SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Implanted GERD Device
Device Trade Name:	Enteryx™ Procedure Kit
Applicant's Name and Address:	Boston Scientific Corporation. One Boston Scientific Place Natick, Massachusetts 01760
PMA Number:	P020006
Date of Panel Recommendation:	January 17, 2003
Date of Notice of Approval to Applicant:	April 22, 2003

II. INDICATIONS FOR USE

The Enteryx™ procedure kit is indicated for endoscopic injection into the region of the lower esophageal sphincter (LES) for the treatment of gastroesophageal reflux disease (GERD) symptoms in patients responding to and requiring daily pharmacological therapy with proton pump inhibitors.

III. CONTRAINDICATIONS

The Enteryx™ procedure kit is contraindicated in patients with esophageal varices particularly related to portal hypertension.

The Enteryx™ procedure kit is contraindicated in patients whom the physician determines to be poor candidates for endoscopic procedures and/or anesthesia.

IV. WARNINGS AND PRECAUTIONS

Please refer to the device labeling for the list of the warnings and precautions.

V. ADVERSE EVENTS OF THE DEVICE ON HEALTH

Discussion of adverse events is based on 85 patients implanted with Enteryx™ in a multi-center, prospective study which evaluated the safety and effectiveness of the device in patients with GERD. A total of 299 adverse events were reported during the clinical trial, 122 (40.8%) of which were considered to be device-related or potentially device-related, 29 procedure-related, and 148 unrelated to either the device or procedure. Seventy-eight (78) of the 85 patients enrolled (91.8%) experienced at least one device-related adverse event.

With respect to severity of the device-related adverse events at onset:

- 63 (51.6%) of the events were rated mild;
- 54 (44.3%) moderate; and
- 5 (4.1%) severe.

All of the device-related events were resolved by the conclusion of the clinical trial. There were no deaths or unanticipated adverse events.

A summary of the device and procedure-related adverse events which occurred is depicted in Table 1. Of note, patients may have had more than one type of event or more than one event of the same type.

Table 1. Summary of Device and Procedure Related Adverse Events

Device-Related Adverse Events		Procedure-Related Adverse Events	
Event	**# (%) of Subjects (N=85)**	**Event**	**# (%) of Subjects (N=85)**
Retrosternal Pain	78 (91.8%)	Pharyngitis	9 (10.6%)
Dysphagia	17 (20.0%)	Nausea/Vomiting	7 (8.2%)
Fever	10 (11.8%)	Nausea Alone	5 (5.9%)
Belching/Burping	6 (7.1%)	Shoulder Pain	3 (3.5%)
Gas-Bloat	5 (5.9%)	Dry Mouth	2 (2.4%)
Body Odor	4 (4.7%)	Anxiety	2 (2.4%)
Rib Pain	1 (1.2%)	Breast Pain	1 (1.2%)
Flu	1(1.2%)		

Although not reported in the clinical study, other potential adverse events which may occur include bleeding, esophageal ulceration, erosion, esophageal perforation, fistula, and mediastinitis.

Please refer to pages 12 through 14 of the Clinical Section for additional information on adverse events observed in the clinical study.

