PMA P010047

NeoMend, Inc.

ProGEL Surgical Sealant

June 12, 2008

FDA EXECUTIVE SUMMARY

Introduction

The subject of this Executive Summary is ProGEL Surgical Sealant premarket approval (PMA P010047) application. The device is a single use, sterile kit containing a chemically modified polyethylene-glycol based bifunctional cross-linker and human serum albumin (HSA) obtained from an FDA licensed supplier. These components are packaged separately in hermetically sealed cartridges with a single use, sterile applicator (i.e., push rod, tip assembly, applicator housing, a vial of sterile water for injection and a syringe). The device is proposed for use as an adjunct to standard tissue closure techniques for sealing or reducing air leaks (ALs) incurred during pulmonary surgery.

This PMA has been reviewed by the Plastic and Reconstructive Surgery Devices Branch of the Division of General, Restorative, and Neurological Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application are greatly appreciated.

This summary includes five sections:

1. The first section describes the challenges facing the FDA with respect to the interpretation of the preclinical and clinical data. It also presents our rationale for presenting this PMA to the advisory panel.

2. The second section describes the device and its Indications for Use proposed by the applicant.

3. The third section describes the results of preclinical studies.

4. The fourth section provides a summary of the clinical study protocol, patient outcomes, and statistical analyses presented in the PMA in support of the safety and effectiveness of the device.

5. The final section summarizes FDA's issues related to this PMA submission which generated the questions to the advisory panel.

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I. Rationale for Presentation to the Panel

This section describes the rationale for presentation of this PMA to the Anesthesiology and Respiratory Therapy Devices Advisory Panel. This PMA application for ProGEL Surgical Sealant is the first-of-a-kind lung sealant device to undergo FDA review. While a product with a similar intended use has previously been presented to the panel the composition of the NeoMend ProGEL Surgical Sealant is sufficiently different to warrant discussion.

In general, the issues which FDA is seeking input from the panel about include the following:

1. The rate of device resorption and the clinical significance of the incidence and severity of late air-leaks and pneumothorax observed in subjects during the clinical study;

2. The route of device clearance and the clinical significance of the incidence, severity and potential device-related nature of renal adverse events observed in the clinical trial;

3. Whether the data presented in P010047 demonstrate that there is reasonable assurance that in a significant portion of the target population, device application for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings will provide clinically meaningful results and provide a reasonable assurance of safety and effectiveness; and

4. Whether the safety profile of ProGel Surgical Sealant use compared to control adequately demonstrates a reasonable level of risk of illness or injury associated with the use of Sealant for its intended uses and conditions of use.

II. Background Information

Applicant and Address:
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Irvine, CA 92618

A. Indications for Use

ProGel Surgical Sealant is intended as an adjunct to standard tissue closure techniques for sealing or reducing air leaks (ALs) incurred during pulmonary surgery.

Contraindications:

The sealant is contraindicated in patients who have a history of an allergic reaction to Human Serum Albumin.

B. Device Description

ProGel Surgical Sealant is a single use, sterile kit containing two components, i.e., 1) a polyethylene-glycol based cross-linker, functionalized with succinate groups (PEG-$(SS)_2$) and human serum albumin (HSA) purchased from an FDA licensed supplier. These components are packaged separately in hermetically sealed cartridges with a single use, sterile applicator.

Product application involves an applicator to mix the crosslinker and HSA solutions so that Sealant is delivered as a spray. When the Sealant contacts lung tissue, it conforms and adheres to the lung tissue. Gel strength is stated to be sufficient to withstand 30 mm Hg air pressure in two minutes with a maximum strength greater than or equal to 90mm Hg in less than ten minutes. The Sealant permits expansion and relaxation of the lung tissue until it biodegrades. As the Sealant biodegrades it is cleared primarily through the kidneys or locally metabolized.

III. Pre-Clinical Studies

In support of the safety and potential effectiveness of the device, the following preclinical studies were performed. In selecting these analyses, the device was considered a prolonged (i.e., greater than 24 hours and less than 30 days) tissue contacting implant.

