SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Sinus Stent
Device Trade Name:	PROPEL® Contour Sinus Implant
Device Procode:	OWO
Applicant's Name and Address:	Intersect ENT 1555 Adams Drive Menlo Park, CA 94025
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P100044/S023
Date of FDA Notice of Approval:	February 23, 2017

The original PMA (P100044) for the PROPEL Sinus Implant was approved on August 11, 2011 and has the following indications for use: "The Propel™ is indicated for use in patients ≥ 18 years of age following ethmoid sinus surgery to maintain patency, thereby reducing the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids. The PROPEL™ separates mucosal tissues, provides stabilization of the middle turbinate, prevents obstruction by adhesions, and reduces edema." The SSED to support the indication is available on the CDRH website (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100044) and is incorporated by reference here. The PROPEL Mini Sinus Implant was approved for use in the ethmoid sinus (P100044/S001) and the frontal sinus opening (P100044/S018). The current supplement for the PROPEL Contour Sinus Implant was submitted to expand the indication to include placement in the frontal and maxillary sinus ostia following sinus surgery.

II. INDICATIONS FOR USE

The PROPEL Contour sinus implant is indicated for use in patients ≥ 18 years of age to maintain patency of the frontal and maxillary sinus ostia following sinus surgery and locally deliver steroids to the sinus mucosa. The PROPEL Contour sinus implant separates/dilates mucosal tissues, prevents obstruction by adhesions/scarring, and reduces edema. The implant reduces the need for post-operative intervention such as surgical adhesion lysis and/or use of oral steroids.

III. CONTRAINDICATIONS

The use of the PROPEL Contour sinus implant is contraindicated in the following patients.

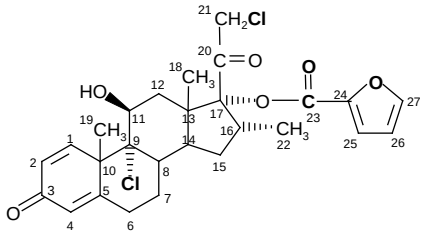
- Patients with suspected or confirmed intolerance to mometasone furoate.
- Patients with a known hypersensitivity to lactide, glycolide or caprolactone copolymers.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PROPEL Contour sinus implant labeling.

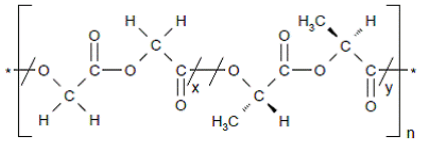
V. DEVICE DESCRIPTION

The PROPEL Contour sinus implant is a bioabsorbable implant designed to maintain patency of the peripheral sinus ostia. The PROPEL Contour sinus implant is manufactured from a synthetic bioabsorbable copolymer, poly (L-lactide-co-glycolide) (PLG). The implant contains mometasone furoate (active ingredient), a synthetic corticosteroid with anti-inflammatory activity. Mometasone furoate is a white to off-white powder. The chemical name is 9α,21-dichloro-11β,17α-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione17-(2-furoate), with the empirical formula $C_{27}H_{30}Cl_2O_6$, and a molecular weight of 521.43 g/mol. Mometasone furoate is a hydrophobic drug that is practically insoluble in water. Mometasone furoate is stable under aqueous, acidic and oxidative conditions. MF can degrade under extreme basic, thermal and photolytic conditions. The chemical structure is shown. The drug is embedded in a bioabsorbable polymer matrix containing poly-(DL-lactide-co-glycolide) and polyethylene glycol (inactive ingredients) which provides for gradual release of the drug.



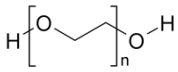
Chemical structure of mometasone furoate

The inactive ingredients on the sinus implant are poly-(DL-lactide-co-glycolide) and polyethylene glycol. Poly-(DL-lactide-co-glycolide) is an amorphous biodegradable polymer. The chemical structure is shown below.



Chemical structure of poly-(DL-lactide-co-glycolide)

Polyethylene glycol is a hydrophilic polyether compound that is highly flexible. It is non-toxic and non-immunogenic. The chemical structure is shown below.



Chemical structure of polyethylene glycol

The implant is designed to accommodate the size and variability of the post-surgical frontal and maxillary sinus ostia. The PROPEL Contour sinus implant is designed to be inserted by a physician under endoscopic visualization and once inserted, the implant is designed to be self-retaining against the mucosa of the surgically enlarged sinus ostia. A delivery system is provided to access the frontal and maxillary sinus opening and insert the implant.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for maintaining patency of the maxillary sinus or frontal sinus opening following functional endoscopic sinus surgery (FESS). These devices are referred to as either packing, structured stents or injectable space-filling gels/stents. They act as space-occupying materials, drainage tubes, or post-operative spacers to prevent obstruction by adhesions, allow ventilation and drainage of fluids, and maintain opening of the frontal sinus drainage pathway. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The PROPEL Contour sinus implant belongs to the PROPEL family of Sinus Implants, which includes the PROPEL and PROPEL Mini Sinus Implants. The PROPEL Contour sinus implant has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects associated with the PROPEL Contour sinus implant are anticipated to be similar to those associated with other sinus stents, gels or packing.

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Potential adverse effects associated with the PROPEL Contour sinus implant include, but may not be limited to:

- Premature displacement of implant or small implant fragments
- Swallowing implant or implant fragments
- Pain/pressure/headache due to the adherence of crusting to, or presence of the implant
- Aspiration of small implant fragments
- Foreign body response, including formation of granulation tissue

Potential risks or side effects associated with intranasal mometasone furoate include:

- Nasal irritation
- Hypersensitivity reaction
- Intranasal bleeding (epistaxis)
- Localized infection (bacterial, fungal or viral) in the nose or pharynx
- Nasal burning
- Nasal dryness
- Susceptibility to secondary infections due to bacteria, fungi or viruses
- Glaucoma/elevation of intraocular pressure
- Cataracts/change in lens opacities
- Headache
- Pharyngitis

Potential risks or general side effects associated with use of oral steroids may include, but not be limited to the following.:

- Alteration of the HPA axis including growth suppression
- Immunosuppression
- Hypersensitivity reactions
- Headache
- Epistaxis/intranasal bleeding
- Coughing
- Vomiting
- Candidiasis
- Glaucoma/elevation in intraocular pressure
- Cataracts/changes in lens opacities
- Arthralgia
- Myalgia

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The following section provides a summary of the non-clinical studies conducted to support the PROPEL Contour sinus implant.

