DE NOVO CLASSIFICATION REQUEST FOR PERMASEAL

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Apical Closure Device. An apical closure device is a prescription device consisting of a delivery system and implant component that is used for soft tissue approximation of cardiac apical tissue during transcatheter valve replacement procedures.

NEW REGULATION NUMBER: 21 CFR 870.4510

CLASSIFICATION: II

PRODUCT CODE: PNQ

BACKGROUND

DEVICE NAME: PERMASEAL

SUBMISSION NUMBER: DEN150029

DATE OF DE NOVO: JUNE 25, 2015

CONTACT: MICRO INTERVENTIONAL DEVICES, INC.
5 CAUFIELD PL.
SUITE 102
NEWTOWN, PA 18940

REQUESTER'S RECOMMENDED CLASSIFICATION: II

INDICATIONS FOR USE

The Permaseal is indicated for soft tissue approximation of cardiac apical tissue during transcatheter valve replacement procedures.

LIMITATIONS

The sale, distribution and use of the Permaseal device is limited to prescription use only.

Limitations on the device use are also achieved through the following statements included in the Instructions for Use:

Contraindications:

- Patients who are allergic to contrast agent.

- Patients who are allergic to platelet inhibitor therapy.
- Patients where a substantial risk of complications due to concomitant therapy, disease state or other condition exists.
- Patients whose target site for deployment has a myocardial wall thickness less than 10mm.
- Tissue that has been compromised due to previous adverse events such as infarction.
- Instances where excessive fat is present at the target site for deployment.
- Procedures where sheath introducers or catheters of more than 30F in outer diameter are needed.

Warnings:

DO NOT use the Permaseal device if the sterile barrier of the packaging has previously been broken, damaged or if the contents of the package appear to be damaged or defective.

DO NOT handle the Permaseal device without ensuring the safety is in the ON position.

DO NOT look into the distal end of the device or point the device at another individual.

DO NOT use rapid pacing when deploying the Permaseal device for cardiac applications.

DO NOT deploy the device at the true apex.

DO NOT attempt to pass sheath introducers or catheters of more than 30F (10mm) in outer diameter through the "operative window" of the Permaseal implant.

DO NOT use the Permaseal device if the expiration date has elapsed, as either sterility or performance may be compromised.

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

DEVICE DESCRIPTION

The Permaseal device is composed of a delivery device and an implant that is deployed to facilitate access and closure. The deployment site is accessed via minimally invasive surgery or percutaneous surgery. The device is compatible with a 0.025" – 0.035" guide wire. The implant is designed to close punctures, incisions or ostomies in the cardiac apical tissue up to 30F, or 10mm in diameter.

The device features a handle designed to facilitate proper device placement and allow for single-handed deployment of the implant. The handle contains a trigger that actuates the device and incorporates a mechanical safety. The handle functions as a tool to grip and position the device. It contains the actuating mechanism to control deployment of the anchor using a trigger mechanism.

With the safety in the ON position, it prevents movement of the trigger and reduces the potential for accidental firing. The insertion tube extends from the handle and contains the implant. The insertion tube is 14cm long to ensure sufficient access to the target site. The device handle and insertion tube can be viewed below in Figure 1.