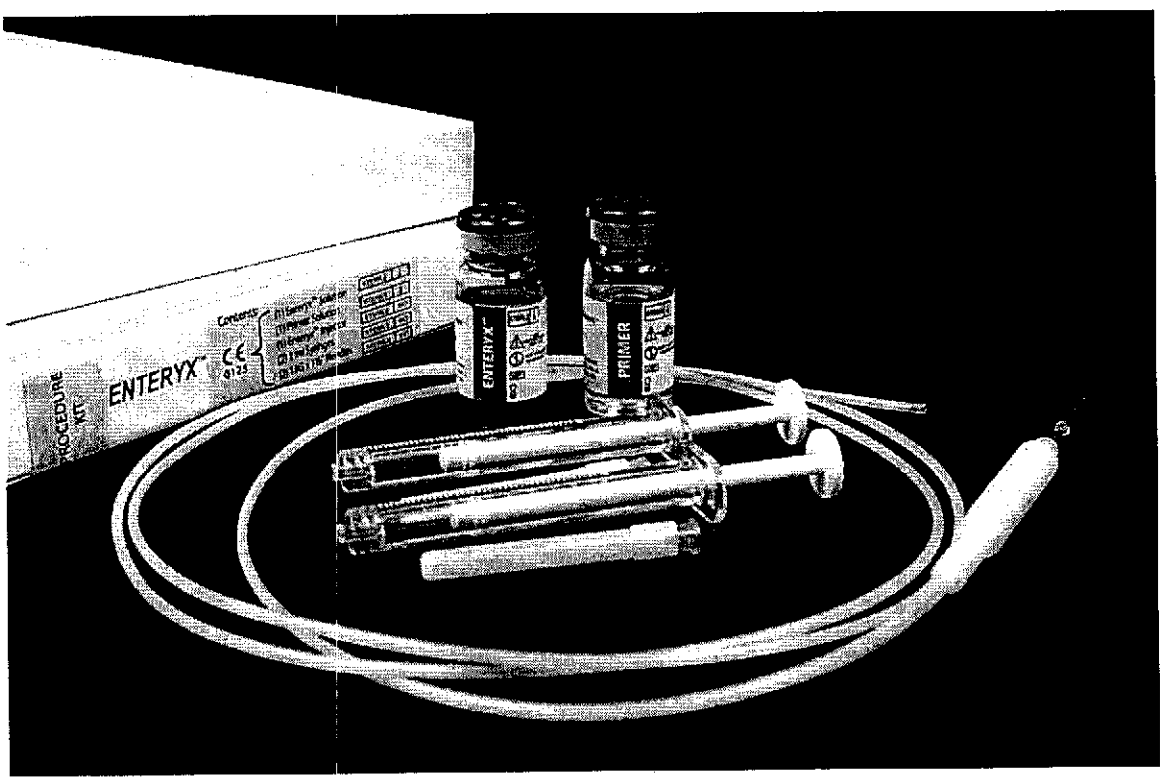
VI. DEVICE DESCRIPTION AND OPERATION

Enteryx™ is an injectable solution comprised of ethylene vinyl copolymer (EVOH) dissolved in dimethyl sulfoxide (DMSO). Micronized tantalum powder is also present in the product as a contrast for visualization under standard x-ray and fluoroscopy.

The Enteryx™ solution and the DMSO are each supplied sterile in 10cc glass vials. The following accessories are also included in the procedure kit:

- DMSO-compatible injection catheter (1);
- DMSO-compatible sterile syringes (2); and
- DMSO-compatible sterile needles (2).

After priming the sclerotherapy-type catheter with DMSO, the liquid Enteryx™ polymer is delivered endoscopically into and along the muscle layer of the lower esophageal sphincter (LES). Circumferential injections may be made with either multiple 1-2ml discrete injections or a continuous injection if an arc or ring forms. Upon contact with polar physiologic fluid, the DMSO solvent diffuses away, resulting in precipitation or solidification of the hydrophobic copolymer and formation of a spongy solid mass.



VII. ALTERNATIVE PRACTICES AND TREATMENTS

Lifestyle/Dietary Modifications
Simple lifestyle or dietary modifications are often recommended as part of the first-line therapy for mild GERD symptoms and may include

- elevating the head of the bed;
- avoiding tight-fitting garments;
- weight loss;
- avoiding alcohol, tobacco, caffeine, acidic foods/beverages; and
- not eating prior to lying down or going to bed

Acid-Suppressive Therapy (Pharmacological)
Patients who fail to respond to lifestyle/dietary modifications are often treated with acid-suppressive medications, typically classified into three broad categories:

- Antacids;
- H_2 Receptor Antagonists (H_2RA); and
- Proton Pump Inhibitors (PPIs).

Surgical Therapy
Several different surgical wrap procedures are performed to treat GERD including the Nissen fundoplication, Belsey operation, and Hill procedure. Often surgery has been reserved for those who have failed medical therapy or younger patients who would otherwise require life-long medication.

VIII. MARKETING HISTORY

Enteryx™ received the CE-mark in May of 2000 and marketing of the device in Europe began. Enteryx™ has not been withdrawn from marketing for any reason related to lack of safety or effectiveness.

IX. SUMMARY OF PRECLINICAL STUDIES

Acute Biocompatibility Testing
Evaluation of biocompatibility was conducted per the FDA guidance "Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices, Part 1: Guidance on Selection of Tests" following the requirements for a permanent implant. Testing was carried out in compliance with 21 CFR Part 58 "Good Laboratory Practice for Nonclinical Laboratory Studies." The testing included cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, subacute toxicity, genotoxicity, and intramuscular implantation (7 day). Except for the 7 day intramuscular implantation testing, the material met the requirements for all the tests. In the 7 day intramuscular implantation testing, histopathological examination revealed that the test article caused a greater local effect compared to the control. The test article sites demonstrated severe

necrosis, marked infiltrations of macrophages, a moderate to marked foreign body reaction, vascularization and fibrosis, and some mineralization. This acute reaction was attributed to the presence of the DMSO. On the basis of the histopathological observation, Enteryx™ failed to meet the requirements of 7 day USP muscle implantation testing. Although Enteryx™ failed the acute muscle implantation test, the histopathology from the long term animal testing (discussed below) demonstrated that the greatest inflammation occurred by day 30. The acute inflammation then stabilized to a mild localized foreign body response.

Long Term Biocompatibility Testing

Carcinogenicity testing

Carcinogenicity testing was conducted by the sponsor using the *ras*H2 transgenic mouse model. Based on the results of the study, Enteryx™ was found to be non-carcinogenic in the *ras*H2 transgenic mouse.

Chronic toxicity testing

Chronic toxicity testing was conducted implanting samples of the device in the muscle in a rabbit model. Implantation with Enteryx™ resulted in an acute inflammatory response occurring early then developing into a chronic inflammatory response. Histopathology of the implantation sites showed that overall the greatest severity of inflammation occurred at day 30. After 90 days, the severity of the inflammatory response decreased, stabilized and was generally characterized as a mild localized foreign body response with some mineralization.

Esophageal implantation studies were also conducted to evaluate the acute and long-term safety of Enteryx™ implanted into the lower esophageal sphincter (LES) in canine and mini-pig animal models.