A. Laboratory Studies

Biocompatibility

Biocompatibility testing for the PROPEL family of sinus implants was conducted in accordance with ISO 10993, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing. The biocompatibility studies were previously provided to FDA in P100044 (PROPEL) and P100044/S001 (PROPEL Mini), and are incorporated by

reference here. The results of these tests were suitable to support the safety and biocompatibility of the PROPEL Contour sinus implant.

In vitro Testing

The PROPEL Contour sinus implant was tested to evaluate mechanical performance after sterilization, extreme conditioning, and simulated transportation to verify the PROPEL Contour sinus implant performs as intended and that the packaging performs as intended by preventing damage to the device and the sterile barrier during sterilization and transportation. This testing included implant testing (dimensional inspection, post deployment diameter testing, integrity inspection, bond joint tensile strength and radial strength, sinus model testing, inherent viscosity), delivery system testing (inspection, functional testing, tensile strength and fatigue testing) and packaging testing. Results of the tests demonstrate that PROPEL Contour sinus implant performs as intended and meets the product specifications.

Test	Sample Size	Acceptance Criteria	Results
Implant Testing			
Dimensional Inspection	20*	Number of Points: 10 Height: $6.5 \leq x \leq 9.0$ mm Waist Diameter: $14.0 \leq x \leq 17.0$ mm Outer Diameter: $25.5 \leq x \leq 28.5$ mm (All samples must pass with 95/95 conf/reliability)	Pass
Post Deployment Waist and Outer Diameter	20	Post Deployment Waist Diameter: $x \geq 10.0$ mm Post Deployment Outer Diameter: $x \geq 18.0$ mm (All samples must pass with 95/95 conf/reliability)	Pass
Implant Cross Joint Integrity Inspection	15	Implant must remain structurally intact overall after four simulated deployment cycles and no two neighboring cross joints can be separated. (All samples must pass with 90/90 conf/reliability)	Pass
Implant Bond (Lap) Joint Tensile Strength	15	$x \geq 0.60$ N (All samples must pass with 90/90 conf/reliability)	Pass
Implant Coating Integrity Inspection (Visual)	15	The total compromised coating surface area is $\leq 8\%$ of nominal implant surface area (220 mm^2) (All samples must pass with 95/90 conf/reliability)	Pass

Implant Radial Strength	20	$x \geq 0.04$ N (All samples must pass with 95/95 conf/reliability)	Pass
Water Cell	20*	No cross joints may be separated > 3 mm from the wall of the hole opening at 14 days.** (All samples must pass with 95/95 conf/reliability)	Pass
Inherent Viscosity (IV)	5*	0.85-1.25 dl/g (All samples must pass with 95/95 conf/reliability)	Pass
Delivery System Testing			
Delivery System Inspection	15	Applicator length must be $11.5 \leq x \leq 13.5$ cm Verify bevel cut at end of the applicator (All samples must pass with 90/90 conf/reliability)	Pass
Delivery System Functional Testing	22	Pusher must not bind during operation The coiled pusher tip must not extend more than 1 mm beyond the distal edge of the bevel tip or reside inside the proximal edge of the bevel tip. (All samples must pass with 90/90 conf/reliability)	Pass
Applicator Tensile Strength	15	$x \geq 2.3$ N (All samples must pass with 95/90 conf/reliability)	Pass
Delivery Handle Tensile Strength	15	$x \geq 5.98$ N (All samples must pass with 95/90 conf/reliability)	Pass
Delivery System Fatigue Testing	29	The pusher must not bind during operation and the wire must remain intact and inside applicator after six bending cycles (All samples must pass with 90/90 conf/reliability)	Pass
Complete Device/Packaging Testing			
External Visual Inspection	22	Packaging must include a labeled chipboard box with an IFU and a labeled, sealed foil pouch placed inside. Information on both labels must match and be legible. Labels must include the product name, model number, product dose, expiration date, and lot number. Foil pouch must be free of visible holes. Seal must be smooth, intact and continuous. No channels, bubbles that extend through both sides of the seal, voids, gaps or other compromised areas in the seals. (All samples must pass with 90/90 conf/reliability)	Pass
Internal Visual Inspection	22	The foil pouch must contain one implant on an implant holder, an applicator with handle, a funnel, a loading tool, an oxygen scavenger, and desiccant. Product must be secured in a tray with a lid. (All samples must pass with 90/90 conf/reliability)	Pass
Bubble Leak Testing	29*	No gross leaks detected (All samples must pass with 95/90 conf/reliability)	Pass
Pouch Peel/Seal Strength Testing	15*	$x \geq 1.0$ lbf/in (All samples must pass with 95/90 conf/reliability)	Pass
Sinus Model	6 (3-frontal, 3-maxillary)	Must successfully execute all required performance aspects per the test method (must answer yes to all questions per protocol P 16006)	Pass

B. Animal Studies

Intersect ENT conducted a series of animal studies evaluating various mometasone furoate-eluting formulations (e.g. drug dosages) and polymer control implants. These animal studies were previously provided to FDA in P100044 (PROPEL), and are incorporated by reference here.. The results of these tests were suitable to also support the safety and biocompatibility of the PROPEL Contour sinus implant.

C. Additional Studies

Chemistry, Manufacturing, and Controls (CMC) Testing

As part of chemistry and manufacturing controls, routine testing (lot release) consistent with the PROPEL and PROPEL Mini sinus implants is also performed on the PROPEL Contour sinus implant to ensure that it meets regulatory specifications. Release rate was validated for the PROPEL Mini sinus implants.

