July 01, 2024

Signum Surgical Limited
Moshe Zilversmit
Chief Executive Officer
Galway Harbour Enterprise Par, New Docks, The Docks
Galway, Galway H91 NNY6
Ireland

Re: DEN240007
Trade/Device Name: BioHealx Anal Fistula Device
Regulation Number: 21 CFR 878.4835
Regulation Name: Anal fistula closure device
Regulatory Class: Class II
Product Code: QML
Dated: February 2, 2024
Received: February 2, 2024

Dear Moshe Zilversmit:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the BioHealx Anal Fistula Device, a prescription device under 21 CFR Part 801.109 with the following indications for use:

> 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.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the BioHealx Anal Fistula Device, and substantially equivalent devices of this generic type, into Class II under the generic name Anal fistula closure device.

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.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE)

determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the Federal Register announcing the classification.

On February 2, 2024, FDA received your De Novo requesting classification of the BioHealx Anal Fistula Device. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the BioHealx Anal Fistula Device into class I or II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the De Novo request, FDA has determined that, for the previously stated indications for use, the BioHealx Anal Fistula Device can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

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

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.

In order to satisfy special control (1) above, FDA has determined that you must conduct a postmarket surveillance study as outlined below.

FDA has determined that you must collect and report postmarket surveillance data acquired under anticipated conditions of use to demonstrate long-term durability and effectiveness associated with closing of fistulas in ano in a population representative of the intended use U.S. population treated by both novice and experienced general and colorectal surgeons in the U.S. Specifically, you must conduct postmarket clinical performance validation testing of the BioHealx Anal Fistula Device in patients from demographic groups representative of the U.S. intended use population, to include populations who had limited representation in the premarket study (e.g., African American, Asian), and have comorbidities similar to the intended use U.S. population. FDA defines long-term durability as the ability of the device to close both internal and external fistula openings following implantation while allowing for continued closure over time thus mitigating recurrence. The comparator group must also be representative of the intended use U.S. population. The study subjects must be followed at 3, 6, 12, and 24 months with a final follow-up at 36 months post-operation. Additionally, the study must monitor patients with mature, cryptogenic, transsphincteric, non-branching fistulae.

FDA expects that the postmarket clinical performance validation testing will include a clinically justified study sample size to confirm that performance of the device in postmarket use is not inferior to the performance observed in the premarket study for the U.S. intended use population.

Within 30 days of receipt of this order, you must submit a complete study protocol for the durability study as described above. FDA expects to work with you to approve your study protocols within 60 days of this order. Your submission should be clearly labeled as a "De Novo Postmarket Study Protocol" and submitted to the Agency as specified below. Please reference the De Novo number above to facilitate processing. If there are multiple protocols being finalized after granting of this De Novo request, please submit each protocol as a separate submission, identified by their unique study name(s).

From the date of study protocol approval, you must meet the following timelines:

- First subject enrolled within 12 months
- 20% of subjects enrolled within 24 months
- 50% of subjects enrolled within 36 months
- 100% of subjects enrolled within 48 months

In addition, you must submit separate periodic reports on the progress of the study as follows:

- Postmarket surveillance progress reports every six (6) months until subject enrollment has been completed, and annually thereafter, from the date of the protocol approval letter, unless otherwise specified by FDA.
- If any enrollment milestones are not met, you must begin submitting enrollment status reports every three (3) months in addition to your periodic postmarket surveillance progress reports, until enrollment has been completed or FDA notifies you otherwise.

- Submit the final postmarket surveillance report three (3) months from study completion (i.e., last subject's last follow-up date).

Each postmarket surveillance report should be submitted to the Agency as specified below, identified as a "De Novo Postmarket Surveillance Report" in accordance with how the study is identified above, and bearing the applicable De Novo reference number.

Be advised that failure to comply with any special control requirement, including the initiation, enrollment, completion, and reporting per the postmarket surveillance data requirements outlined above, may result in the adulteration and misbranding of your device.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov.

In addition, this is a prescription device and must comply with 21 CFR 801.109.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the Anal fistula closure device they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD&C Act; 21 CFR 1000-1050).

A notice announcing this classification order will be published in the Federal Register. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the De Novo request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

All required documents should be submitted, unless otherwise specified, to the address below and should reference the above De Novo number to facilitate processing.

De Novo Postmarket Surveillance
U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Alternatively, documents can be submitted electronically through the CDRH Portal. For more information on the CDRH Portal, please visit https://www.fda.gov/medical-devices/industry-medical-devices/send-and-track-medical-device-premarket-submissions-online-cdrh-portal.

If you have any questions concerning the contents of the letter, please contact Nils Potter at (240) 402-7130.

Sincerely,

Barton Sachs -S
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for Binita S. Ashar, M.D., M.B.A., F.A.C.S.
Director
OHT4: Office of Surgical
and Infection Control Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health