Canine LES Implant Study

The objective of this study was to evaluate the safety of the device and to develop an endoscopic technique for placing Enteryx™ into the LES. Enteryx™ was injected into the LES and was also intentionally injected transmurally above and below the LES. The results showed that when Enteryx™ was placed within the muscle layers of the esophagus, the implants appeared stable.

Superficial intramural injections sloughed in approximately half of the implants with resultant transient crevice-like mucosal ulcers. A contributing factor to sloughing may have been a pyothermic reaction when the DMSO was rapidly injected, and may have contributed to the acute mucosal response. Luminal cooling of the esophageal injection sites during implantation decreased the acute tissue response and decreased the incidence of mucosal erosion at the injection site and the subsequent sloughing of the implant.

Intentional transmural esophageal and gastric injections resulted in local deposition of material in the peritoneal cavity, pleural space, lung and liver parenchyma, and intravascular depositions when the injection occurred into the adjacent parenchymal structures. This resulted in extensive focal inflammatory reaction, but no apparent behavioral change or systemic toxicity. Extramural implants were tolerated in the lungs and pleura with very minor adjacent scar formation.

Intraperitoneal and subserosal implants resulted in almost no tissue reaction. There were three cases of presumed intentional injection into the pulmonary or hepatic vasculature. Although there is an acute inflammatory response at 12 months following injection, follow-up showed no or very minimal tissue reaction around major vessels, trachea and right atria. There was no evidence of systemic migration by full body x-ray. The study indicated that at 12 months Enteryx™ is well tolerated with a mild inflammatory response.

Yucatan Minipig LES Implant Studies

Minipigs were used to evaluate the dosing and location of implants required to modify the LES and to evaluate the acute and chronic safety associated with submucosal or intramuscular LES implants. Animals were evaluated at 2 weeks, 4 weeks, 5 weeks, 6 weeks, 3 months, 6 months and 12 months post-implantation. All animals tolerated the implants, continued to thrive, ate without difficulty, gained weight, and had no behavioral or other changes. The histological assessment demonstrated evolution of the tissue response to the implant from acute inflammation through a sub-acute inflammatory process with accompanied fibrosis to a well-developed foreign body reaction and some mineralization. The presence of mineralization within the LES was not believed to be clinically significant. By three months post-implantation, the tissue surrounding the implant sites was quiescent. Mature, well-delineated capsules of varying thickness surrounded the sites, separating them from the esophageal muscle or the interstitial connective tissue. In some animals there was a discrepancy between the number of implants injected and the number present at animal sacrifice. This discrepancy was attributed to the minipig's thin esophageal musculature and either the coalescing of two or more independent implants into one, or the sloughing of implants placed superficially in the mucosa. Compared to the dog study, there was greater success placing the material correctly in the minipig LES.

DMSO Compatibility

The EVOH and tantalum components in Enteryx™ are dissolved in the organic solvent dimethyl sulfoxide (DMSO). Upon contact with tissue fluid, the DMSO diffuses away, resulting in precipitation of the polymer, forming a cohesive spongy mass. Although DMSO has been approved as a drug for one indication (treatment of interstitial cystitis), the DMSO component of Enteryx™ is not considered to be a drug in this situation as it is an integral component intended solely as a vehicle to allow the EVOH polymer and tantalum to be injected into the lower esophageal sphincter. The therapeutic effect of Enteryx™ (i.e., treatment of GERD) is provided by the EVOH polymer; DMSO is not intended to provide any therapeutic effect.

Systemic and Localized Effect The potential systemic or localized effects of exposure to DMSO after injection of Enteryx™ were evaluated. The Physician's Desk Reference describes the pharmacology of DMSO used in the drug Rimso-50, for the treatment of interstitial cystitis. DMSO is also used as an anti-inflammatory agent for joint pain and arthritis. DMSO is metabolized by oxidation to dimethyl sulfone or by reduction to dimethyl sulfide. Dimethyl sulfoxide and dimethyl sulfone are excreted in the urine and feces. Dimethyl sulfide is eliminated through the breath and skin and is responsible for the characteristic odor from patients treated with dimethyl sulfoxide medication. Dimethyl sulfone can persist in serum for longer than two weeks after a single intravesical (bladder) instillation. Following topical application, dimethyl sulfoxide is

absorbed and generally distributed in the tissues and body fluids. Metabolism of the DMSO in Enteryx™ would be expected to use the same route, although it is probable that some of the DMSO diffuses out into the lumen of the esophagus after injection. The oral LD_{50} in the dog is greater than 10 gm/kg. Extrapolating to a 70kg human the LD_{50} would be 700 grams, much higher than the 9.6 grams present in a treatment with Enteryx™. Other than a bad taste or body odor experienced by 4.7% of the subjects in the clinical study, there were no other apparent systematic effects from the DMSO in Enteryx™. Garlicky breath is often reported in patients who use DMSO for the treatment of arthritis.

In addition to the potential systemic effects from DMSO, localized tissue responses to the device (both tantalum and the DMSO) were evaluated in animal testing conducted before the clinical study was initiated. As discussed previously, testing was conducted in rabbits (muscle implantation), dogs (LES implantation), and mini-pigs (LES implantation).