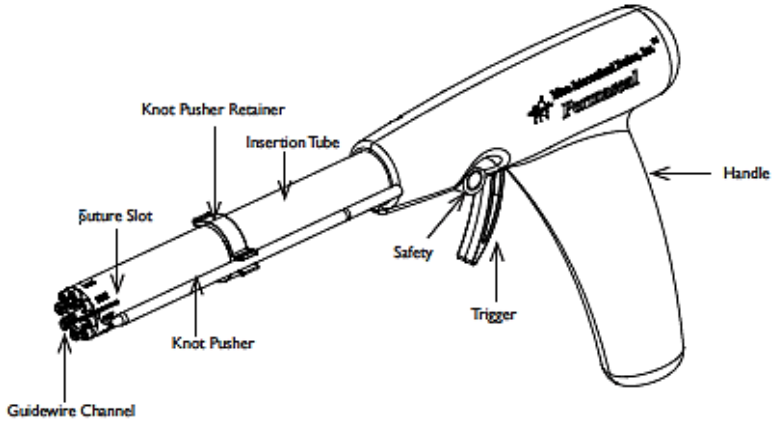

Figure 1. Permaseal™ Delivery System

The implant is composed of an array of eight polypropylene anchors connected by a 2-0 braided, coated polyester suture U.S.P, as seen in Figures 2 and 3. The suture was separately cleared to market through K021019.

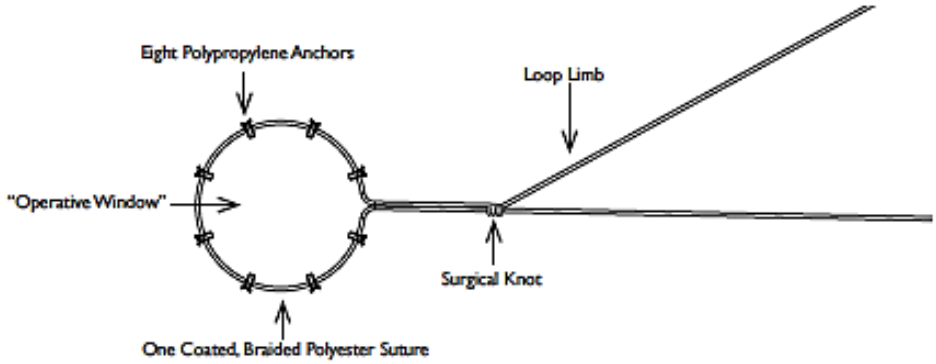

Figure 2. Permaseal Implant

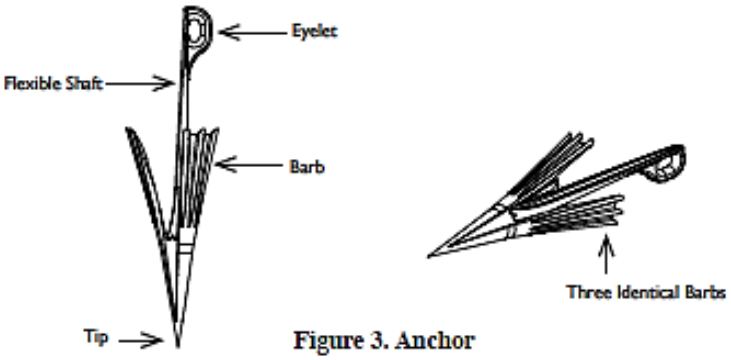

Figure 3. Anchor

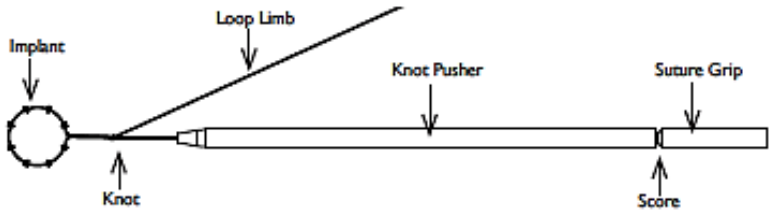

Figure 4. Knot Pusher

The suture is threaded through the eyelets of the eight anchors in a circular pattern and terminates in a surgical knot. The excess suture provided is referred to as the loop limb. The opening that is formed in the center of the implant is referred to as the 'operative window.' The knot is tightened at the end of the procedure by advancing the knot pusher toward the implant. The knot pusher is shown in Figure 4, above. The knot pusher is affixed to the insertion tube by the knot pusher retainer and is removed from the tube before the implant is deployed.

Upon release of the safety and actuation of the trigger, a spring-loaded pusher tube connected distally to 8 pusher pins is released, transmitting the force of the spring through the pusher pins to the anchors, simultaneously embedding the 8 anchors firmly into the tissue at the target site. A properly deployed anchor is demonstrated in Figures 5 through 7, below.

