fully; a series of audible clicks will be heard during the knob rotation. After the implant is fully delivered the knob can no longer be turned ('bottoms out'), signaling to the user to begin retraction via counterclockwise rotation of the knob. The barbs (**Figure 1**) that radially extend from the implant provide anchorage in the tissue releasing the implant from the driver coil and leaving the implant to remain surrounding the internal opening of the fistula tract. Once the driver coil is retracted, the user removes the delivery device from the patient.

SUMMARY OF NONCLINICAL/BENCH STUDIES

Non-clinical/Bench studies conducted on the BioHealx Anal Fistula Device demonstrate safety and effectiveness and are summarized below.

Table 1

Test	Purpose	Method	Acceptance Criteria	Results
Implant Verification Testing	Demonstrate that the BioHealx Implant maintains sufficient strength to support tissue healing for a minimum of 3 weeks post implant delivery (a strength equal to or greater than (b) (4)	The break strength was evaluated at T=0, 3, 4, 6 weeks following simulated in-vitro degradation in buffer solution at (b) (4)	Tensile (implant break) strength must be (b) (4) (T=0) and (b) (4) (T=3 weeks, 4 weeks, 6 weeks).	All testing passed the acceptance criteria.
Delivery Mechanism Verification	Demonstrate that the BioHealx delivery mechanism is capable of successful implant delivery. Determine the torque requirement to remove	Each test sample (Finished Device) was removed from the packaging and verified to meet specifications. The BioHealx implant was delivered to between (b) (4)	a) The BioHealx Anal Fistula Device must be capable of consistent successful delivery of the BioHealx implant, to a controlled depth, being delivered to simulated tissue.	All testing passed the acceptance criteria.

Test	Purpose	Method	Acceptance Criteria	Results
	an implant from the drive coil assembly (implant lock testing).	into the simulated tissue surface.	b) The drain capture mechanism must be capable of withstanding a (b) (4) load without failure and allow attachment of USP size 2-0 bioabsorbable suture via a secure knot. c) The implant must maintain integrity and form (geometry) post implant delivery.	
Implant Migration	Demonstrate resistance to migration / extrusion of the BioHealx implant.	The BioHealx implant resistance to migration/extrusion was evaluated under the conditions of simulated rectal pressure cycling on BioHealx implant position. All bench testing was performed in an anatomically relevant model.	a) The applied force required to cause implant migration and extrusion force in the gel model must be (b) (4) axial force (b) (4) . b) The BioHealx implant final position (post pressure cycling) must remain within the required delivery depth specification of (b) (4) (b) (4)	All testing passed the acceptance criteria.
Drain Attachment	Demonstrate that the drain capture mechanism is: - Capable of withstanding anticipated loading - Allows attachment of 2-0 bioabsorbable suture using a secure knot. - When attached to suture (drain capture/suture assembly) can withstand anticipated loading while (i) retracting the lock and (ii) post retraction of lock.	Each test sample (Finished Device) was removed from the packaging and tested on the bench to ensure that the drain capture mechanism could withstand the anticipated loading.	a) Drain capture mechanism must withstand an applied load (b) (4) without failure. b) Drain capture mechanism shall allow attachment of 2-0 bioabsorbable suture using a secure knot. c) Drain capture/ suture assembly must withstand an applied (b) (4) load while (i) retracting the lock and (ii) post retraction of lock.	All testing passed the acceptance criteria.

Test	Purpose	Method	Acceptance Criteria	Results
Drain Release Force	Assessment of the force required to release the suture /drain from a delivered BioHealx implant.	BioHealx implants were delivered to a simulated fistula tract in a representative model. For each fistula tract/implant delivered, a simulated drain using suture material was created. A tensile load was applied to each drain to determine the force required to cause detachment.	This testing was used to collect representative data to determine the force required to release the suture/drain from a delivered BioHealx implant.	The average force (95%/95% confidence reliability) required to release the stop knot (3 throws of a figure 8) and to cause the drain to detach was (b) (4) Kg equivalent.)
In Vivo Performance Testing (GLP)	Evaluate the safety and performance of the BioHealx Anal Fistula Device for its intended use to appose tissues in the repair of anal fistulas using a porcine anal fistula model.	Cohort of six (6) pigs (species strain Sus scrofa scrofa/ domestic. Yorkshire cross – white) were treated in the study. - Four perianal fistulas, with a seton placed, were created at the 3,5,7 and 9 o'clock positions in each animal. - After 4-weeks recovery, a second surgical procedure was performed per the BioHealx implant procedure. This involved the creation of a small mucosal incision at the internal opening site, and partial fistulectomy as necessary followed by placement of the BioHealx device in each of the fistula tracts.	Animals were observed for any adverse clinical signs of disease or ill health. Fistula healing, as assessed by histopathology analysis. Determine that the BioHealx device does not adversely affect the incidence and rate of perianal healing nor have any detrimental effect as determined by histopathology).	All testing passed the acceptance criteria. Testing concluded that there was no evidence of adverse tissue reaction associated with the BioHealx device in any of the evaluated samples.
Human Factors/ Summative Evaluation Testing	Demonstrate the components of the BioHealx system can be used by the intended users without serious use errors or problems,	Users: 7 x EU, 10 x US representative colorectal surgeons. 100% (17/17) participants performed	a) User must unpackage the device without causing damage to the device. b) User must remove the device from the tray	All implanters successfully completed implant training and effectiveness evaluation.