DMSO Compatibility with Kit Components
Glass vials are used to package the Enteryx™ and the DMSO. Glass does not react with the organic solvent DMSO. The vials are sealed with Teflon-lined silicone stoppers and aluminum closures. The stoppers were tested to verify DMSO compatibility. Testing was conducted to evaluate whether there are any effects by DMSO on the other kit components. The results demonstrated that the injection catheter and syringes were DMSO-compatible.

Gastroscopes that have a working channel lined with polytetrafluoroethylene (PTFE), polyethylene or polypropylene have also been demonstrated to be compatible with DMSO.

Sterilization
Vials of Enteryx™ and the DMSO are sterilized using a dry heat sterilization process to a sterility assurance level of at least 10^{-6}. The process was validated using the half-cycle overkill method. Testing was conducted to support a 36 month shelf life.

The injection catheter and syringes are sterilized using ethylene oxide to a sterility assurance level of 10^{-6}. Ethylene oxide residuals are in compliance with ISO 10993-7. The validation method is the Half-Cycle Overkill method as described in the current ANSI/AAMI/ISO Guidelines; "Medical Devices, Validation and Routine Control of Ethylene Oxide Sterilization." The catheter and syringes are packaged in heat-sealed Tyvek pouches.

X. SUMMARY OF CLINICAL STUDIES

A. Feasibility Studies
Two feasibility studies were performed to evaluate Enteryx™ as an implantable agent in subjects with GERD. The first study was conducted at a single site in the U.S. involving 9 subjects scheduled for esophagectomy. For each subject, multiple injections of 1-2 cc were made within the esophagus immediately prior to surgery. Histologic evaluation was

performed after resection of the specimen. Eighty-eight percent (88%, 30/34) of the attempted implants were successfully placed. Four were found lying subserosally or attached to the exterior of the gastroesophageal junction (GEJ).

The second study was performed at 2 sites in Europe. Fifteen (15) subjects with GERD symptoms requiring PPI therapy were enrolled and received 4-6cc of Enteryx™ into the region of the LES. At 6 months, mean heartburn symptom scores decreased 44% compared to baseline (assessed off medications). All subjects were able to discontinue daily PPI use although 27% were using the drugs on an as needed basis at the 6-month follow-up. Eight (8) of the subjects (53%) experienced transient retrosternal pain lasting not more than 3 days. One subject (7%) experienced transient dysphagia, although no intervention was required. Chest x-rays at 6 months showed that 60% of the subjects were estimated to have retained at least 50% of the original implantation volume of Enteryx™.

B. Pivotal Study (IDE G000065)

Study Design

The study was a multi-center, prospective, non-randomized trial in which each subject served as his or her own control. Patients at least 18 years of age with symptoms of PPI-responsive GERD for at least 3 months were considered for implantation of the device.

Endpoints

Reduction in PPI requirement was used as the study's primary effectiveness endpoint. Device effectiveness was determined by comparing the difference in daily PPI dose required at the 12-month follow-up to that required at baseline. Subjects who reduced their dose by at least 50% were considered to have had a clinically significant reduction.

The secondary endpoints which were evaluated included:

- all adverse events;
- improvement in the Velanovich GERD-HRQL symptom score;
- improvement in SF-36 symptom score;
- reduction in acid reflux as measured by 24-hour ambulatory pH;
- assessment of LES function by manometry; and
- reduction in erosive esophagitis if present by endoscopy.

GERD-HRQL (Velanovich) Score

The GERD-HRQL is a validated symptom questionnaire designed to assess the severity of GERD symptoms. It consists of a series of 9 questions related to symptoms experienced by the subject in the 5 preceding days. The response to each question is rated 0-5 based on the following scale:

- 0 = no symptoms;
- 1 = symptoms noticeable but not bothersome;
- 2 = symptoms noticeable and bothersome but not every day;
- 3 = symptoms bothersome every day;
- 4 = symptoms affect daily activities; and
- 5 = symptoms are incapacitating.

Total scores for the GERD-HRQL are obtained by adding the individual scores for the 9 questions and can therefore range from 0 (asymptomatic) to 45 (worst case).

Patient Selection

Patient Inclusion Criteria included the following:

- history of heartburn, regurgitation, or both prior to initiation of PPI therapy;
- on daily PPI treatment for at least 3 months;
- responsive to PPI as manifested by baseline GERD-HRQL score of ≤11;
- surgical candidates in event of a complication (ASA I or II);
- at least 18 years of age;
- not pregnant, negative pregnancy test or had undergone surgical sterilization;
- agreed to participate, understood and signed the consent form;
- GERD symptoms returned upon discontinuing PPI therapy for 10-14 days as manifested by a GERD-HRQL symptom score of ≥20*; and
- patients who had a confirmed diagnosis of GERD by prolonged (>12 hour) ambulatory pH analysis (pH-metry) with a ≥5% of total time pH ≤4 or ≥3% of the supine hours pH≤4;

* Changed to: GERD-HRQL score off medications >9 above score while on medications.