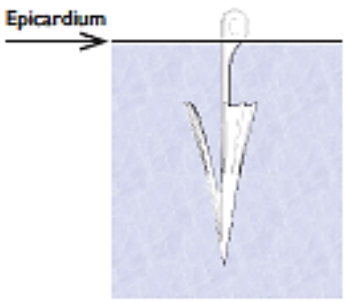

Figure 5. Properly Deployed Anchors

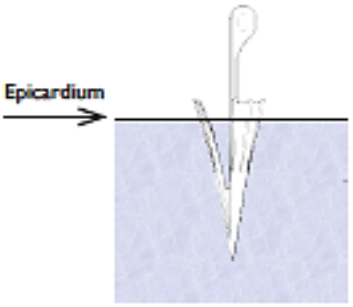

Figure 6. Partially Deployed Anchors

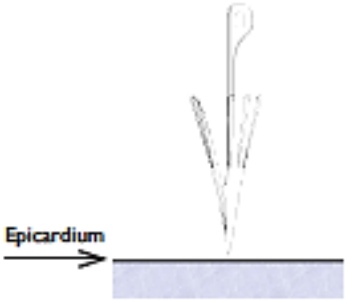

Figure 7. Un-Deployed Anchors

The anchors are deployed at a pre-determined depth with the sutures resting on the surface of the heart. Once deployed, the polyester suture and eight anchors create an 'operative window' in a pattern approximating that of a purse-string suture pattern. The anchors provide a secure attachment site for the suture that connects the multiple anchors together. The suture serves as a means to bring the incised tissue edges into apposition so as to close the puncture. Advancing the surgical knot in the suture with the knot pusher creates sufficient tension on the anchors to pull them and the tissue together so as to close punctures, incisions or otomies in the cardiac apical tissue up to 30F, or 10mm in diameter.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Permaseal implant is tissue contacting and the delivery system is a limited contacting, external communicating device that comes in contact with tissue.

The distal 10cm of the delivery system, including the implant, was tested to assess the biocompatibility of the delivery system. This was appropriate because all limited contact exposure materials are contained within the distal 10cm of the device. In accordance with ISO 10993-1 and relevant subparts, cytotoxicity, sensitization, and irritation testing was performed to assess the delivery system.

The Permaseal implant was tested separately using the following biocompatibility tests: cytotoxicity, intracutaneous reactivity, sensitization, material mediated pyrogenicity, acute systemic toxicity, hemolysis and bacteria reverse mutation. The implant did not require implantation, sub-chronic toxicity and chronic toxicity based on existing animal study data and OUS clinical data. Carcinogenicity testing was omitted considering that the suture is cleared and that there were no relevant concerns with the animal or clinical data reviewed as part of the *de novo* submission. An overview of the biocompatibility testing performed to evaluate the biocompatibility of Permaseal is provided in Table 1. The Permaseal implant and delivery system were determined to be biocompatible based on these tests.

Table 1. Biocompatibility Tests for Permaseal Delivery System and Implant

Test	Purpose	Results
Delivery System		
Cytotoxicity MEM Elution Using L-929 Mouse Fibroblast Cells (GLP)	Assessment of biological reactivity of mammalian cell cultures following incubation with test device extracts	Non-cytotoxic
Sensitization Guinea Pig Maximization Sensitization Test (GLP)	Determine the potential for the test device extract to elicit contact dermal allergenicity	Non-sensitizing
Irritation Intracutaneous Irritation Test (GLP)	Assess potential of the device to produce irritation following a single intradermal injection of specific extracts prepared from a test device	Non-irritant
Hemolysis Hemolysis Assay – Direct Contact Method (GLP)	Evaluate the hemolytic potential of test articles	Non-hemolytic
Systemic Toxicity Acute Systemic Injection Test (GLP)	Screen test article extracts or solutions for potential toxic effects as a result of a single-dose systemic injection in mice.	Non-toxic
Pyrogenicity Materials Mediated Rabbit Pyrogen (USP and GLP)	Evaluate the test device extract for leachates that have the potential to induce material-mediated pyrogenicity following a single dose injection	Not pyrogenic
Implant		
Cytotoxicity (In Vitro Cytotoxicity Study)	Evaluate an extract of a test article for cytotoxicity to mammalian cells in culture	Non-cytotoxic
Sensitization (Maximization Sensitization Study)	Evaluate the potential of test article to cause delayed dermal contact sensitization	Non-sensitizing