Biological Testing (Biocompatibility)

- *Cytotoxicity* - Unpolymerized crosslinker and the *in situ*-polymerized device were non-cytotoxic in L929 cell Agar Overlay assays. The crosslinker, device extracts and *in-situ* polymerized device were also non-cytotoxic in inhibition of mammalian cell growth (i.e., colony suppression) assays using BALB/c-3T3 cells.

- *Sensitization* – Saline extracts of the polymerized device with: (1) a human serum albumin and 2) commercially available guinea pig serum albumin) caused hypersensitivity responses in Guinea Pig Maximization assays. Studies repeated with sponsor-produced guinea pig albumin (i.e., low endotoxin) alone and guinea pig device-derived extracts did not elicit sensitization reactions. In an additional study, no sensitization reaction was observed when the low endotoxin guinea pig albumin device form was applied via *in situ* polymerization on guinea pigs' "breached skin" at first and second induction and subsequent rechallenge.

- *Human repeat insult patch test* – the device was non-irritating and non-sensitizing after induction (via *in situ* polymerization) and challenge on the skin of 10 normal human volunteers. 18 normal volunteers started the study and 10 finished. One volunteer was dropped from the study when decongestant and antibiotic therapy were initiated and seven subjects withdrew due to scheduling conflicts.

- *Irritation* - the device was a non-irritant after *in situ* polymerization on intact rabbit skin and a mild irritant after *in situ* polymerization in the conjunctival sac of rabbits' eyes. Saline and PEG 400 extracts of the polymerized device were non-irritants in an intracutaneous rabbit reactivity test.

  The device was a moderate to severe irritant when injected intracutaneously in rabbits followed by *in situ* polymerization. The center of injection sites were raised, hardened and pale/blanched with a palpable device under the skin. Eschar was present at the center of all injection sites by day 14. Dermal erythema scores of 2 on a 4 point scale were recorded at all injection sites at 24 hours and 14 of 15 sites at 14 days after implantation.

- *Acute Systemic Toxicity* - No systemic toxicity was observed in mice after saline and sesame seed oil extracts of the polymerized device were injected into the peritoneal cavity.

- *Subchronic toxicity* – No systemic toxicity was noted at 7 and 14 days after both the human and rat albumin forms of the Sealant were polymerized onto the serosal

surface of a rat's peritoneal cavity. At 7 days after implantation both device forms elicited slight to moderate inflammation at the implant site. Inflammation was reduced at 14 days post-implantation.

Device polymerization onto the serosal surface of a rat's peritoneal cavity caused no systemic toxicity in a 28 day study. At day 8, but not day 29, after *in situ* device polymerization, enteropathy (i.e., visual observation of dark, raised or pale areas with microscopic findings of neovascularization and hemorrhage) was observed at the treatment site of both test and control animals with the incidence and severity of these findings being greater in several mid and high dose animals.

Device polymerization onto the serosal surface of a rat's peritoneal cavity at 50 times the anticipated clinical dose caused no systemic toxicity during a 7-day follow-up study. Enteropathy was observed again in both treated and control animals with a higher incidence in the treatment animals. Animals that underwent *in situ* device polymerization with additional saline instillation in the abdominal cavity displayed decreased incidence and severity of enteropathy.

- *Genotoxicity* – Saline and DMSO extracts of the polymerized device as well as an aqueous solution of the PEG crosslinker alone were non-mutagenic in an Ames Mutagencity (*Salmonella typhimurium*/*Escherichia coli*) assay under conditions with and without metabolic activation. Saline and DMSO extracts of the polymerized device were also non-mutagenic in the Mouse Lymphoma, Rat Micronucleus and Chromosome Aberration Assays.

- *Hemolysis* - saline extracts of the polymerized device and an aqueous solution of the PEG crosslinker alone were non-hemolytic in an assay with human blood.