Test	Requirement
Appearance	Implants are visually inspected and verified to meet the acceptance criteria. The implant must contain the appropriate number of loops and cross joints. The implant must be free from damage, deformation, and contamination. Implant coating must have the appropriate texture and appearance.
Drug Identity	Assays are conducted to verify the identity of the drug substance, mometasone furoate, on the implant. The MF peak retention time and maximum wavelength must agree with the reference standard.
Drug Content	Assays are conducted to quantitatively determine the total amount of mometasone furoate on the implant and to verify the drug content meets the specification. The average value of the samples tested must lie within 7% of label claim.
Content Uniformity	Ten units are tested to verify the content uniformity meets the specification. The Content Uniformity is calculated per USP <905> as a Case 5 (solids in single unit containers with multiple components).
Degradation Products/Impurities	Assays are conducted to quantitatively determine the amount of impurities and degradation product on the implant and to confirm the acceptance criteria is satisfied. Individual Impurities ≤ 1% Total Impurities ≤ 2%
Release Rate	The *in-vitro* release is measured by quantifying the amount of drug released at multiple time points. The release rate must be within the specified range at each time point following USP <724>.
Residual Solvent	Assays are conducted to verify that residual levels of solvents used in the manufacturing process are below the acceptable levels established for finished goods release.

Stability/Shelf-Life

Stability and aging studies were conducted to establish the shelf-life/expiration date for the PROPEL Contour sinus implant. Stability testing was conducted per ICH Q1A (R2), Stability Testing of New Drug Substances and Products. Appropriate mechanical, functional and packaging integrity tests were also performed on aged product to ensure that the PROPEL Contour sinus implant performed within specification throughout the stated shelf-life of the product.

Expiration dating for this device was established and approved at 12 months.

Sterilization
Sterilization validation was previously conducted for the PROPEL and PROPEL Mini sinus implants, and was adopted for the PROPEL Contour sinus implant to demonstrate the sterilization cycle of the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6}.

Packaging
The packaging utilized for the PROPEL Contour sinus implant was validated according to the requirements of ISO 11607-1, Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems, to ensure that packaging integrity is maintained following worst-case sterilization, extreme conditioning, and transportation simulation. The packaging validation also verified that the packaging system performs as intended by preventing damage to the device during sterilization, transportation, storage, and distribution, per testing using the standard methodologies below.

Test	Standard Referenced
Initial Manual Handling	ASTM D5276-98
Vehicle Stacking	ASTM D642-00
Loose Load Vibration	ASTM D999-08
Low Pressure	ASTM D6653 / D6653M - 13
Vehicle Vibration	ASTM D4728-06
Final Manual Handling	ASTM D5276-98
Package Integrity - Sterile Barrier Gross Leak Testing	ASTM F2096 -11
Packaging Integrity - Seal Strength/Pouch Peel Testing	ASTM F88-09

Cadaver Testing
Intersect ENT conducted simulated use testing in human cadavers using the PROPEL Contour Sinus Implant prior to clinical study. The cadaver testing was conducted by two board-certified otolaryngologists using similar instrumentation available in an ENT office or operating room. Cadaver testing was performed on Propel Contour devices that were manufactured and packaged in compliance with GMP/QSR regulations. All test samples were representative of the finished device intended for clinical use. A sample size of 16 PROPEL Countour Sinus Implants were implanted into 2 cadaver heads after sinus surgery and balloon dilation. All 16 PROPEL Contour sinus implants tested were successfully placed in the frontal and maxillary sinus ostia of the two cadaver models. This study demonstrated the PROPEL Contour product is expected to function as intended in the frontal and maxillary sinus ostia in a clinical setting.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a pivotal clinical study (PROGRESS, Nova* cohort) to establish a reasonable assurance of safety and effectiveness of the use of the PROPEL Contour sinus implant following Functional Endoscopic Sinus Surgery (FESS) to maintain

patency of the frontal sinus opening in patients with chronic sinusitis in the US.

The applicant also performed a feasibility clinical study (EXCEED) to confirm reasonable assurance of safety and effectiveness of the device following FESS to maintain patency of the maxillary sinus in patients with chronic sinusitis. Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical studies are presented in the following subsections.

**Note: The name of the device was formally changed from PROPEL "Nova" to "Contour" after the studies were completed. However, the "PROGRESS, Nova Cohort" study title will remain in use to refer to the study within the information below.*

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects
EXCEED	Prospective, single-arm, open label feasibility study	To assess the performance, safety, and initial signals of efficacy of the drug-eluting PROPEL Contour Sinus Implant when used in chronic sinusitis (CRS) patients undergoing sinus surgery of the peripheral (frontal , maxillary) sinus ostia	2	15
PROGRESS Nova Cohort	Prospective, randomized, blinded, controlled, multicenter pivotal study utilizing an intra-patient control design	To assess the safety and efficacy of the PROPEL Contour Sinus Implant when placed in the frontal sinus opening following frontal sinus surgery in patients with CRS	12	80

A. Study Design

PROGRESS, Nova Cohort

Patients were treated between July 7, 2015 and June 6, 2016. The database for this Panel Track Supplement reflected data collected through July 13, 2016 and included 80 patients. There were 12 investigational sites.

The PROGRESS clinical study (Nova cohort) was a prospective, randomized, blinded, concurrently controlled, multicenter study that enrolled 80 subjects at 12 US sites. The objective of the study was to assess the safety and efficacy of the PROPEL Contour sinus implant in the frontal sinus opening following frontal endoscopic sinus surgery (ESS) to improve clinical outcomes and reduce the frequency of post-operative interventions, such as surgical lysis or adhesions, and use of oral steroids to control recurrent inflammation. The study utilized an intra-patient control design to assess the safety and effectiveness of the PROPEL Contour sinus implant compared to endoscopic sinus surgery alone with standard post-operative care. Subjects

returned for follow-up evaluations over a total of 90 days. Results from the PROGRESS Nova Cohort study are presented here.