Test	Purpose	Results
Irritation (Intracutaneous Reactivity Study)	Evaluate the local dermal irritation of a test article extract following intracutaneous injection in rabbits	Non-irritant
Acute Systemic Toxicity (Systemic Toxicity Study)	Evaluate acute systemic toxicity of test article extract following injection in mice	Non-toxic
Pyrogenicity (Material Mediated (USP and GLP))	Determine whether an extract of the test article induced a pyrogenic response following intravenous injection in rabbits	Non-pyrogenic
Hemocompatibility (Hemolysis – Direct (GLP))	Evaluate the potential to cause hemolysis	Non-hemolytic
Genotoxicity (AMES Assay Bacterial Reverse Mutation)	Evaluate the mutagenic potential of the device test article by measuring its ability to induce DNA reverse mutations in *S. typhimurium* and *E. coli* in the presence and absence of microsomal enzymes	Non-mutagenic

SHELF LIFE/STERILITY

Packaging validation, sterilization validation and shelf life testing were performed to evaluate the Permaseal device, as summarized in Table 2 below. The Permaseal device was determined to have a 1-year shelf life, based on the real time aging.

Table 2. Packaging Validation, Sterilization Validation and Shelf Life Testing Overview for the Permaseal

Test	Purpose	Acceptance Criteria	Results
Packaging Validation	Produce objective evidence that the package obtained using the design for the individual package of Micro Interventional Devices (MID) meets the requirements of MID, the manufacturer's drawings and product specifications when the package is made.	Seal Visual Inspection: No burns, channels, voids, pleats or foreign matter Peel Samples: Minimum peel force 1 lb/in Burst Samples: Minimum burst values recorded Bubble Samples: No seal leaks/seal bubbles accepted Dye Samples: No complete seal dye penetration accepted	All tests passed

Test	Purpose	Acceptance Criteria	Results
Sterilization Validation	Evaluate the sterilization procedure for the Permaseal device and the ability to sterilize the device according to the pre-identified criteria, including achieving a Sterility Assurance Level of 10^{-6}	Bioburden: b(4) Bacteriostasis/Fungistasis: Neither acceptable EO Residual: Total recoverable mass b(4) Bacterial Endotoxin: b(4) EtO Acceptable Limit: b(4)	All tests passed
Shelf Life	Evaluate the impact of one year real time aging on the Permaseal device	Visual and Functional assessments (i.e., successful ex-vivo device deployment) at baseline and one year	All visual inspections and functional tests passed
Environmental Conditioning and Package Integrity	Evaluate the Permaseal devices after being subjected to a range of temperatures, humidity and simulated distribution testing	Verification testing, performance testing (i.e., successful deployment in porcine heart, compatibility with sheath, functionality of suture grip, knot pusher, knot and anchor eyelets), packaging verification testing, average peel force >1.0lbf/in	All tests passed, any deviations appropriately explained
Package Integrity	Demonstrate that the Permaseal device packaging will provide sufficient protection such that the function of the device and package integrity are not compromised as a result of typical package handling processes	Seal Peel: No irregularities or delamination of the seals observed, peel strength greater than 1 lbf/in Dye Penetration: No dye penetrates through seal	All tests passed

PERFORMANCE TESTING – BENCH

The Permaseal device functionality was assessed using two sets of bench testing, including design verification and a performance verification test, as described in Table 3.