Test	Purpose	Method	Acceptance Criteria	Results
	for the intended uses and under the expected use conditions. The specific objectives are: - Confirm that the BioHealx device can be safely delivered. - Confirm that the BioHealx device can be effectively delivered. - Confirm no unanticipated serious use errors attributable to the system user interfaces. - Evaluate the simulated model as an effective training tool for BioHealx system users.	several BioHealx implantations in an anatomically relevant simulated use bench top model. Clinical investigators (N=6) also completed an in vivo simulated use (porcine) animal model. Note: The human factors simulated use *in vivo* testing was for training effectiveness evaluation only and was a separate activity to the GLP *in vivo* performance testing (described above).	without damage to the device (e.g., drop device) c) User feedback on the tissue stabilization features must not identify risks/complaints. d) User must not cut gloves/cause self-injury during device use. e) User must successfully attach suture to the device attachment loop. f) User must successfully place speculum and must not complain about device interface experience with speculum.	The objectives to confirm that the BioHealx device can be safely and effectively delivered were met. There were no close calls or use errors observed during the evaluation. The simulated use model was demonstrated to be an effective training tool.
Biocompatibility Testing – Implant. Rabbit Blood Hemolysis Test.	To determine the potential hemolytic activity, via the induction of increased levels of free plasma hemoglobin in rabbit blood, in response to the BioHealx implant test article and its extract.	ASTM F756, ISO 10993-12, ASTM F619	Acceptance criteria per ISO 10993-4 (2017), ISO 10993-12 (2012), ASTM F756-17, ASTM F619-14.	All testing met the acceptance criteria. The BioHealx implant was determined to be non-hemolytic.
Biocompatibility Testing – Implant. 90-Day Systemic Toxicity in Rats via Intramuscular Implantation.	To determine the toxicity potential of a test material administered by muscle implantation in rats for 90-days.	ISO 10993-6 (2016), ISO 10993-11 (2017), OECD 408, ISO 10993-12 (2012).	Acceptance criteria per ISO 10993-6 (2016), ISO 10993-11 (2017), OECD 408, ISO 10993-12 (2012).	All testing met the acceptance criteria. The BioHealx implant did not demonstrate any local or systemic signs of toxicity when implanted in rats for 90-days.
Biocompatibility Testing – Implant. 26-week Systemic Toxicity in Rats via	To determine the toxicity potential of a test material administered by muscle implantation in rats for 26-weeks.	ISO 10993-6 (2016), ISO 10993-11 (2017), OECD 408, ISO 10993-12 (2012).	Acceptance criteria per ISO 10993-6 (2016), ISO 10993-11 (2017), OECD 408, ISO 10993-12 (2012).	All testing met the acceptance criteria. The BioHealx implant did not demonstrate any local or systemic signs of toxicity when implanted

Test	Purpose	Method	Acceptance Criteria	Results
Intramuscular Implantation.				in rats for 26 weeks.
Biocompatibility Testing – Implant. Intracutaneous Injection Test - ISO	To determine the potential irritation effects of the BioHealx implant test article extract after intracutaneous injection in New Zealand White rabbits	ISO 10993-10 (2010), ISO 10993-12 (2012).	Acceptance criteria, per ISO 10993-10 (2010), ISO 10993-12 (2012).	All testing met the acceptance criteria. The BioHealx test article met the requirements of the ISO 10993-10.
Biocompatibility Testing – Implant. Kligman Maximization Test – ISO (Sensitization)	To determine the potential allergenic or sensitizing capacity of the BioHealx test article.	ISO 10993-10 (2010), ISO 10993-12 (2012).	Acceptance criteria per ISO 10993-10 (2010), USP 141, ISO 10993-12 (2012).	The BioHealx test article met the requirements of the ISO 10993-10. All testing met the acceptance criteria.
Biocompatibility Testing – Implant. L929 Neutral Red Uptake Test (4 Conc'ns) - ISO	To determine the potential biological reactivity of a mammalian cell culture (L929) in response to the BioHealx implant test article extract.	ISO 10993-11 (2017), ISO 10993-12 (2012).	Acceptance criteria per ISO 10993-5 (2009), ISO 10993-12 (2012).	All testing met the acceptance criteria. The BioHealx test article met the requirements of ISO 10993-5.
Biocompatibility Testing – Implant. Systemic Injection Test - ISO	To determine the potential toxic effects of the BioHealx implant test article extract as a result of a single-dose systemic injection in mice.	ISO 10993-11 (2017), ISO 10993-12 (2012).	Acceptance criteria per ISO 10993-11 (2017), ISO 10993-12 (2012)	All testing met the acceptance criteria. The BioHealx test article met the requirements of ISO 10993-11.
Biocompatibility Testing – Implant. Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay - ISO	To determine the potential mutagenicity of the BioHealx implant test article extract on various strains of Salmonella typhimurium (S. typhimurium) and Escherichia coli (E. coli) bacteria, via a change in their dependence for histidine or tryptophan.	ISO 10993-3, 2014 ISO/TR 10993-33, 2015 OECD 471 ISO 10993-12, 2012,	Acceptance criteria per ISO 10993-3(2014), ISO/TR 10993-33 (2015), Part 33, OECD 471, ISO 10993-12 (2012).	All testing met the acceptance criteria. The BioHealx implant test article was found to be non-mutagenic.
Biocompatibility Testing – Implant. Mouse Lymphoma	To determine the potential mutagenicity effect on mouse lymphoma cells (heterozygous thymidine kinases	ISO 10993-3 (2014), ISO 10993-33 (2015), OECD 490, ISO 10993-12 (2012).	Acceptance criteria per ISO 10993-3 (2014), ISO 10993-33 (2015), OECD 490, ISO 10993-12 (2012).	All testing met the acceptance criteria. The BioHealx implant test