Patient Exclusion Criteria included the following:

- esophageal dysmotility (≥50% non-propagated waves after wet swallow);
- multi-system disease compromising the ability to tolerate the procedure;
- prior gastric or GERD surgery;
- scleroderma;
- persistent esophagitis ≥ Grade III (Savary-Miller) ;
- Barrett's epithelium ;
- hiatus hernia ≥3cm by endoscopic evaluation;
- gross obesity (BMI≥35);
- autoimmune disorder requiring therapy within the last 2 years;
- suspected or confirmed esophageal or gastric cancer;
- esophageal or gastric varices;
- use of anticoagulants other than 300mg aspirin or equivalent per day; or
- unwilling to participate in all of the follow-up studies.

Patient Demographics and Baseline Characteristics

A total of 85 subjects were enrolled and treated at 8 different investigational sites in the United States (6), Canada (1), and Belgium (1). This included 49 males and 36 females. The average age of subjects at enrollment was 49.6 years. Caucasians comprised 92.9% of those enrolled, African Americans 3.5%, Hispanics 2.4%, and Asians 1.3%.

At baseline, 62% of subjects were taking standard doses of PPI (e.g., omeprazole 20mg/day), 30% were on higher and 7% on lower than standard daily doses. In addition, 7% were taking supplemental H_2RAs and 14% supplemental over-the-counter antacids.

The mean baseline GERD-HRQL score while taking medications was 5.3 and while off medications, 26.4. The average baseline percent total time with pH≤4 on pH-metry was 14.8%. The mean baseline LES resting pressure was 13.6mmHg. At baseline endoscopy, 25% of the subjects had Grade I esophagitis (by the Savary-Miller classification) and 9% Grade II esophagitis.

Pre-Implant Procedures and Treatment
Prior to treatment all subjects underwent a medical history and physical exam, esophagogastroduodenoscopy (EGD), barium swallow, 24-hour ambulatory pH study (off medications), and esophageal manometry. In addition, each subject completed GERD-HRQL and SF-36 quality of life questionnaires both on and off PPIs.

During treatment, EGD was performed under fluoroscopy and conscious sedation. Circumferential 4-quadrant injections were made with Enteryx™ in the region of the LES with each injection consisting of 1-2cc for a total of 6-8cc. More than 8cc may have been injected if a continuous arc or ring resulted during treatment. After routine post-endoscopy monitoring, subjects were discharged on a soft diet (for 5 days) and their original dose of PPI (for 10 days).

Follow-Up
After 10 days, subjects discontinued PPI medications and recorded symptoms and medication use with a home-diary. Office follow-up occurred 1, 3, 6, and 12 months after the initial injection. Quality of life questionnaires were completed at each visit. Chest x-rays, ambulatory pH and manometry studies were performed at 3, 6, and 12 months. In addition, EGD which was optional at month 6 was required at month 12. A subject was deemed eligible for retreatment if his or her 1-month GERD-HRQL score was ≥15. All retreatments were required to be completed prior to the 3-month visit.

Patient Accountability and Protocol Deviations
All 85 enrolled subjects underwent treatment. Of these, 81 (95.3%) completed 6 months of follow-up and 77 (90.6%) completed 12 months.

Several protocol deviations occurred during the clinical trial including:

• Not off PPI for 10-14 days before baseline evaluations	11 events
• 12 Month pH study not performed	10 events
• 12 Month endoscopy not performed	9 events
• 12 Month manometry not performed	8 events
• Retreatment despite GERD-HRQL < 15	7 events
• Hiatal Hernia > 3cm	7 events
• pH study lasting < 12 hours	5 events
• Baseline manometry, pH, or barium swallow > 3 months prior to treatment	3 events
• Not off PPI for 10 days prior to pH study	2 events

Effectiveness:

Primary Effectiveness Endpoint: Reduction in PPI Use

After 12 months of follow-up, 76.5% (65/85) of the subjects had reduced their PPI dose requirement by ≥50% when compared to baseline, 67.1% (57/85) were off PPIs entirely, and 56.5% (48/85) were not taking any anti-secretory medications (including over-the-counter antacids, H_2RAs, or PPIs). Of the 65 subjects who were able to eliminate or reduce their PPI use by ≥50% at 12 months, 26% (17/65) were taking over-the-counter antacids or H_2RAs on at least an as-needed basis at that time. No statistically significant differences for PPI reduction were found among sub-populations of patients (age, gender, etc.) although the study was not designed (powered) to detect such differences.

Although there was no correlation of the amount of material *injected* compared to PPI reduction, all those subjects estimated to have ≥5cc *remaining* on x-ray at 12 months were able to reduce their PPI consumption by at least 50% (versus 79% of those subjects with <5cc remaining).

Secondary Endpoint: GERD-HRQL

For the 77 subjects reaching 12 months of follow-up, the mean GERD-HRQL symptom score was 26.2 at baseline (off PPI) and 8.9 at 12 months - a 66% reduction. A 12-month score of zero (0) was obtained by 27% of the subjects and an additional 45% were able to reduce their score by ≥50% when compared to baseline. Forty-five percent (45%) of subjects had a 12-month score which was lower than that obtained at baseline while *on* PPIs. Approximately 40% of subjects, however, had a score which increased between the 6 and 12-month follow-ups (average of 7 point increase).