Table 3. Bench Testing Overview

Test	Purpose	Results
Design Verification Testing	Ensure that the design meets the design inputs as defined in the Product Performance Specifications for the Permaseal	All acceptance criteria met, any deviations appropriately justified
Device Weight	Ensure that the device weight meets specification	All passed
Dimensional Verification	Ensure that the following measurements meet specification: - Overall device length, height, width - Insertion tube length, diameter - Anchor overall length - Knot location on suture	All passed
Color/Appearance Verification	Ensure that the handle, insertion tube and safety meet color/ appearance specifications	All passed
Device Operation Verification	Ensure that the device operates to specification by evaluating the following: - Trigger safety functionality - Guidewire compatibility - Trigger pull force - Safety disengagement force - Inability to fire with an engaged safety - Anchor deployment depth using the delivery system	All passed
Implant Performance Verification	Evaluate if the implant meets the following criteria: - Accommodates intended sheath sizes - Suture grip detaches from knot pusher - Knot pusher functionality - Suture knot functionality and slip force - Anchor eyelet functionality under tension and axial pull force - Anchor barb extraction from tissue without breakage - Peak anchor insertion force	All passed
Performance Verification Testing	Conduct functional performance verification testing in porcine *ex vivo* hearts	All criteria passed
Anchor Pull Out Test	No anchor pull out from the tissue at a tensioning force of 1N	Passed, no anchor pull out
Leakage Test	No leakage of solution shall occur at a pressure of 180mmHg	Passed, no leakage

The Permaseal also underwent verification of component materials, packaging configuration and labeling verification. These verifications demonstrated the conformance of the packaging, labeling and component material to predetermined acceptance criteria, thus further supporting the device safety profile.

PERFORMANCE TESTING – ANIMAL

The Permaseal was rigorously evaluated under a chronic animal study comparing the Permaseal device to conventional mattress suture closure in a porcine model at 30 days as summarized in Table 4. The device was also assessed using an investigational analysis, specifically *in vivo* testing of the Permaseal configuration with the molded polypropylene anchors.

Table 4. Nonclinical Animal Study Testing Overview

Test	Purpose	Acceptance Criteria	Results
Chronic Animal Study at 30 Days	Demonstrate the performance of the Permaseal Device (test article) to traditional mattress suture closure b(4) cardiovascular surgical applications	Success in facilitating the transapical access following a transapical puncture of the left ventricle in a simulated transcatheter heart valve implantation procedure acutely and with respect to wound healing chronically (30 day survival) in a porcine model	b(4) all animals survived to the designated end point with no significant adverse clinical observations or procedural complications related to the test devices. Pathological changes were minimal and expected for this type of procedure.
Acute Investigational Analysis, *in vivo* testing of Permaseal configurations	Evaluate the performance of the Permaseal in an *in vivo* porcine model	Assessment of performance of the polypropylene anchors, the interaction between the suture and the insertion tube during deployment, the tensioning process to achieve wound closure, the performance of implant deployment, passage of transapical sheath and achieving hemostasis	Three separate deployments were completed in one animal with acceptable results.

SUMMARY OF CLINICAL INFORMATION

The STASIS (Secure Transapical Access and Closure) study, a non-randomized, multi-center, prospective, open-label, observational safety and performance study, was conducted to evaluate the Permaseal device. There were 34 patients undergoing transapical transcatheter aortic valve replacement (TA-TAVR) at five clinical sites in Germany and the Netherlands. Table 5 details the population demographics and baseline characteristics of the patients in STASIS.

Table 5. STASIS Demographics and Baseline Characteristics

Number of subjects enrolled	34
Age	79.4 +/- 7
Female	47.1%
Hypertension	88.2%
Coronary artery disease	70.6%
Mitral valve disease	41.2%
COPD	11.8%
Coagulopathy	2.9%
Cancer	11.8%

The STASIS endpoints were as follows:

Primary Effectiveness Endpoint:
Rate of pulsatile bleeding requiring significant surgical intervention (more than one pledgeted suture) at discharge and at 30-day follow-up. The literature derived performance goal was 15%.