Test	Purpose	Method	Acceptance Criteria	Results
Mutagenesis Assay - ISO	mutant TK±L5178Y) in response to the BioHealx implant test article extract.			article was found to be non-mutagenic.
Biocompatibility Testing – Implant. Intramuscular Implantation Test for Absorbable/Degradable Materials – ISO 2-week implantation	To evaluate the BioHealx implant test article for local tissue responses and the potential to induce local toxic effects after implantation (for 2-weeks) in the muscle tissue of albino rabbits. Absorption of the test article was assessed.	ISO 10993-6 (2016), 10993-12 (2012).	Acceptance criteria per ISO 10993-6 (2016), 10993-12 (2012).	All testing met the acceptance criteria. The BioHealx implant test article was considered non-reactive and met the requirements of ISO 10993-6.
Biocompatibility Testing – Implant. Intramuscular Implantation Test for Absorbable/ Degradable Materials – ISO 8-week implantation	To evaluate the BioHealx implant test article for local tissue responses and the potential to induce local toxic effects after implantation (for 8-weeks) in the muscle tissue of albino rabbits. Absorption of the test article was assessed.	ISO 10993-6 (2016), 10993-12 (2012).	Acceptance criteria per ISO 10993-6 (2016), 10993-12 (2012).	All testing met the acceptance criteria. The BioHealx implant test article was considered non-reactive and met the requirements of ISO 10993-6.
Biocompatibility Testing – Implant. Rabbit Pyrogen Test (Material Mediated) - ISO	To determine the potential presence of chemical pyrogens in extracts of solid materials in order to limit to an acceptable level the risk of febrile reaction following administration of the BioHealx implant (product) to a patient.	ISO 10993-11 (2017), 10993-12 (2012).	Acceptance criteria per ISO 10993-11 (2017), 10993-12 (2012).	All testing met the acceptance criteria. The results supported that the BioHealx implant is non-pyrogenic and meets the requirements of the Pyrogen Test, ISO 10993-11.
BioHealx Implant Endotoxins Test Validation	To validate the gel clot lysate method for endotoxin testing	10993-12 (2012).	Study was conducted based on USP 41, NF 36 (2018), <85> Bacterial Endotoxins Test, 10993-12 (2012).	The test articles, Signum Surgical BioHealx, meet the requirements of the Amoebocyte Lysate Endotoxin Validation Test, Gel Clot Method

Test	Purpose	Method	Acceptance Criteria	Results
				according to the USP guidelines. The test articles do not inhibit or enhance the assay. All testing met the acceptance criteria.
BioHealx Delivery System ISO Guinea Pig Maximization Sensitization Test	To evaluate the potential of the BioHealx Delivery Device test article extract to cause delayed dermal contact sensitization in the guinea pig maximization test. The Magnusson and Kligman method has been effective in identifying a variety of allergens.	10993-10 (2021), 10993-12 (2021)	Acceptance criteria per ISO 10993-10 (2021), 10993-12 (2021).	All testing met the acceptance criteria. The BioHealx Delivery System test article was not considered a sensitizer in the guinea pig maximization test.
BioHealx Delivery System Cytotoxicity Study Using the ISO Elution Method	To determine the potential of a test article extract to cause cytotoxicity.	ISO 10993-5 (2009), 10993-12 (2021).	Acceptance criteria per ISO 10993-5 (2009), 10993-12 (2021).	All testing met the acceptance criteria. The BioHealx Delivery System test article extract showed no evidence of causing cell lysis or toxicity.
BioHealx Delivery System ISO Intracutaneous Irritation Study-Extract	To evaluate the local dermal irritation of a test article extract following intracutaneous injection in rabbits.	10993-23 (2009), 10993-12 (2021).	Acceptance criteria per ISO 10993-23 (2009), 10993-12 (2021).	All testing met the acceptance criteria. The BioHealx Delivery System test article showed no evidence of causing irritation.
BioHealx Delivery System USP Rabbit Pyrogen Study, Material Mediated	To determine whether an extract of the test article induced a pyrogenic response following intravenous injection in rabbits.	USP <151 > ISO 10993-11 (2017), 10993-12 (2021).	Acceptance criteria per USP <151 >, Pyrogen Test, ISO 10993-11 (2017), 10993-12 (2021).	All testing met the acceptance criteria. The BioHealx Delivery System test article met the requirements

Test	Purpose	Method	Acceptance Criteria	Results
				for the absence of pyrogens.
BioHealx Delivery System ISO Acute Systemic Toxicity Study in Mice	To evaluate the acute systemic toxicity of a test article extract following injection in mice.	ISO 10993-11 (2017), 10993-12 (2021).	Acceptance criteria per ISO 10993-11 (2017), 10993-12 (2021).	All testing met the acceptance criteria. The BioHealx Delivery System test article showed no mortality or evidence of systemic toxicity from the extracts injected into mice.

BIOCOMPATIBILITY/MATERIALS

The BioHealx Anal Fistula Device components were classified as follows for the purpose of performing biocompatibility testing per ISO 10993 and FDA Guidance on the "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (September 2020) as described below. Based on the outcomes of the biocompatibility evaluation, the BioHealx Anal Fistula Device Implant and Delivery System patient contacting components are considered biocompatible.

BioHealx Implant

The BioHealx implant is a permanent implant (> 30 days), absorbable device having direct contact with patient tissue. Degradation information was addressed in the implant implantation testing, sub-chronic/chronic toxicity testing and the in vivo performance (animal) study. Carcinogenicity was addressed through a toxicological risk assessment.

Biocompatibility endpoints were addressed through ISO standard testing for the BioHealx implant including:

- Cytotoxicity
- Sensitization
- Irritation Testing, Intracutaneous reactivity
- Acute systemic toxicity
- Material mediated pyrogenicity
- Genotoxicity
- Implantation
- Hemocompatibility
- Chronic Toxicity (26- weeks)

All tests met their test requirements.

BioHealx Delivery System

The BioHealx Anal Fistula Device delivery system is an external communicating device having limited contact (≤ 24 hours, note: less than 5 minutes in clinical use) with patient tissue during device deployment. Each component of the delivery device that may come into contact with tissue during implant deployment is fabricated from 304 stainless steel.

Biocompatibility endpoints were addressed through ISO standard testing for the BioHealx Delivery System including:

- Cytotoxicity
- Sensitization
- Intracutaneous reactivity
- Material mediated pyrogenicity
- Acute Systemic Toxicity

All tests met their test requirements.

SHELF LIFE/STERILITY

The BioHealx Anal Fistula Device is a sterile, single use system. The finished BioHealx Anal Fistula Device is packaged in a tray, sealed in a labelled pouch and placed in a labelled finished device box. The BioHealx Anal Fistula Device is sterilized using an e-beam sterilization process; the process has been validated in accordance with VD_{max} methodology per ANSI/AAMI/ISO 11137-1:2006(R)2015, ANSI/AAMI/ISO 11137-2:2013, ANSI/AAMI/ISO 11137-3:2006(R)2017 to a sterility assurance level of 10^{-6}.