Secondary Endpoint: SF-36 QOL

For the 74 subjects with available SF-36 QOL scores at 12 months, the mean score improved approximately 14% (43.4 to 49.4) on the physical component and <1% (50.2 to 50.5) on the mental component when compared to baseline scores while off medications.

Secondary Endpoint: Intra-esophageal pH

Intra-esophageal pH results from prolonged ambulatory studies were available at baseline and 12 months for 67 subjects. The mean percent total time with pH≤4 for these patients was 14.3% at baseline while off medications and 9.2% at 12 months. This represents a 36% reduction in acid exposure time. The mean number of acid reflux episodes per 24 hours decreased from 162 to 115 over that same period of time – a 31% reduction. Of the 67 subjects evaluable at 12 months, 39% (26/67) normalized their total pH (total percent time with pH≤4 of <5%). Thirty-three percent (33%, 22/67) of subjects, however, had a higher total percent time with pH≤4 at 12 months when compared to baseline values.

Secondary Endpoint: Esophagitis

Of the 30 subjects with esophagitis on baseline endoscopy, 23 had upper endoscopy results for comparison at 12 months. Seventeen (17) of these subjects had Grade I esophagitis and 6 Grade II at baseline. Esophagitis healed (Grade 0) in 43% (10/23) of the subjects with baseline esophagitis. It improved or remained stable in another 26% (6/23). In 31% (7/23) the esophagitis grade was higher at 12 months than at baseline

(Grade II versus Grade I). In addition, 27% (12/45) of the remaining subjects with 12-month endoscopy developed esophagitis. At 12-months, 37% (25/68) of the evaluable subjects had esophagitis including 22% (15/68) with Grade II esophagitis. No subjects developed Grade III/IV esophagitis or evidence of stricture during the 12 months of follow-up.

Secondary Endpoint: Manometry
Mean resting LES pressure was reduced approximately 8% (14.3mmHg to 13.1mmHg) while the mean LES length increased approximately 8% (2.6cm to 2.8cm) for the 69 subjects undergoing manometry at 12 months.

Retreated Subjects – Effectiveness
Between the 1- and 3-month follow-up times, 19 of the 85 subjects (22%) underwent a second treatment procedure. Although the protocol required a 1-month GERD-HRQL score of ≥15 in order to be eligible for retreatment, some subjects received an additional treatment due to low residual implant based on x-ray appearance. Approximately 68% of the retreated subjects eventually met success criteria (≥ 50% reduction in PPI use) at 12 months from their *original* treatment. Their mean GERD-HRQL score at 12 months was 13.6, compared to 28.8 at baseline, and the mean percent total time with pH≤4 was 10.9%, compared to 11.9% at baseline. Thirty-one percent (31%) of the retreated subjects normalized their intra-esophageal pH results. Esophagitis was present in 40% of these subjects at 12 months.

Adverse Events:
A total of 299 adverse events were reported in 81 subjects during the course of the clinical trial. The events were classified by investigators as device-related, procedure-related, or unrelated. They were also rated by severity at onset as either severe, moderate, or mild in nature. No deaths or life-threatening events were reported during the study.

Device-Related Adverse Events
A total of 122 adverse events in 78 subjects were reported as device-related by the study investigators. These are shown in Table 2.

Table 2. Severity of Device Related Adverse Events

Adverse Event	Mild	Moderate	Severe	Total #	% of Subjects
Retrosternal Pain	39	35	4	78	91.8%
Dysphagia	10	7	0	17	20.0%
Fever	7	3	0	10	11.8%
Belching/Burping	3	3	0	6	7.1%
Gas-Bloat	1	3	1	5	5.9%
Body Odor/Bad Taste	2	2	0	4	4.7%
Rib Pain	0	1	0	1	1.2%
Flu	1	0	0	1	1.2%

Retrosternal Pain

Retrosternal pain occurred in 91.8% of the subjects after initial treatment, usually beginning within 2 days. Fifty-six percent (56%) of the cases resolved within 1 week and 83% within 2 weeks. Four subjects (5%) had symptoms persist more than 30 days with the maximum being 14 weeks. Seventy-one percent (71%) of the subjects who experienced the symptom were treated with prescription-strength pain medications, 9% with over-the-counter pain medications, and 20% required no therapy. As noted in Table 2, 4 subjects experienced severe pain at onset. In all of these cases, the severe symptoms decreased to moderate or mild within 7 days. Although all subjects who received ≥8cc of material experienced retrosternal pain, some subjects with as little as 4cc implanted also experienced the symptom. There were no long term sequelae noted.

Dysphagia

Dysphagia occurred in 20% of the subjects after initial treatment (including one case of odynophagia) with a median time to symptom onset of 4 days. Approximately 47% of the cases resolved within 2 weeks. Only one subject underwent subsequent dilation – at both 25 and 35 weeks after initial injection. That patient eventually met success criteria at 12 months. The remaining subjects had resolution of symptoms with conservative therapy. No correlation of the occurrence of dysphagia to the total amount of material injected was noted.

Fever

Fever occurred in 11.8% of subjects following the initial treatment procedure and although 30% were classified as moderate, all were considered "low-grade." Half of the subjects received antibiotics and all cases resolved within two days.