Secondary Effectiveness Endpoint:
Treatment parameters that include procedure time, any reported assessment of ease of use, and the appearance of new hypo- or akinesis at 90 days and 12 months.

Safety Endpoint:
All adverse events (AEs) and serious adverse events (SAEs) occurring during the TA-TAVR procedure and follow-up periods of 30 days, 90 days and 12 months. The safety analysis involved reporting of all SAEs and AEs as well as their severity and relation to the Permaseal device and transapical approach. Valve Academic Research Consortium (VARC) 2 (*J Thorac Cardiovasc Surg 2013;145:6-23*) definitions were used.

Results

Primary Effectiveness:
The rate of pulsatile bleeding requiring more than one pledgeted suture at hospital discharge and 30-day follow-up was 6.5% (2/31), meeting the primary effectiveness endpoint target. Of the 34 total patients in the STASIS study, only 31 patients were included in the effectiveness analysis. One of the excluded patients was a roll-in, while the remaining two patients were excluded due to protocol violations.

Secondary Effectiveness:
The results of STASIS with respect to secondary endpoints and clinical outcomes are provided in Table 6 and Table 7.

Table 6. STASIS Procedural Secondary Endpoints and 30-Day Clinical Outcomes

Number of Subjects	34
TAVR Procedural Success	100%
Mortality (30-days)	0.0%
Myocardial Infarction (30-day)	0.0%
Stroke (30-day)	0.0%
Vascular Complications	2.9%
Conversion to Sternotomy	0.0%
New Permanent Pacemaker	12.1%
Procedure Time (min)	86.0 +/- 19.6
Need for Transfusion (>2 units)	8.8%
Hospital Stay	10.6 +/- 3.7

Table 7. STASIS Clinical Outcomes and Secondary Endpoints at 90 Days

Number of Subjects	3
Mortality	3.1%
Myocardial Infarction	0.0%
Stroke	0.0%

One patient death due to non-cardiovascular causes subsequent to orthopedic surgery was reported prior to 90-day follow-up. There was no change in wall motion reported for any patient between screening and hospital discharge. At the 90-day follow-up one patient improved from moderate hypokinesis to normal and one improved from moderate to mild hypokinesis. One patient developed mild hypokinesis and one developed moderate hypokinesis. One patient with moderate hypokinesis at screening was reported akinetic at 90-day follow-up.

Safety Endpoints:
There were no deaths, myocardial infarctions or strokes for any patients during the 30-day follow-up period. This favorable safety profile was maintained at 90-days clinical follow-up. One patient died at day 37 due to pulmonary embolism subsequent to a hip replacement surgery. This death was determined to not be related to either the procedure or device.

Thirty-three (33) SAEs were reported during the study, of which two were considered device-related. The two device-related SAEs involved setting the pre-tied knot before achieving hemostasis, requiring the addition of extra sutures. These events occurred at one site, early in the study, indicating a need for additional training on the Permaseal IFU, which was implemented and no further device-related SAEs were reported.

LABELING

Labeling provided for the Permaseal includes Instructions for Use and packaging labels. The labeling provided satisfies the requirements of 21 CFR § 801.109 Prescription devices, and

includes information regarding specifications, instructions for use, contraindications, warnings, and cautions, as well as a prescription statement.

Important components of the labeling include:

- Contraindication to exclude patients with myocardial wall thickness less than 10mm, due to the risk of myocardial wall perforation; and
- Detailed instructions explaining each step of Permaseal use

RISKS TO HEALTH

Table 8 identifies the risks to health that may be associated with use of the Apical Closure Device and the measures necessary to mitigate these risks.