The shelf life of the BioHealx Anal Fistula Device has been validated for 24 months (real-time aging). Shelf-life testing has validated:

1. Stability of the BioHealx Anal Fistula Device (Implant and Delivery System) post real-time aging (24-months) for implant tensile strength requirements and implant delivery verification requirements.
2. Packaging integrity testing was performed to evaluate the packaging and device performance post 24-months real-time aging. Testing addressed:
    - Packaging stability (climatic conditioning ASTM D4332)
    - Transportation simulation ASTM D4169 Cycle 13, Assurance Level 1)
    - Transportation Integrity
    - ASTM F1886- Visual Inspection
    - ASTM F2096- Bubble leak
    - ASTM F88 - Peel strength
    - Tray device retention preference (inspection of tray retention features)
    - Label performance (visual inspection)

All testing had passing results.

MAGNETIC RESONANCE (MR) COMPATIBILITY

A risk-based scientific evaluation and testing concluded that the BioHealx implant (a fully implanted passive device) is electrically nonconductive, non-magnetic and poses no known hazards in all MR environments, justifying the BioHealx implant as MR safe.

PERFORMANCE TESTING - BENCH

Bench testing (implant strength/integrity testing, implant delivery verification, aging/transport testing, human factors/simulated use testing biocompatibility, chronic toxicity and degradation studies) have demonstrated the safety of the delivery device and the implanted device against available, applicable international standards, with passing test results, see table above for summarized testing, method, acceptance activities and results.

Human Factors/Usability Testing

Human factors testing was completed with seventeen representative implanters across several geographical locations. For each of the human factors testing sessions, all study participants completed training prior to simulated use with the BioHealx device and evaluation of user interface interaction to:

- Confirm that the BioHealx device can be safely delivered.
- Confirm that the BioHealx device can be effectively delivered.
- Confirm no unanticipated serious use errors attributable to the system user interfaces.

Representative (i.e., fully finished devices, labeled in finished device packaging) BioHealx devices, Instructions for Use and surgical accessories were used in all testing.

Simulated use testing in benchtop and animal models evaluated all procedural steps, inclusive of the instructions provided in the device labeling (*Note: the human factors simulated use in vivo testing performed was limited to training effectiveness only and was a separate activity to the GLP In Vivo Performance Testing*). Simulated use/human factors testing included all critical and several non-critical tasks associated with surgical site preparation, device unpackaging and the implant procedure. Testing included the evaluation of users while implanting the device at multiple circumferential locations in the simulated rectal model. This included awkward angles, for example the 3 o'clock position for right-handed users (9 o'clock position for left-handed users). Users reported that for awkward/difficult positions, patient positioning is considered for easier access of specific fistula internal opening locations required. The awkward positioning as presented to the user resulted in consistent successful device delivery across all users evaluated. Human factors testing was completed with seventeen representative implanters across several geographical locations.

Description	Simulated Testing (Model)		Users	Evaluation Type
	Bench	Animal		
Device Validation Testing – Usability/Human Factors Summative -Report	X	X	4 x EU	All participants performed several BioHealx implantations in a bench top and *in vivo* porcine model.
Device Validation Testing – Usability/Human Factors Summative -Report	X		1 x EU 2 x US	All participants performed several BioHealx implantations in a bench top model.
Device Validation Testing – Usability/Human Factors	X	X	2 x EU	All participants performed several BioHealx implantations

Description	Simulated Testing (Model)		Users	Evaluation Type
	Bench	Animal		
Summative -Report (SP001 Site 003)				in a bench top and *in vivo* porcine model.
Device Validation Testing – Usability/Human Factors Summative – Report (US Participants)		X	8 x US	All participants performed several BioHealx implantations in a bench top model.

All user participants in human factors evaluation testing were practicing colorectal surgeons or general surgeons with specialty interest in colorectal/gastroenterological surgery. Users were of varying experience levels, from 5-years post medical school experience to more than 40 years' experience and practicing across a range of clinical settings, including academic and community settings and from both small, medium, and small clinical environments.

All human factors participants received training in the implant procedure per the instructions for use/labelling prior to attempting BioHealx implant using the delivery system in the gel model. Human factor study participants used the device independently, without interference or influence from the training team or usability/human factors evaluator. The instructions for use were available to participants for reference and for use as per the study participant preference. The results of the human factors testing with the gel model have not identified any unanticipated or increased use related risks, including use error, misuse, or close calls.

A User Survey, based on Likert scale scoring (from human factors/summative testing) concluded that:

- 87.5% clinicians indicated that they would be likely to use the Signum Surgical BioHealx device more often than any other fistula repair if indicated.
- 100% of users found the instructions for use either easy or very easy to understand.
- 100% of users demonstrated successful delivery of the BioHealx implant during human-factors evaluation.
- 100% of users indicated that the device would not increase risk to the patient.

HUMAN FACTORS TESTING

Human factors validation testing was performed to assess the usability of this device. 10 practicing colorectal surgeons in the US and 7 practicing general surgeons in Europe (Hungary and Ireland) participated in this study. The study utilized a simulated gel model to and tested for 3 main attributes - (i) detachment of the implant from the driver coil (barbs), (ii) detachment of the implant from the driver coil (lock feature) and (iii) depth of delivery (i.e., visualization/measurability of the depth of the implant depth). In addition, a porcine animal study was also implemented with 6 of the users for further validation.

From observation, it was determined that all participants were able to successfully complete all tasks associated with delivery of the device. In addition, 16 of the 17 participants returned

completed surveys reporting that the device was either "very easy" or "easy" to use. 14/16 noted that they would use the device routinely and 9/16 noted that they would use the device more often than any other repair option.

PERFORMANCE TESTING - ANIMAL

A GLP *in vivo* performance study assessed simulated fistula tracts in the animal model of between 1 - 2 cm in length (due to variations in local animal anatomy). Tracts shorter than the 2cm tracts represent a "worst-case" implantation with minimal surrounding tissue to help stabilize the device. All fistula defects were 2mm in diameter and were maintained at that size by insertion of a seton that remained in place for 1 month prior to the BioHealx implant procedure. This is the largest diameter fistula tract that is indicated for treatment in the labeling and considered the worst case.