Belching/Burping

Belching/burping was reported by 7.1% of the subjects. With the exception of one case which persisted more than 6 months, all other cases resolved within 2 weeks.

Bloating/Flatulence

Bloating/flatulence was reported in 5.9% of subjects. One patient listed the symptom as severe as it interfered with sleeping. No specific treatments or interventions were required to treat the symptoms in any of these subjects.

Body Odor/Bad Taste

Several subjects reported transient body odor or bad taste similar to garlic. This was most likely due to the DMSO used as a solvent during the injection.

Procedure-Related Adverse Events

A total of 29 procedure-related adverse events were reported in 26 subjects. These adverse events are summarized in Table 3.

Table 3. Severity of Procedure Related Adverse Events

Adverse Event	Mild	Moderate	Severe	Total #	% of Subjects
Pharyngitis	8	1	0	9	10.6%
Nausea/Vomiting	3	4	0	7	8.2%
Nausea	3	2	0	5	5.9%
Shoulder Pain	1	2	0	3	3.5%
Dry Mouth	1	1	0	2	2.4%
Anxiety	1	1	0	2	2.4%
Breast Pain	0	1	0	1	1.2%
TOTAL	17	12	0	29	

Unrelated Adverse Events

Table 4 lists the adverse events reported during the study which were classified by the sponsor as unrelated to the device or procedure.

Table 4. Unrelated Adverse Events

Adverse Event	% of Subjects	Adverse Event	% of Subjects
Heartburn	24.7%	Ear Pain	2.4%
Pain	10.6%	Rash	2.4%
Abdominal Pain	9.4%	Sinus Infection	2.4%
Epigastric Pain	8.2%	Stomach Ulcer	2.4%
URI	8.2%	Allergic Reaction	1.2%
Nausea	7.1%	Anxiety	1.2%
Pharyngitis	7.1%	Asthma	1.2%
Diarrhea	5.9%	Belching	1.2%
Back Pain	5.9%	Cold Sore	1.2%
Chest Pain	4.7%	Eye Infection	1.2%
UTI	4.7%	Decrease Appetite	1.2%
Nausea/Vomiting	4.7%	Dry Mouth	1.2%
Regurgitation	4.7%	Dyspepsia	1.2%
Cough	3.5%	Dyspnea	1.2%
Flu	3.5%	Eczema	1.2%
Hiccup	3.5%	Fatigue	1.2%
Abscess	2.4%	Herpes Simplex	1.2%
Bloating	2.4%	Hoarseness	1.2%
Constipation	2.4%	Hypertension	1.2%
Depression	2.4%	Nasal Stuffiness	1.2%
Dizziness	2.4%	Odynophagia	1.2%
Dysphagia	2.4%	Pneumonia	1.2%
Hypotension	2.4%	Vertigo	1.2%
Muscle Pain	2.4%	Yeast Infection	1.2%

Device Retention/Stability
Subjects underwent chest x-rays at follow-up visits and investigators were asked to estimate the remaining volume on x-ray by quartile (e.g., 76-100%, 51-75%, etc.) when compared to the 1-month x-ray for subjects who underwent 1 procedure or the 3-month x-ray for those who underwent a repeat procedure.

Of the subjects receiving only one procedure, 55% were estimated to have retained 76-100% of their implant at 12 months, 17% retained 51-75%, and 28% had retained ≤ 50%. Of the subjects who underwent retreatment, 59% were estimated to have retained 76-100% of their implant volume, 23% retained 51-75%, and 18% retained <50% at the 12 month follow-up. The majority of subjects (97%) had stable amounts of implant after the 6-month follow-up point.

Retreated Subjects
The 19 subjects who underwent retreatment were evaluated for adverse events after their second treatment. Retrosternal pain was reported in 68.4%, dysphagia in 10.5%, bloating in 5.3%, and pharyngitis in 5.3% of patients after their second treatment.

C. Other Clinical Studies
In addition to the pivotal trial, the PMA submission contained preliminary data from 2 on-going clinical studies. The first is an expanded-access study conducted under the original IDE (G000065). Data for 36 patients who completed 3 months of follow-up was provided. The patient demographics for these subjects are similar to those in the pivotal study. At 3 months, 61% of the subjects were able to eliminate PPI use and an additional 25% were able to reduce their daily PPI dose by ≥ 50%. Mean GERD-HRQL symptom scores decreased from 24.5 at baseline (off medications) to 7.1 at 3 months. Retrosternal pain occurred in 88% of the treated subjects, dysphagia in 24%, fever in 22%, burping/belching in 17%, and gas/bloating in 15%.

At the time of PMA approval the second study was being performed at multiple institutions in Europe under a separate protocol. Data was available for 40 subjects who had completed 6 months of clinical follow-up. This study enrolled a higher percentage of males (68%) and Caucasians (98%) when compared to the pivotal study. At 6 months, 75% of the subjects were off all PPI medications and an additional 20% were able to reduce their dose requirement by ≥ 50%. The mean GERD-HRQL symptom score improved from 22.2 at baseline to 7.3 at 6 months. The mean percent total time with pH ≤4 deceased from 11.0% at baseline to 9.9% at 6 months. Retrosternal pain was reported in 81% of the subjects, dysphagia in 22%, and fever in 26%.