The rationale for selection of endoscopic sinus surgery alone as the choice of control was to compare the outcomes of stenting to the current standard of care. The patient underwent bilateral endoscopic frontal sinus surgery following which only the treatment side received the PROPEL Contour sinus implant.

Use of an intra-patient control was selected as this study design minimizes variability that would be inherent in a parallel patient group design – most notably, variability introduced by concomitant medication usage. To eliminate the potential for bias in endoscopic grading, implants were removed at Day 21 and a blinded sinus surgeon independently graded the Day 30 endoscopic videos.

The primary efficacy endpoint of reduction in need for post-operative interventions was selected to provide evidence of a clinically meaningful patient benefit to clearly demonstrate the contribution of a mometasone furoate coated implant in the frontal sinus opening.

Pre-Specified Statistical Analysis Plan:
The primary effectiveness hypothesis was that the PROPEL Contour sinus implant would reduce the need for Post-Operative Interventions at Day 30 compared to the control. The planned analysis was McNemar's test for correlated proportions.

1. Clinical Inclusion and Exclusion Criteria

   The study population included adult patients with chronic rhinosinusitis (CRS), scheduled to undergo frontal endoscopic sinus surgery (primary or revision), and in whom placement of the PROPEL Contour sinus implant was both feasible and medically appropriate. Enrollment in the PROGRESS study, Nova Cohort was limited to patients who met the selection criteria below:

Inclusion and Exclusion Criteria for the PROGRESS Nova Cohort Study

Inclusion Criteria	Exclusion Criteria
General Inclusion Criteria	**General Exclusion Criteria**
Written informed consent obtained, informed consent approved by an IRB.	Known history of immune deficiency such as immunoglobin G or A subclass deficiency, or Human Immunodeficiency Virus (HIV).
Age ≥ 18.	Oral-Steroid dependent condition such as chronic obstructive pulmonary disease (COPD), asthma or other condition.
Compliance with protocol requirements.	Known history of allergy or intolerance to corticosteroids or mometasone furoate.
Diagnosis of CRS by CT scan defined as symptoms lasting longer than 12 consecutive weeks' duration, with inflammation of the mucosa of the nose and paranasal sinuses.	Clinical evidence of acute bacterial sinusitis (e.g. acute increase in purulent discharge, fever, facial pain, etc.).

Inclusion Criteria	Exclusion Criteria
Has a clinical indication and has consented for ESS including bilateral frontal sinus surgery.	Clinical evidence or suspicion of invasive fungal sinusitis (e.g. bone erosion on CT scan, necrotic sinus tissue, etc.).
Ability to tolerate general anesthesia.	Evidence of active viral illness (e.g., tuberculosis, ocular herpes simplex, chickenpox or measles).
Treatment with the PROPEL Contour sinus implant is technically feasible and clinically indicated in the frontal sinus opening.	Concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease (e.g., cancer, HIV, etc.).
Female patients of child-bearing potential must not be pregnant and must agree to not become pregnant during the course of the study.	Clinical evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90-day follow-up period.
Female patients of child-bearing potential must agree to use consistent and acceptable method/s of birth control during the course of the study.	Current or recent participation in another clinical trial.
CT Imaging Inclusion Criteria	History of insulin dependent diabetes.
CRS diagnosis confirmed by CT scan within 6 months of the FESS procedure.	Previously undergone ESS and experienced a CSF leak or has compromised vision as a result of a complication in a prior ESS procedure.
Bilateral disease in both frontal sinuses confirmed by Lund-Mackay score of ≥1 on each side.	**Intra-Operative Exclusion Criteria**
Surgical Inclusion Criteria	Significant complication during the current ESS including frontal sinus surgery such as excessive blood loss, CSF leak or punctured lamina papyracea.
Planned ESS includes bilateral ethmoidectomy (if judged necessary) and frontal sinus surgery using Draf II (A or B) dissection and/or balloon dilation, with minimum of 5-mm diameter opening created.	Current ESS including frontal sinus surgery is aborted for any reason.
Technique used for frontal sinus surgery was the same on both sides (e.g. surgical dissection alone bilaterally, balloon dilation alone bilaterally, or both bilaterally).	At least one side is not amenable for implant placement.
Septoplasty for access to the ostio-meatal complex is permitted.	
ESS including bilateral frontal sinus surgery has been successfully completed without significant complication that, in the opinion of the investigator, would confound study results, and the patient's anatomy remains amenable to implant placement.	

2. Follow-up Schedule

Baseline evaluations included a routine history and physical exam, ENT-HNS evaluation and CT scan to confirm chronic rhinosinusitis diagnosis (if not performed within past 6 months) and candidacy for sinus surgery. Follow-up assessments occurred prior to hospital discharge or clinic release and at post-operative Days 7, 21, 30 and 90.

The follow-up assessments included independent, blinded endoscopic examinations and CT outcomes assessed at Day 30 and Day 90 visits, respectively. On-site investigators conducted endoscopic examinations at all time points. At Day 21, the implant or its remnants were to be removed to allow for blinded review of video endoscopies at the Day 30 visit. Adverse events and serious adverse events were recorded and tabulated through day 30 and 90. Where possible and if applicable, adverse events were localized to a sinus location.

3. Clinical Endpoints

The primary efficacy endpoint was the reduction in need for Post-Operative Interventions at Day 30, as determined from video-endoscopies reviewed by a panel of three independent blinded sinus surgeons. Post-Operative Intervention was a composite endpoint that included:

- Surgical Intervention required to debride obstructive adhesions or scar tissue formation in the frontal sinus opening and/or
- Oral Steroid Intervention warranted to resolve recurrent inflammation or polypoid edema in the frontal recess/ frontal sinus opening.