Six (6) pigs (species strain Sus scrofa scrofa/domestic. Yorkshire cross – white) were treated in the study. Four perianal fistulas, with a seton placed, were created at the 3,5,7 and 9 o'clock positions in each animal. No fistula formed at the 5 o'clock position in animal subject P9-07 (seton lost), resulting in 3 BioHealx Anal Fistula Device treatments for this animal. All other animals had 4 treatments (i.e., BioHealx implant to close the fistula) resulting in a total of 27 fistulas for subsequent treatment. After 4-weeks recovery, a second surgical procedure was performed per the BioHealx implant procedure. This involved the creation of a small mucosal incision at the internal opening site, and partial fistulectomy as necessary followed by placement of the BioHealx device in each of the fistula tracts.

The GLP Study objectives and acceptance criteria were as follows:

1. Evaluate the safety of the device, as measured by the observation of any device related adverse clinical signs of disease, ill health or detrimental effect on the incidence and progression rate of perianal healing (fistula were surgical created for the purpose of the study).
2. Evaluate the effectiveness of the BioHealx device in the repair of anal fistula. The effectiveness of the device in effecting tissue apposition of the surgically created tract was measured at 3 timepoints (14 ± 1, 30 ± 2 and 42 ± 2 days post implant). Healing (fistula closure by tissue apposition) was measured by histopathology analysis.

After 6 weeks (i.e., 42± 2 days), the BioHealx implant remained present (minimal degradation occurs in the first 6 weeks). Across the study population, a normal cellular response and healing progression was observed. Per the board-certified veterinary pathologist, there was progressive, uncomplicated healing of 100% treated fistulae, with no evidence of adverse tissue reactions associated with the device at any time point and uncomplicated healing of the treated fistulae was seen, meeting the criteria that the device was safe for its intended use. The study met the objectives / acceptance activities of the protocol.

SUMMARY OF CLINICAL INFORMATION

Introduction: A multi-center, prospective, non-randomized clinical study was provided to support the safety and effectiveness of the BioHealx Anal Fistula Device. Effectiveness was measured by closure repair of the anal fistula as determined by absence of drainage from the external opening site. Co-primary endpoints were defined as non-recurrence incidence at 6 and

12 months as determined by closure of the external fistula opening. Safety was evaluated through a review of all adverse events, whether deemed to be device-related or not for indication of unanticipated events and/or higher than expected event occurrence.

Thirty-two patients were treated at three investigational sites in Hungary; the inclusion criteria stated adults (18 – 75 years), male and female, with the presence of a single continuous anal fistula and at least one failed or recurrent anal fistula closure. The primary objective of the clinical study was to evaluate the safety and effectiveness of the BioHealx Anal Fistula Device in adults with recurrent anal fistula.

Inclusion/Exclusion Criteria: The study inclusion criteria stated adults (18 – 75 years), male and female, with the presence of a single continuous anal fistula and at least one failed or recurrent anal fistula closure. The device was not tested in patients with a fistula tract shorter than 2cm, patients with rectal prolapse, pregnant patients or those suffering from Crohn's disease.

Study Population: Males and Females age > 18 undergoing elective treatment for a persistent anal fistula.

Demographics and Baseline Data: 32 patients with recurrent transsphincteric fistula were implanted with BioHealx Anal Fistula Device. The mean age was 49.9 years (33 – 76 years). 84.5% of patients were male, 15.6% were female and 96.9% were Caucasian. The mean BMI was 28.15 kg/m^2 (18.8 – 41.5). The mean baseline pain score was 2.00 (range 0 – 8). Patient demographics and medical history are shown in **Table 2** and **Table 3** respectively.

Table 2 Baseline Demographics and Characteristics

Characteristic	BioHealx (N=32)
Gender: n/N (% Male)	27/32 (84.4%)
Age: Mean, Median, Std. Deviation (Min, Max)	49.9, 49.0, 11.61, (33, 76)
Height (cm): Mean, Median, Std. Deviation (Min, Max)	176.3, 176.0, 8.73, (158.0, 190.0)
Weight (kg): Mean, Median, Std. Deviation (Min, Max)	87.2, 88.5, 15.70, (53, 120)
BMI (kg/m^2): Mean, Median, Std. Deviation (Min, Max)	28.15, 28.52, 5.369, (18.8, 41.5)
Ethnicity: White	31/32 (96.9%)
Ethnicity: Black	0/32 (0%)
Ethnicity: Asian	0/32 (0%)
Ethnicity: Hispanic	0/32 (0%)
Ethnicity: Other	1/32 (3.1%)

Table 3 Summary of Medical History

Medical History	BioHealx Study (N=32)		
	Yes (n/N, %)	No (n/N, %)	Unknown (n/N, %)
Anemia	0/32 (0.0%)	32/32 (100%)	0/32 (0.0%)
Diabetes	3/32, (9.4%)	29/32, (90.6%)	0/32 (0.0%)
Congestive Heart Failure (CHF)	0/32 (0.0%)	31/32, (96.9%)	1/32, (3.1%)
Hypertension	14/32, (43.8%)	18/32, (56.3%)	0/32 (0.0%)
Coagulation Abnormality	0/32 (0.0%)	32/32 (100%)	0/32 (0.0%)
COPD	0/32 (0.0%)	32/32 (100%)	0/32 (0.0%)
Obesity (> 150 % of ideal weight)	5/32, (15.6%)	27/32, (84.4%)	0/32 (0.0%)
Smoker	6/32, (18.8%)	26/32 (81.3%)	0/32 (0.0%)
Current active abscess or infection	0/32 (0.0%)	32/32 (100%)	0/32 (0.0%)
Other significant condition	7/32, (21.9%)	25/32, (78.1%)	0/32 (0.0%)

The 7 clinical subjects with at least an "other significant condition" (coded by MedDRA, SOC) were as follows: Cardiac Disorders: 1/32 (3.1%) with a cardiac atrial fibrillation; Endocrine Disorders: 1/32 (3.1%) with hypothyroidism; Gastrointestinal Disorders: 2/32, (6.3%) gastroesophageal reflux disease; Metabolism and Nutrition Disorders: 2/32, (6.3%); Nervous System Disorders: 1/32, (3.1%) with epilepsy; and Vascular Disorders: 2/32, (6.3%) with hypertension.