- *Pyrogenicity* – saline extracts of the polymerized device were not pyrogenic in a rabbit pyrogen assay.

<u>Additional Animal Studies</u>

- *7 Day wound healing study in pigs* - the device was polymerized *in situ* on an imperfect staple line in Yorkshire pigs that had undergone resection of the caudal portion of the cranial lobe of the left lung. Four of six animals required one, one animal required two and one animal required three Sealant applications. At day 7, there were no air leaks or evidence of an immune response observed during the histopathological examination of implant sites. In addition, little Sealant was present on the tissue, but a squamous metaplasia was observed at the implant site. Review of photomicrographs suggested that inflammation and fibrosis at the metaplasia tissue site was associated with adhesion formation related to surgery.

- *28 day wound healing study in pigs* – in a second study, pigs were examined at 1, 4, 7, 14 and 28 days after *in situ* device polymerization. The outcome of wounds with: 1) the device applied inside a wound and subsequently closed with staples followed by device application to the pleural surface of the wound (n=7) was compared to 2) a

wound with no Sealant applied (n=1) and 3) wounds with Sealant applied to the pleural surface after stapling (n=5). Sealant was present at the implant site at days 4 and 7, but not 14 days after implantation. No evidence of a foreign body or macrophage response was observed. Wound repair progressed normally in the presence of Sealant. As in the prior pig study, application of the device led to squamous metaplasia forming at the sites of adhesion formation.

- *Pharmacokinetics Studies* – The clearance of ^{14}C-labeled crosslinker used during *in situ* device polymerization was examined after application to the peritoneal musculature of a rat. In a pilot study, no gender difference was observed, urine was the primary route of clearance (70%) and the majority of excretion occurred within 1-3 days after implant. In a follow-up study, over 50% of the ^{14}C-labeled device was excreted by day 1 and virtually all radioactivity was recovered from rats at 14 days post-implant.

Sterilization

- The chemistry kit containing the crosslinker and human serum albumin components are sterilized by electron beam radiation. Pyrogenicity will be measured on a lot-by-lot basis.

  The human serum albumin (HSA-USP) used in Sealant manufacture is obtained from an FDA licensed supplier. The protein is derived from plasma collected from donors who have been screened and tested according to the methods specified by the FDA. These methods minimize the possibility that drawn blood will contain communicable diseases or viruses such as hepatitis and HIV. The manufacturing processes for HSA-USP also include a validated viral inactivation step.

Mechanical Studies

- *Gel Time* – a gel time of 8.0 sec was measured with two lots of investigational product.

- *Burst strength* – burst strengths of 154 and 165 mm Hg were determined with two lots of investigational product.

- *Elastic modulus* – elastic modulus was assessed as a function of shear rate for the proposed commercial device. Values for the elastic modulus (10^5 dyn/cm^2) ranged from 1.06 at lower shear values of 0.100 (rad/s) to 1.16 at a high shear rate (100 rad/s).

Thus, *in vitro* and *in vivo* studies as well as a human repeat insult patch test with 10 volunteers suggest that ProGel Surgical Sealant is:

- Non-cytotoxic, non-toxic, non-hemolytic, non-pyrogenic, a non-sensitizer, non-mutagenic and non-immunogenic.

- Data from rat and pig studies suggest that the device is rapidly cleared from the body, e.g., 50% of ^{14}C-labeled crosslinker in a polymerized device was excreted by day 1 from rats and some Sealant polymerized on pigs' lungs was present by 7 days, but absent by 14 days after implantation.

- Because 70% of the radioactivity associated with ^{14}C-labeled crosslinker in a polymerized device was recovered in the urine, kidneys appear to be the major pathway for elimination of the device.

- Ocular and intracutaneous implant studies in rabbits suggest that the device may be an irritant. The sponsor suggested that this response reflects a local osmotic shift caused by polymer hydration in the limited subcutaneous space and pressure necrosis resulting from the implant's presence in the subcutaneous space.