Secondary efficacy endpoints pertaining to the frontal sinus opening included endoscopic assessment of adhesions/scarring, inflammation, polypoid tissue changes, sinus patency (including ostial diameter) and the need for surgical and oral steroid interventions to preserve sinus patency.

The safety endpoint was assessment of adverse events and serious adverse events Day 90.

To be considered successful, the PROGRESS Study needed to pass the primary efficacy hypothesis. The hypothesis is that the drug-coated implant reduces the need for post-operative interventions at Day 30 compared to the control. The null and alternative hypotheses are

H_0: $P_T \geq P_C$ vs.
H_a: $P_T < P_C$,

where P_T and P_C represent the proportion of patients who warrant post-operative interventions on the treatment and control sides, respectively. These proportions can be expressed as $P_T = P_{11} + P_{10}$ and $P_C = P_{11}+P_{01}$, where P_{10} is the proportion of patients who warrant surgical intervention only on the treatment side, P_{01} is the corresponding proportion for the control side, and P_{11} is the proportion who warrant interventions for both sides. The above hypotheses are equivalent to a test of

H_0: $P_{10} \geq P_{01}$ vs
H_a: $P_{10} < P_{01}$.

Denoting $P^* = P_{01}/(P_{01}+P_{10})$, the hypotheses become H_0: $P^* \leq 0.5$ vs H_a: $P^* > 0.5$.

The planned analysis was McNemar's test for correlated proportions, arising from the intra-patient control design, where only discordant pairs of observations contribute to evidence of a treatment effect. A pair of observations is discordant when one sinus side requires intervention and the other does not.

EXCEED

The EXCEED study was a prospective, single-arm, open label feasibility study that enrolled 15 subjects at 2 study sites in the United States. The objective of the study was to assess the performance, safety and initial signals of efficacy of the drug-eluting PROPEL Contour sinus implant when used in chronic rhinosinusitis patients undergoing sinus surgery of the peripheral sinus ostia. Eligible patients underwent endoscopic sinus surgery (ESS) that included enlargement of peripheral sinus ostia using traditional surgical technique and/or balloon dilation in the operating room or office setting. Following successful ESS, subjects were implanted with at least 2 and a maximum of 4 PROPEL Contour sinus implants in the frontal and/or maxillary sinuses.

1. Clinical Inclusion and Exclusion Criteria

The clinical inclusion and exclusion criteria are provided below:

Inclusion and Exclusion Criteria for the EXCEED Study

Inclusion Criteria	Exclusion Criteria
General Inclusion Criteria	**General Exclusion Criteria**
Written informed consent obtained, informed consent approved by an IRB.	Presence of grade 3 or 4 polyposis, unless removed during surgery and preceding implant placement.
Age ≥ 18 years.	Presence of adhesions/scarring grades 3 or 4, unless removed during surgery and preceding implant placement.
Compliance with protocol requirements.	Known history of immune deficiency (e.g., IGG subclass deficiency or IGA deficiency, HIV).
Diagnosis of CS as confirmed by CT scan and defined as symptoms lasting longer than 12 consecutive weeks in duration with inflammation of the mucosa of the nose and paranasal sinuses.	Concurrent condition requiring active chemotherapy and/or immunotherapy management for the disease (e.g., cancer, HIV, etc.)
Planned intervention involving sinus surgery in the operating room or office setting.	Oral-steroid dependent condition such as COPD, asthma or other condition.
Condition and the planned intervention will involve at least two and a maximum of four peripheral sinuses (frontal or maxillary sinuses or combination of both).	Known history of allergy or intolerance to corticosteroids or mometasone furoate.

Inclusion Criteria	Exclusion Criteria
Nasal polyps no greater than grade 2.	Clinical evidence of acute bacterial sinusitis (e.g. acute increase in purulent discharge, fever, facial pain etc.).
Nasal polyps greater than 2 are eligible after their reduction/removal during ESS without significant complications that would confound the study results and leaving the patient's anatomy amenable to sinus implant placement, as judged by the operating physician.	Clinical evidence or suspicion of invasive fungal sinusitis (e.g. bone erosion on prior CT scan, necrotic sinus tissue, etc.).
Female patients of child-bearing potential must not be pregnant and must agree to not become pregnant during the course of the study.	Evidence of disease or condition expected to compromise survival or ability to complete follow-up assessments during the 90-day period.
Female patients of child-bearing potential must agree to use consistent and acceptable method/s of birth control during the course of the study	Current or recent participation in another clinical trial.
CT Imaging Inclusion Criteria	History of insulin dependent diabetes.
CS diagnosis confirmed and documented by CT Scan within 6 months of the procedure.	Previous FESS with a known complication of CSF leak or compromised vision.
Minimum total CT stage of 6 (Lund-Mackay method).	Known dehiscence of the lamina papyracea.
Disease in frontal and/or maxillary sinuses confirmed by CT scan.	Evidence of active viral illness (e.g., tuberculosis, ocular herpes simplex, chickenpox or measles).
Surgical Inclusion Criteria	**Intra-Operative Exclusion Criteria**
Planned bilateral total ethmoidectomy. (if judged necessary), frontal sinus surgery using Draf II (A or B) dissection and/or balloon dilation, with minimum of 5 mm diameter opening created. In the case of maxillary sinus surgery, traditional antrostomy or balloon dilation, with or without removal of uncinate process, should be performed with minimum of 5 mm diameter opening created. Septoplasty for access to the ostio-meatal complex is permitted.	Complication during the current peripheral ostia surgery/such as excessive blood loss, CSF leak or punctured lamina papyracea.
	Current surgical intervention (operating room or office setting) is aborted for any reason.
Technique used for frontal or maxillary sinus surgery was the same on both sides (e.g. surgical dissection alone bilaterally, balloon dilation alone bilaterally, or both bilaterally).	

2. Follow-up Schedule

   Subjects returned for follow-up visits at Days 7, 30, 45 and 90. Follow-up assessments included endoscopic examinations, objective endoscopic grading and patient-reported outcomes.