XI. CONCLUSIONS DRAWN FROM STUDIES

The preclinical and clinical data provide reasonable assurance of the safety and effectiveness of the Enteryx™ Procedure Kit for the treatment of gastroesophageal reflux disease symptoms in patients responding to and requiring daily pharmacological therapy with proton pump inhibitors, when the device is used in accordance with its labeling.

Results from the preclinical testing demonstrated that in the animal studies (out to 12 months of follow-up) implantation of Enteryx™ resulted in a tissue response which evolved from an acute inflammation through a sub-acute inflammatory process with accompanied fibrosis to a well developed foreign body reaction with some mineralization.

Results from the pivotal clinical trial indicate that 12 months after treatment, 67% of the subjects were able to eliminate use of their proton pump inhibitor medications for GERD symptoms, and an additional 10% were able to reduce their required daily dosage by at least half. On average, patients were able to reduce symptoms of GERD (as assessed by the GERD-HRQL) by 66% over that same period of time.

Intra-esophageal data (ambulatory pH-metry) indicated that the mean total percent time with pH≤4 decreased by 36% from baseline to 12 months and that 39% of subjects normalized this parameter (percent total time with pH≤4 of <5%). Sixty-one percent (61%) of subjects still had an abnormal pH. Of the small number of patients with baseline esophagitis, 43% had resolution at 12 months as assessed by endoscopy. While 22% of subjects had evidence of Grade II esophagitis at 12 months, none had Grade III or IV. No clinically significant changes in manometry measures were noted at follow-up.

The majority of patients (>90%) experienced retrosternal pain following the treatment. In addition, transient dysphagia was reported in 20%, fever in 12%, pharyngitis in 11%, and belching or gas/bloating in 5-10% of subjects. No long-term sequelae were noted from the reported adverse events.

Insufficient data was available to adequately assess the safety and effectiveness of the device in patients who underwent retreatment procedures.

XII. PANEL RECOMMENDATIONS

The PMA was referred to the Gastroenterology and Urology Devices Advisory Panel for review and recommendations on January 17th, 2003. The panel recommended the application be approved subject to the following conditions:

- modify the Indications for Use to state that Enteryx™ is for the treatment of symptoms of GERD that require and are responsive to pharmacologic therapy;

- modify the physician labeling as follows:

  a. remove the statement in the labeling that prophylactic antibiotics should be given,
  b. remove the statement that prophylactic pain medications should be given,
  c. remove the statement regarding dietary modifications,
  d. include additional information on techniques in the use of fluoroscopy,
  e. include a precaution for patients with an esophageal stricture, and
  f. include a precaution for patients with symptoms refractory to pharmacologic therapy;

- provide consistency in the patient labeling and physician labeling; and

- conduct a post-marketing randomized controlled study with 3 years of follow-up to evaluate the long-term safety and efficacy of Enteryx™. The post-market study should address the need for and guidelines for retreatment with Enteryx™.

XIII. CDRH DECISION

CDRH concurred with most of the Panel's recommendations.

1. The Indications for Use were modified to "The Enteryx™ procedure kit is indicated for endoscopic injection into the region of the lower esophageal sphincter (LES) for the treatment of gastroesophageal reflux disease (GERD) symptoms in patients responding to and requiring daily pharmacological therapy with proton pump inhibitors."

2. The physician labeling was modified and statements regarding use of prophylactic antibiotics, pain medications, and dietary modifications were removed. Expanded information on fluoroscopic technique was added. The precautions were modified to include esophageal stricture and patients with symptoms refractory to pharmacologic therapy.

3. The patient labeling was modified to be consistent with the physician labeling.

4. The post-market study will enroll at least 300 subjects for 36 months of follow-up. Some of those will be new subjects and some will be subjects enrolled in the IDE study (see Approval Order for further details). Patients will be followed for: adverse events; any subsequent procedures or interventions related to GERD or Enteryx™; medication use; and GERD-HRQL symptoms at baseline, day of treatment, one month, six months, twelve months, twenty-four months, and thirty-six months. Patients returning at least one month after treatment or retreatment with inadequate symptom control may be retreated. Approximately half of the enrolled subjects will be contacted by the investigator at least quarterly to obtain current adverse event information. The final study visit will be thirty-six months after the last Enteryx™ injection. The sponsor is not being required to conduct a randomized controlled study as recommended by the panel. This type of study design would be necessary if the sponsor had not demonstrated adequate safety and effectiveness and would be required pre-approval.

The applicant addressed all issues raised by the Panel and CDRH. Based on the information provided in the PMA, CDRH has determined that there is reasonable assurance Enteryx™ is safe and effective for the indication of the treatment of symptoms due to gastroesophageal reflux disease (GERD) in patients responding to and requiring daily pharmacological therapy with proton pump inhibitors. FDA inspection of the

manufacturing facilities determined that the applicant was in compliance with the Quality Systems Regulation (21 CFR 820). The Approval Order was issued by the FDA on April 22, 2003.

XIV. APPROVAL SPECIFICATIONS

Professional Labeling

- Physician Information – Instructions For Use

Patient Labeling

- Patient Information Brochure

Hazards to Health from Use of the Device

See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-Approval Requirements and Restrictions

See Approval Order