Table 8. Identified Risks to Health and Mitigation Measures

Identified Risk	**Mitigation Measure**
Infection	Sterilization Validation Shelf Life Testing Labeling
Adverse Tissue Reaction	Biocompatibility Evaluation *In vivo* Performance Testing
Bleeding ▪ At ventricular puncture or anchor deployment sites	Non-clinical Performance Testing *In vivo* Performance Testing Labeling
Tissue Damage ▪ Apical tearing ▪ Myocardial tearing (local or diffuse)	Non-clinical Performance Testing *In vivo* Performance Testing Labeling Training
New Hypokinesia or Akinesis of Apex	*In vivo* Performance Testing Labeling
Thromboemboli and Full Thickness Injury	*In vivo* Performance Testing Labeling Training
Pericardial Tamponade	*In vivo* Performance Testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the Apical Closure Device is subject to the following special controls:

1. The patient contacting materials must be evaluated to be biocompatible.
2. Performance data must validate the sterility of the patient-contacting components of the device.
3. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the labeled shelf life.
4. Non-clinical performance testing data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:

a. Consistent and reliable implant deployment;
b. Assessment of implant pull-out force; and
c. Sheath size compatibility with implant.

5. *In vivo* evaluation of the device must demonstrate device performance, including device operation resulting in closure of the myocardial wound.
6. Labeling must include the following:
    a. Detailed information explaining how the device operates;
    b. Sheath size that device can accommodate;
    c. Identification of the minimum myocardial wall thickness to ensure optimal device function; and
    d. A shelf life.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical laboratory tests, animal studies, and data collected in a clinical study as described above. In the STASIS clinical study, SAEs occurring in the population included vascular complications (2.9%) and new permanent pacemaker (related to TAVR placement) (12.1%) at 30 days post-procedure. There were no deaths, myocardial infarctions, or strokes for any patients during the 30-day follow-up. Within 90 days post-procedure, the mortality rate was 3.1%. No tearing or psuedoaneurysm of the apex was observed. No myocardial infarctions were observed and apical myocardial function was preserved. Considering the STASIS data, the probability of any adverse event related to the device are extremely low. Any harmful events requiring additional therapy would be expected to be observed within the 90-day STASIS study. There were no additional patient risks associated with the Permaseal over the standard of care, including the risks of bleeding, aneurysm, or pseudoaneurysm.

The probable benefits of the device are also based on nonclinical laboratory, animal studies as well as data collected in a clinical study as described above. The Permaseal provides a minimally invasive reproducible technique for apical closure that distributes tension equally and circumferentially around a trans-apical access point. Apical device closure, defined as freedom from pulsatile bleeding requiring significant surgical intervention (more than one pledgeted suture), was achieved in 93.5% of patients. No patients required re-operation for bleeding at the apical access site and results were durable through 90 days. There was also no death or stroke observed in the 30-day follow-up interval of the STASIS trial.

Additional factors to be considered in determining the probable risks and benefits for the Permaseal include that the placement of the Permaseal device is at least as safe and effective as the current standard of care. The additional probable benefits of the Permaseal device include reduction of apical bleeding complications, the minimization of apical myocardial injury that might result in apical akinesis or dyskinesis, reduction in procedural time, and reduction in procedural bleeding related to apical leak. Furthermore, patients would likely value a secure and less traumatic procedure available with the use of the Permaseal device. It is also important to note that the standard of care, which is closure using manually placed purse-strings or mattress sutures during surgery, is not precluded by the Permaseal if failure were to occur. Finally, the Permaseal is placed epicardially as a cinching mechanism and no device components remain in contact with the bloodstream or intra-ventricular cavity.

Patient Perspectives
This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion
In conclusion, given the available information above, the data supports that for soft tissue approximation of cardiac apical tissue during transcatheter valve replacement, the probable benefits outweigh the probable risks for the Permaseal device. The device provides substantial benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* request for the Permaseal is granted and the device is classified under the following:

Product Code: PNQ
Device Type: Apical Closure Device
Class: II
Regulation: 21 CFR 870.4510