3. Clinical Endpoints

The primary efficacy endpoint of this study was implant delivery success which was defined as successful access and deployment of the PROPEL Contour sinus implant into the target sinus ostium within 2 attempts.

Secondary efficacy endpoints included endoscopic measures of ostial patency, degree of inflammation and polypoid edema and patient reported outcomes of Sino-Nasal Outcomes Test 22 (SNOT-22) scores.

The primary safety endpoint was based upon the frequency of serious unanticipated adverse device effects (UADEs). The study was considered successful if no serious UADEs occurred.

B. Accountability of PMA Cohort

PROGRESS, Nova Cohort

A total of 80 patients were enrolled in the study and 79 completed the follow-up visits through Day 90, representing a follow-up rate of 98.8%. No patient required termination from the study due to an adverse event through Day 90. The efficacy analyses were based on the intent-to-treat (ITT) population, which consists of all randomized patients who underwent implant placement.

EXCEED

Sixteen patients were enrolled between June 25, 2014 and September 16, 2014 at 2 investigational centers. One patient did not meet the eligibility criteria. Of the 16 patients enrolled in the study, 15 met final eligibility criteria. PROPEL Contour sinus implant placement was intended in 15 patients and involved 47 sinuses. Two sinuses to be treated in the office setting were not amenable to implant placement.

One patient receiving an implant in the office setting withdrew consent following the Day 7 visit due to the long travel distance to the study site. Overall study visit compliance was 100% (15/15) at 7 days, 100% (14/14) at 30 days, 86% (12/14) at 45 days, and 100% (14/14) at 90-days post procedure.

C. Study Population Demographics and Baseline Parameters

PROGRESS, Nova Cohort

The demographics of the study population (table below) are typical for a sinus implant study performed in the US. The study population consisted of 66.3% males, and the mean age was 49.5 years. At baseline, 55.0% patients had polypoid edema (grade 2) in the frontal recess/ frontal sinus opening, 45.0% patients had asthma; 8.8% patients had aspirin intolerance/allergy and 6.3% patients had Samter's Triad. The mean baseline total Lund-Mackay (L-M) score was 14.8, and 51.3% patients underwent at least 1 prior ESS. Control and treatment sides were well balanced with respect to mean L-M CT stage (7.4 control vs. 7.4 treatment side). All patients underwent bilateral frontal sinus surgery followed with implant placement on 1 randomized side.

Demographic and Baseline Characteristics: Intent-to-Treat Population

	All Patients (N=80)
Age, years [Mean (SD)]	49.5 (13.36)
Gender [1]	
Male	53 (66.3%)
Female	27 (33.8%)
Number of Prior ESS [1]	
0	39 (48.8%)
1	24 (30.0%)
2	11 (13.8%)
3	1 (1.3%)
>=4	5 (6.3%)
History of Aspirin Intolerance or Allergy [1]	7 (8.8%)
History of Asthma Diagnosed by Physician [1]	36 (45.0%)
History of Samter's Triad [1]	5 (6.3%)
History of Smoking [1]	25
Current	3 (3.8%)
Former	22 (27.5%)
Polypoid Edema in Frontal Recess/ FSO, Grade 2 [1] [2]	44 (55.0%)
Lund Mackay Score, Total (Left + Right) [Mean (SD)]	14.8 (4.87)

[1] Percentage is calculated based on Intent-to-Treat Population.

[2] Patients with Grade 2 polypoid edema at either right sinus or left sinus sides.

EXCEED

All 15 subjects and 45 sinuses were included in the safety analyses. The mean age was 50.6 (SD 13.24) years, and most subjects (86.7%) were male, white (86.7%), and not Hispanic or Latino (66.7%). Seven subjects (46.7%) had prior ESS. Nine subjects (60.0%) had allergic rhinitis, 4 (26.7%) had asthma, and 1 (6.7%) had aspirin intolerance/allergy. The mean total Lund-Mackay (L-M) score at screening was 12.7 (SD 5.57), with a mean L-M score for the frontal sinuses of 2.5 (SD 1.19), and 2.3 (SD 0.98) for the maxillary sinuses.

Ten of the 15 subjects were treated in the office setting and 5 were treated in the operating room setting. In the frontal sinuses, sinus surgery was mainly performed using balloon dilation alone (92.3%). In the maxillary sinuses, sinus surgery was performed using balloon dilation alone (81.0%) or balloon dilation with rigid surgical instrumentation (19.0%). Baseline endoscopic assessments were performed prior to sinus surgery using balloon dilation and implant placement in all subjects.

D. Safety and Effectiveness Results

PROGRESS

1. Safety Results

   The analysis of safety was based on the intent-to-treat population in the Nova cohort of 80 patients available for the 90 day evaluation.

Adverse effects:

The table below provides a tabulation of the adverse events (AE) reported in ≥ 2% of patients in the PROGRESS trial (Nova cohort) through Day 90. Sinusitis (acute and chronic) and headache were the most frequently reported AEs, in 16 (20.0%) patients and 5 (6.3%), respectively. Three adverse events (headache, epistaxis, acute sinusitis) were judged by clinical investigators as having an indeterminate relationship to the implant and these events resolved without sequelae. No patients withdrew due to an adverse event, and no deaths occurred in this clinical study. There were no serious adverse events in the study that were related to the implant.

Adverse Events Observed in ≥2% of Patients in the Nova Cohort of PROGRESS Study through Day 90

Preferred Term	All Events (N=80)
Patients with Any Adverse Events	47 (58.8%)
Acute Sinusitis	16 (20.0%)
Asthma	6 (7.5%)
Headache	5 (6.3%)
Chronic Sinusitis	4 (5.0%)
Upper Respiratory Tract Infection	4 (5.0%)
Fungal Sinusitis	2 (2.5%)
Nasopharyngitis	2 (2.5%)
Nausea	2 (2.5%)
Neck Pain	2 (2.5%)
Sinus Headache	2 (2.5%)
Streptococcal Pharyngitis	2 (2.5%)

2. Effectiveness Results

The analysis of effectiveness was based on the 61 evaluable patients at the 30 day time point. The table below provides an overview of the primary and secondary endpoints and their outcomes.