Table 4 Fistula Variables at Baseline

Characteristic	BioHealx (N=32)
Type of Fistula: Trans-sphincteric	32/32 (100%)
Est. Length of Fistula Tract (cm): Mean Median (Min, Max)	 4.42 4.00 (2.50 – 8.00)
No. of Fistula Openings: n/N (%) Internal 1 opening:	 32/32 (100%)
External 1 opening:	32/32 (100%)
External 2 openings:	0/32 (0%)
Recurrent Fistula: n/N (%)	32/32 (100%)
Pain [a] Mean (Min, Max)	 2.00 (0 – 8)

[a] Pain Scale: 0-10 (0=No pain, 5=Moderate pain, 10=Worst pain)

100% of clinical subjects had at least one previous treatment (failed) for the anal fistula for which they had enrolled in the study.

Effectiveness Endpoints: The primary effectiveness of the Signum Surgical BioHealx™ Anal Fistula Device measured by successful closure repair of the anal fistula as determined by absence of drainage from the external opening site. Co-primary endpoints were defined as non-recurrence incidence at 12 months as determined by continued closure of the external fistula opening. Secondary effectiveness endpoints included:

- Fecal incontinence score at each follow-up visit
- Quality of life data collected at each follow-up visit
- Pain scores recorded at each follow-up visit
- Analgesic and antibiotic use after the surgery and at each follow-up visit
- Healing analysis: detailed information on changes in fistula condition and the type of any observed discharge/drainage at each follow-up visit.

Safety Endpoints: Safety endpoints included the evaluation of any presence and persistence of anal fistula as it is associated with significant morbidity. In addition to a high risk of recurrence, the condition can result in abscesses, local and systemic infection, fever, itching and bleeding. Various medications are prescribed to alleviate these complications and their symptoms.

- All reports of adverse events were recorded whether deemed to be device-related or not.
- Incidence, severity, and persistence of adverse events were to be tabulated and compared to such rates as reported in the literature for other anal fistula treatments.

Medication use was recorded and as applicable, tabulated against rate of usage as reported in the literature for other fistula treatments.

Follow-Up Schedule: Post-treatment follow-up visits occurred at 1-week, 1-month, 3-months, 6-months, and 12-months. To collect longer term data, patients were reconsented to attend an additional post-12-month follow-up visit. At each post-treatment follow-up visit, the following data was collected:

- Vital signs (blood pressure, heart rate, body temperature)
- Presenting symptoms (pain, fecal incontinence, infection),
- Patient reported health status (SF-36 Form, Fecal Incontinence, FACES Pain),
- Presence of bleeding/fistula discharge,
- Antibiotic and immunosuppressant use and any other medications (e.g., pain medications)
- Presence Suture Drain
- Extent of Closure repair (Observational)
- Extent of Closure repair/Fistula Closure (from 6-month post treatment visit only, flush test, if applicable)

Adverse Events, Adverse Device EventsPatient perspectives data was collected, via questionnaire, at the post 12-month follow-up visit.

Subject Accountability: All 32 patients were followed for a minimum of 12-months; 18 (of 32) patients, presented for a post 12-month follow-up visit to provide post-implant data of up to 40-months (average 23.4 months).

Clinical Results: By the last visit, 59.4% (19/32) of patients were fully healed (external opening scarred over, with no drainage). Of the 32 patients, 9.4% (3/32) of patients had an unsuccessful result, i.e., recurrence of the original treated fistula. All recurrent fistulas had occurred by 12-months.

An additional 31.2% (10/32) of patients had been downgraded from transsphincteric fistula to either sinus or superficial fistula. Downgrading of the fistula is defined as conversion from transsphincteric fistula to superficial fistula or sinus, which may undergo a secondary treatment (e.g., fistulotomy or silver nitrate) to promote transition to fully scarred over.

There were 28 adverse events in total, one of which was considered serious (resolved) and no unanticipated or serious adverse device related events. 50% (16/32) of clinical subjects experienced at least one adverse event; adverse events have been reviewed and found to be classified as either mild or moderate. There was one serious adverse event reported (resolved), identified as unrelated to the BioHealx device. The serious adverse event was reported as wound bleeding at the outer site of the partial fistulectomy.

From baseline to the last visit:

- There were no reports of incontinence, sphincteric damage, severe persistent pain (FACES-WONG >4), nerve or vascular injury, device migration or extrusion.
- There was a 71% reduction in mean pain score (10-point Wong-Baker FACES®) when compared to baseline.
- FIQL scores improved across all four components (lifestyle, coping behavior, depression/self-perception and embarrassment); the increases ranged from 7.2% - 11.6% improvement in quality-of-life score when compared to baseline.
- SF-36 Quality of Life outcomes showed indications of positive (improved quality of life scores) changes in physical component score (increase from 59.93±0.876 (post-surgery/hospital discharge) to 60.66±0.424 (at 12-months)) and mental component scores (59.51±0.941 (post-surgery/hospital discharge) to 59.83±0.991 (12 months)).
- There was no change in pain medications used by the study cohort during the follow-up period; pain medication use was limited to the immediate post-surgery period only.

Pediatric Extrapolation

The BioHealx Anal Fistula Device is indicated for patients aged 18 and older. For medical devices, the FD&C Act defines patients before their 22nd birthday as pediatric patients. It was appropriate to indicate the device for individuals 18 and older because patients aged 18 – 21 do not carry additional differences or risks relative to the patient population.