	Treatment (Tx) (n=80)	Control (Ctrl) (n=80)	p-value
PRIMARY EFFICACY RESULTS [a,¥]			
Need for Post-Operative Interventions, N (%)	7 (11.5%) (n=61)[§]	20 (32.8%) (n=61)[§]	0.0023
SECONDARY EFFICACY RESULTS [b,I]			
Need for Post-Operative interventions, N (%)	12 (16.0%) (n=75)[§]	25 (33.3%) (n=75)[§]	0.0039
Need for Surgical Interventions, N (%)	3 (4.0%) (n=75)[§]	11 (14.7%) (n=75)[§]	0.0156
Inflammation (100-VAS, mm), Mean (SD)	23.1 (24.23) (n=79)[§]	35.6 (31.12) (n=77)[§]	0.0005

Occlusion/Restenosis, N (%)	10 (13.3%) (n=75)[§]	27 (36.0%) (n=75)[§]	<0.0001

[¥] *All eighty patients returned for the Day 30 visit and had their endoscopy recorded for grading by independent reviewer; however, data were considered missing if the independent reviewer could not grade a video due to sub-optimal video quality or inadequate imaging of the relevant anatomy. Inadequate imaging of the relevant anatomy can occur when presence of significant edema or an adhesion prevents access into the frontal sinus. Since the planned statistical test (McNemar's test of correlated proportions) requires patients with an observed pair of outcomes, 19 patients could not be included in the test. McNemar's exact binomial test was employed to obtain the 2-sided p-value at alpha level of 0.05 for the primary efficacy endpoint and other categorical efficacy endpoints; T-tests were performed for all continuous efficacy data on the side-to-side difference in scores*

[l] *p-values adjusted using a Holm's step-down method to control for familywise type I error*

[a] *Determined at Day 30 by the independent reviewer based on video-endoscopy review*

[b] *Determined at Day 30 by clinical investigators*

[§] *Number of patients with evaluable sinuses*

SD=Standard Deviation, VAS=Visual Analog Scale

The primary efficacy endpoint was met. The rate of Post-Operative Intervention was 32.8% on the control sides compared to 11.5% on the treatment sides. This difference was statistically significant (p=0.0023) and represented a 65% relative reduction in the need for Post-Operative Interventions.

Statistically significant reductions in the need for post-operative interventions, need for surgical intervention, inflammation scores and rate of occlusion/restenosis were observed at day 30 as determined by clinical investigators (see overview table above). The implant delivery success rate was 100%.

The incidence of adverse events was consistent with those seen in prior studies for the PROPEL drug-coated sinus stents. The incidence of each individual AE type by side (control vs. drug-coated stent) was quite similar. Overall, review of the safety data reveals no significant concerns related to adverse events.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

- Usage of intranasal steroid sprays prior to 30 days,
- Presence of PROPEL or PROPEL Mini Sinus Implants in the ethmoid sinuses,
- Usage of intranasal steroid sprays prior to 30 days AND Presence of Propel or Propel Mini Sinus Implants in the ethmoid sinuses

There were no confounding effects on the primary efficacy endpoint.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

EXCEED

1. Safety Results

There were no serious unanticipated AEs and the study primary safety endpoint was met.

Adverse effects: A total of 12 adverse events of any type were reported in 9 subjects (60.0%). None of the adverse events were implant-related. Most adverse events were considered related to morbid or comorbid conditions (41.7%), or the surgical/endoscopic procedure (33.3%). One adverse event was considered serious and related to the morbid/co-morbid conditions and resolved within 30 days.

Summary of Reported Adverse Events through Day 90

	All Events (N=15)
Subjects with Adverse Events	9 (60.0%)
Subjects with Serious Adverse Events	1 (6.7%)
Total number of Adverse Events	12 (80.0%)
Total number of Serious Adverse Events	1
Subjects with	
Acute Sinusitis	1 (6.7%)
Bronchitis	1 (6.7%)
Chronic Sinusitis	1 (6.7%)
Crusting not in sinus. Front of nostrils	1 (6.7%)
Nasal Congestion	3 (20.0%)
Polyps	1 (6.7%)
Right anterior pain*	1 (6.7%)
Upper Respiratory Infection	1 (6.7%)
Vasovagal Reaction	1 (6.7%)
Sinus drainage / green	1 (6.7%)

Percentages are based on the number of subjects specified in the header.
Subjects reporting the same adverse event more than once are counted only once.
*Right anterior pain was confirmed by biopsy as squamous cell carcinoma and categorized as a serious adverse event.

2. Effectiveness Results

The study results showed an overall implant delivery success rate of 97.8% (100% in frontal sinuses; 95.2% in maxillary sinuses), demonstrating that the primary performance endpoint was met. Observed endoscopic improvements at Day 90 included a 46.8% increase in ostial patency, a 75.0% reduction in polypoid edema, a 19% reduction in grade 2 and 3 adhesion/scarring, and a 38.1 mm decrease in inflammation score. The mean total SNOT-22 score decreased from 1.94 (SD 0.672) at baseline to 0.94 (SD 0.909) at Day 90, resulting in a treatment effect size of 1.09*.