LABELING

Labelling has been provided including the instructions for use and package labels. The labelling meets the requirements of 21 CFR 801.109 for prescription devices and includes a description of the device, information for use including indications, methods, hazards, contraindications and precautions under which practitioners licensed to administer the device can use safety and for the purpose for which it is intended. A summary of the clinical validation data provides expected performance for intended use populations. Other patient conditions that may affect performance of the device are listed in the labelling.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with the use of the anal fistula closure device and the measure necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Product failure or malfunction • Inability to deliver the implant • Recurrence • Extrusion / migration • Lack of fistula closure	Clinical performance testing Postmarket surveillance Non-clinical performance testing Animal performance testing Shelf life testing Labeling
Adverse tissue reaction	Animal performance testing Non-clinical performance testing Biocompatibility evaluation Labeling
Infection	Clinical performance testing Postmarket surveillance Animal performance testing Sterilization validation Shelf life testing Labeling
Adverse events associated with improper device use or fistula repair and subsequent sequelae, including: • Fecal incontinence • Perirectal abscess • Tissue trauma during device placement • Bleeding • Pain	Clinical performance testing Postmarket surveillance Animal performance testing Non-clinical performance testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the anal fistula closure device is subject to the following special controls:

(1) Premarket clinical performance testing and postmarket surveillance acquired under anticipated conditions of use must demonstrate that the device performs as intended in the intended patient population unless FDA determines based on the totality of the information provided for premarket review that data from postmarket surveillance is not required. Testing must:
   (i) Demonstrate the ability to deliver the device to the fistula site;
   (ii) Demonstrate the ability to achieve fistula closure of both the internal and external openings with absence of drainage;
   (iii) Assess safety endpoints including tissue trauma, migration/extrusion, infection, perirectal abscess, bleeding, incontinence of stool or flatus, and pain; and

(iv) Assess fistula healing and recurrence, time to healing, surgical time required, and number of re-operative procedures needed to completely heal the fistula, including any need for seton maturation of the fistula.

(2) Animal performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Testing must assess histopathology, device migration/extrusion, infection, surgical time required, and tissue integration.

(3) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be evaluated:
   (i) Materials characterization of all components, including physical characteristics and compositional identity and purity;
   (ii) Mechanical strength of the implant;
   (iii) Mechanical integrity and functionality of any delivery systems; and
   (iv) For absorbable devices:
      (A) Residual strength over a clinically relevant timeframe; and
      (B) Evaluation of absorption at clinically relevant timepoints.

(4) The device must be demonstrated to be biocompatible.

(5) Performance data must demonstrate the sterility of the device.

(6) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

(7) Labeling must include:
   (i) The material composition, including any dyes or coatings;
   (ii) A detailed summary of the clinical performance testing conducted with the device, including device- and procedure-related adverse events;
   (iii) An expiration date or shelf life; and
   (iv) A detailed summary of the postmarket surveillance data collected and any necessary modifications to the labeling to accurately reflect outcomes based upon the postmarket surveillance data collected.

BENEFIT-RISK DETERMINATION

The risks of the device are based on data collected in the nonclinical *in vivo* study in addition to the clinical study described above. The risks and benefits of Signum Surgical's BioHealx Anal Fistula Device have been considered using the– Ligation of the Inter-sphincteric Fistula Tract (LIFT) surgical procedure as a frame of reference, particularly in the context of the risk of fistula persistence, recurrence, and procedure related sphincter damage/incontinence.

There are several existing treatment options including surgical fistulotomy, cutting seton, advancement flap procedure, LIFT procedure. A common complication of anal fistula surgery is the persistence or recurrence of the pathology, both considered a failure of surgery. Recurrent

anal fistulas, after previous surgery, represent an increasingly challenging problem since they are usually associated with a higher risk of re-recurrence and continence disturbance. Alternate options - fibrin sealants, cell therapies and fistula plugs – have a lower risk of surgical sphincter damage/potential permanent incontinence but are associated with variable healing rates and greater recurrence than their surgical counterparts.

The BioHealx clinical data reported 0% incontinence, 0% device extrusion/migration, 59.4% (19/32) fistula complete healing at 12 months (N=32) with a further 31.2% (10/32) downgraded from transsphincteric fistula to either sinus or superficial fistula. For a subpopulation of the study (N=18), the clinical data further reported on long term durability of the BioHealx closure repair post 12 months follow up (N=18, 13 – 40 months, average 23.4 months). The recurrence rate at 12 months (N=32) and > 12-months (N=18) was 9.4% (3/32 clinical subjects).

There were 28 adverse events in total which were experienced across half (50%, 16/32 patients) of the study population. All adverse events were classified as either mild or moderate, with the exception of one serious adverse event (wound bleeding at the outer site of the partial fistulectomy – resolved), which resolved and was identified as unrelated to the study device.

There were no adverse events associated with sphincteric damage, incontinence, severe (FACES-WONG>4) persistent pain, nerve or vascular injury, device migration or extrusion. No events were unanticipated or occurred at a higher than anticipated frequency. The BioHealx safety results demonstrated that the overall safety profile is acceptable and showed no unanticipated events.

The subject device provides uniform treatment of fistulas in ano eliminating user variability and simplifying the treatment of the condition by accurately identifying and closing the internal opening allowing healing by primary intention. In the Human factors study, which enrolled general and colorectal surgeons 50% of which were U.S. surgeons over 90% felt that the device was easy to use and provided a secure closure. A draining suture provides for drainage of the remaining fistula tract to the external opening. This has been shown to decrease the time required for surgical treatment of fistulas in ano.

Literature was used to provide comparator information; the literature had several limitations including poor quality OUS studies with variable definition of success. The BioHealx study was intended to recruit 35 patients and due to selection criteria only enrolled 32 patients for statistical analysis. Five subjects were noted to have protocol deviations (4 for BMI>35 and one for age >75) but were included in the study's statistical analysis. All thirty-two subjects have had 12 month follow up and 18 have had greater than 12 month follow up. The subject with the longest follow up is 40 months. These subjects all presented with recurrent transsphincteric fistulas and had undergone previous treatment. Subject meeting the primary and co-primary endpoints of complete and sustained healing of both the external opening without drainage at 12 months or longer follow up was 50 and 60% respectively. These results compared well with the literature comparator LIFT procedure which had a 12-month success rate in 9000 patients reported of 74% with a range of 40-94%. The 38 studies selected to evaluate the LIFT procedure were all OUS mostly Asian and of poor to moderate quality using the GRADE scoring system. However, of all the sphincter sparing procedures, the LIFT procedure most closely approximated the mechanism of action of the subject device and is the best comparator for evaluating the subject device. While the LIFT studies had variable definitions of success, most defined healing as complete closure of the external opening and no drainage.

The 32 patient BioHealx single arm pilot study reported no episodes of infection, device migration/ extrusion or incontinence and had a low recurrence rate of 9% all trans sphincteric. The LIFT studies report an average recurrence rate of 14% (30% intersphincteric and 70 % recurrent transsphincteric) with an incontinence rate of 9%. BioHealx appears to be safer than the LIFT procedure with a slightly lesser success rate at 12 or more months.

The probable risks of the subject device include recurrent or persistent fistula with perirectal abscess, incontinence of feces or flatus, device malfunction resulting in injury to the anal canal and surrounding musculature, foreign body sensation, sepsis, death, bleeding, etc. Recurrences requiring multiple repairs with multiple anesthetic risks is perhaps the most concerning. Only one episode of self-limited bleeding in a patient on Rivaroxaban who underwent a partial fistulotomy in addition to BioHealx placement, 7 minor post procedure infection and small abscesses, all self-limited and treated with antibiotic or local surgical drainage and a 9% recurrence rate were the only adverse events reported in the small multicenter single arm study submitted by the sponsor. The Instructions for Use has been revised instructing users that BioHealx should only be used in patients with cryptogenic, mature, simple transsphincteric, non-branching fistulas. These are the only fistulas for which BioHealx was studied clinically.

The uncertainty around the benefits and risks of the subject device still exist due to the small study sample size of 32 patients. The pre- clinical porcine model poorly informs the safety and effectiveness of the subject device performance in humans. The safety of BioHealx appears to be better than the LIFT procedure comparator with a slightly less effectiveness in the treatment of fistulas in ano. The success rate is based on the most common definition of healing for both devices: closure of both the internal and external opening with no drainage. The sponsors offer a downgraded fistula as an added definition of healing which includes fistula healing with a persistent external opening with clear drainage. They have not substantiated this as healing of the entire fistula tract with imaging studies or exam under anesthesia. The sponsor described a "Flush" test performed in the clinic which showed no communication between the external and internal openings suggesting that the drainage was from a superficial fistula or sinus. However, this test was performed without rectal dilation, without anesthesia, and in most cases using Betadine alone as a flush without the propulsive force of gas forming hydrogen peroxide. These are important reasons to suspect a high false negative rate for the Flush test to demonstrate a communication between the internal and external fistula openings. Therefore, the most common definition of healing with closure of both the internal and external opening without drainage as the definition of success, which is the definition used by the majority of the OUS LIFT studies, will be considered successful fistula healing. In the Human Factors Study reported over 90% of participants felt that the device was easy to use, provided good visualization of the internal opening and securely closed the opening. 88% felt they would use the device to treat fistulas in ano, 6% felt they would use it selectively and 6% would use it only in a clinical study.

While the 12-month data show complete healing of both the internal and external opening without drainage in 59% of subjects, 41% failed to achieve healing leaving this subgroup of patients at risk of recurrent perirectal abscess with perineal sepsis which can lead to anal sphincter damage with incontinence, need for reoperation, Fournier’s gangrene, systemic sepsis and even death in patients with significant comorbidities such as diabetes. Post market actions which can mitigate the uncertainty regarding the safety and effectiveness of BioHealx may include:

1. A new, separate postmarket study to demonstrate the durability of BioHealx treatment of cryptogenic fistulas in ano including patients with the same inclusion and exclusion criteria as studied in the premarket study for at least 3 years that includes US patients and US general and colorectal surgeons.

The benefit-risk analysis supports that the BioHealx- implant procedure for the BioHealx device is straightforward and delivery depth/position is controlled via the delivery system. The surgical procedure time is short for implantation of the BioHealx, with limited/no impact to existing anesthesia time, short hospital stays and no impact on medications use. A Postmarket Study will be conducted to further characterize benefit-risk due to the limitations of the small study size and uncertainty of generalizability of device performance in a patient population representative of the US.

The BioHealx Anal Fistula Device is intended for repair of soft tissue defects via tissue apposition. It is indicated for closure of the internal opening of mature, cryptogenic, transsphincteric, non-branching fistulas in ano via tissue apposition.

The risks of the BioHealx's technology and clinical study limitations are mitigated by the special controls, labeling, and post market study. Based on the totality of evidence and data with proposed mitigations of the BioHealx device, the probable risks are outweighed by the probable benefits.

Patient Perspectives

Patient feedback was additionally provided (72.2%, 13/18) at the post 12-month follow up visit via a study specific patient questionnaire. Prior to treatment with BioHealx, of the clinical study population, 53.8% (7/13) had endured their anal fistula for 1-8 (mean 3.17) years, the remainder for ≤ 6 months. 58.3% (7/12) listed discomfort and/or pain as affecting their life, 33.3% (4/12) indicated that discharge affected their life. Note: Not all respondents answered all questions.

Patient perspective data, post treatment with BioHealx, were obtained from self-reported quality of life (Fecal Incontinence Qualify of Life, SF-36 Qualify of Life) and pain scores (FACES-WONG) in the clinical study. There were no reports of incontinence or sphincter damage in the study. There were improvements in the Fecal Incontinence Quality of Life (FIQL) scores from baseline to 12-month visit across all four components (lifestyle, coping behaviour, depression/self-perception and embarrassment) that ranged from 7.2% - 11.6% improvement when compared to baseline. There was a 71% reduction in mean pain score (10-point Wong-Baker FACES®) from baseline to the last visit.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for the following intended use statement:

The Signum Surgical BioHealx Anal Fistula Device is indicated for closure of the internal opening of mature, cryptogenic, transsphincteric, non-branching fistulas in ano via tissue apposition.

The probable benefits outweigh the probable risks for the BioHealx Anal Fistula Device. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the BioHealx Anal Fistula Device is granted and the device is classified as follows:

Product Code: QML
Device Type: Anal fistula closure device
Regulation Number: 21 CFR 878.4835
Class: II