*This represents the normalized score that was obtained by dividing the total score (ranging from 0 – 110) by the number of questions answered. The total SNOT-22 score decreased from 42.6 (SD 14.9) at baseline to 20.6 (SD 19.3) at Day 90, resulting in a treatment effect size of 1.14.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 29 investigators of which none were full-time or part-time employees of the sponsor and 1 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: *None*
- Significant payment of other sorts: *One*
- Proprietary interest in the product tested held by the investigator: *None*
- Significant equity interest held by investigator in sponsor of covered study: *None*

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ear, Nose and Throat Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The preclinical and clinical data for the Propel Contour sinus implant demonstrate that the device is safe and effective for its intended use in the frontal and maxillary sinus ostia. In the EXCEED feasibility study, the primary performance endpoint was met. Favorable endoscopic and patient-reported outcomes were confirmed during the 90-day follow up. In the PROGRESS pivotal study (Nova Cohort), the primary efficacy endpoint was met. Results from the Nova Cohort confirmed the hypothesis that the steroid-releasing implant reduces the need for post-operative interventions in patients with chronic rhinosinusitis. The study also demonstrated that, compared to surgery alone, placement of the PROPEL Contour sinus implant in the frontal sinus opening maintains sinus patency by reducing inflammation, scarring and occlusion/restenosis and that these endoscopic findings could be translated into measurable clinical benefits.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies (EXCEED and PROGRESS Nova Cohort) conducted to support PMA approval as described above. The primary safety endpoints were met. No unanticipated adverse device effects were reported in either of the clinical studies. There were no deaths in either study and only 2 serious adverse events in both studies, which were likely unrelated to the device and are consistent with those potentially associated with any sinus procedure. Overall, the incidence and types of adverse events were similar to those reported in clinical studies for the similar drug-coated PROPEL and PROPEL Mini sinus implants indicated for the ethmoid sinus and frontal sinus opening. The incidence of non-serious adverse events was consistent in both the control and treatment group. The absence of implant-related serious adverse events and very low incidence of adverse events supports the safety of the PROPEL Contour sinus implant. These studies confirmed that the addition of the drug to the sinus implant poses negligible safety risks.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above.
The benefits of the device as an adjunctive therapy after functional endoscopic sinus surgery (FESS) for patients with chronic rhinosinusitis (CRS), are based on clinical data from a well-designed and conducted multi-center, randomized, within-subject controlled clinical trial. The results demonstrated that the device has a clinically meaningful benefit over standard surgery of the frontal sinus opening region without use of the implant. The study met its primary endpoint: the need for medical and surgical interventions was reduced postoperatively in the device-treated side. This result was robust when challenged with numerous sensitivity analyses. Likewise, the secondary effectiveness endpoint, i.e., the need for postoperative intervention over time on Days 21, 30, and 90 was significantly greater on control frontal sinus openings than on device-treated frontal sinus openings. Additional clinical data from a prospective, single-arm, open-label feasibility study demonstrated that the device also benefited patients over the same period of time when implanted in the maxillary sinus, as measured by successful delivery, blinded endoscopic evaluation comparing baseline and postprocedure recordings, and patient reported symptom reduction and comfort. The use of this device is expected to benefit patients by reducing the need for post-operative interventions for CRS patients, thus reducing risks of side effects from using typically prescribed oral steroids or antibiotics, reducing the risk of infections, and to assist in the prevention of adhesions during healing.

In addition, the risks of the PROPEL Contour sinus implant are well-characterized and based on data collected from clinical studies of the similar PROPEL and PROPEL Mini sinus implant devices, and are considered low in severity. In the clinical study for the PROPEL Contour sinus implant, there were no reported deaths

and no serious adverse events related to the use of the device. In the pivotal study, sinusitis (acute and chronic), and headache were the most frequently reported AEs, in 20 (25.0%), and 5.0 (6.3%) patients, respectively. Respiratory, thoracic and mediastinal disorders occurred in 12.5% of patients. AE related to asthma, fungal sinusitis, headache, nasopharyngitis, nausea, neck pain, sinus headache, streptococcal pharyngitis and upper respiratory tract infections, occurred in 2.5-5% of patients. The incidence of adverse events was consistent with those seen in prior submissions of drug-coated sinus stents.

Patient Perspectives

Patient perspectives considered during the review included the use of the following in the EXCEED feasibility study:

- Sino-Nasal Outcome Test 22 (SNOT-22) at screening and all time-points, and
- Patient Preference Questionnaire (PPQ) at Day 7 and 90

The SNOT-22 questionnaire is a validated instrument used to evaluate the impact of chronic rhinosinusitis on patient quality of life, and may also be used to measure the outcome of surgical intervention.

These tools were used to evaluate patient symptoms/preference of the implant in the maxillary and frontal sinuses, as a secondary efficacy endpoint of the study. The SNOT-22 data collected showed that patients experienced a decrease in key chronic rhinosinusitis symptoms such as nasal blockage, post-nasal discharge, thick nasal discharge, facial pain/pressure and decreased sense of smell/taste. The PPQ revealed the majority of patients felt increased improvement in sinusitis symptoms as a result of the implant procedure and revealed recommendations that they would 'definitely'/'very-likely' 'choose the procedure instead of medications to treat sinus symptoms' and would 'recommend the implant to close friends/family members with sinus problems'.

In conclusion, given the available information above, the data support that for use of the PROPEL Contour sinus implant in patients ≥18 years of age following sinus surgery to maintain patency of the maxillary sinus or frontal sinus opening, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The safety, efficacy and performance of the PROPEL Contour sinus implant has been demonstrated in nonclinical laboratory and animal testing, a prospective, multi-center clinical study and a prospective, single-arm, open-label clinical study, both conducted in the United States. The primary safety, efficacy and performance endpoints in the clinical studies were met. The clinical data confirmed the hypothesis that the addition of the corticosteroid to the stent coating would augment the device's ability to physically maintain maxillary and frontal sinus opening patency by reducing inflammation, adhesions and polyposis and that these endoscopic findings could be translated into measurable clinical benefits. The studies confirmed that the addition of

the drug to the stent poses negligible safety risks. The data generated provides a high level of evidence that the PROPEL Contour sinus implant offers meaningful clinical benefits to patients in terms of reducing the incidence of post-operative interventions. The results demonstrate that the PROPEL Contour sinus implant provides a reasonable assurance of safety and effectiveness when used in the maxillary and frontal sinus opening of chronic rhinosinusitis patients undergoing sinus surgery.

XIII. CDRH DECISION

CDRH issued an approval order on February 23, 2017.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.