- Device polymerization onto the serosal surface of rats' peritoneal cavity resulted in short term slight to moderate inflammation at the implant site. At day 8, but not 29 days after *in situ* device polymerization, enteropathy was observed at the treatment site of both test and control animals with the incidence and severity of these findings being greater in several mid and high dose animals. Animals that underwent *in situ* device polymerization with additional saline instillation in the abdominal cavity displayed a decrease in the incidence and severity of enteropathy.

The Panel will be asked to consider the results of the preclinical, bench, animal and human studies in their deliberations.

IV. Clinical Data

A. Study Description

ProGel Surgical Sealant was studied in an open-label, randomized (2:1 ratio), stratified, controlled, multi-center study conducted by five thoracic surgeon investigators and five sub-investigators at five centers. Investigators received detailed training, which included animal model practice; the sub-investigators received basic bench - top training. Subjects were stratified according to their pulmonary function status at screening (i.e., percent predicted FEV1 ≤ 40%, >40%). Subjects who had at least one clinically significant intraoperative air leak (IOAL) greater than or equal to 2 mm in size following surgery, as determined by an air leak test, were randomized within the study. Qualifying patients received study device after evaluation per standard protocol and initial attempt to close parenchymal air leaks with standard care (suture / staples). Up to three attempts were permitted; no maximum dose was pre-specified. Chest tube management was pre-specified; the use of water seal, duration of air leak cessation before chest tube removal, as well as the use of Heimlich valves for continued outpatient care of an air leak during clinical study was per investigator discretion, without uniform criteria, confounding interpretation of endpoints affected by these variables. Follow-up, until 30 days post-operatively, included evaluation of chest x-rays, chest tube air leak, chest tube drainage, laboratory values, adverse events, and time to chest tube removal and patient discharge.

The primary objective of the study was to evaluate the safety and effectiveness of the ProGel Surgical Sealant to seal or reduce intraoperative air leaks (IOALs) in patients undergoing a thoracotomy for pulmonary resection, decortication, or biopsy and thereby reduce the incidence of postoperative air leaks (POALs). Performance of the device, when used adjunctively with standard techniques, was compared with performance of standard techniques alone (i.e., sutures, staples, cautery).

- Study Entry Criteria

Study inclusion criteria included patients undergoing open thoracotomy and intra-operative air leak (≥ 2mm) following surgery, at least 18 years of age, a signed informed consent document, willing and able to complete the entire study and females willing to maintain effective birth control for the study duration (i.e., 4 - 6 weeks post-surgery)

The study excluded patients, who were pregnant or breast feeding, with significant clinical disease that might complicate surgery and / or post-operative recovery (in the investigator's opinion), a known hypersensitivity to human albumin, enrollment in the National Emphysema Treatment Trial, enrollment in any other study involving tissue sealants, (i.e., synthetic or natural) and participation in any other study not approved by the sponsor.

- Follow-up Care

Chest tube management was pre-specified as to:

- Chest tubes placed on 20-25 cm water suction for the first 24 hours following surgery.
- After 24 hours, the chest tube could be transferred to water seal at the discretion of the investigator.
- Chest tubes were removed when:
    - There was no more air leakage;
    - The lung had expanded sufficiently and/or, there is no significant increase in the size of a pneumothorax, in the investigator's opinion, that would prevent discontinuation; and
    - Drainage had reduced to < 5 cc/kg/24 or <2.5 cc/kg/12 hours.

- Regarding Heimlich valves: the protocol stated that occasionally the attending physician will decide to discharge a subject, who still has an air leak, with a Heimlich valve. When this occurs, the subject will be asked to return on a weekly basis until the tube is removed. The date the air leak ceased will be the day the tube is removed.

The use of water seal, duration of air leak cessation before chest tube removal, as well as the use of Heimlich valves for continued outpatient care of an air leak during the clinical study was determined per investigator discretion, without predetermined and uniform criteria, potentially confounding the interpretation of endpoints affected by these variables.

B. Study Endpoints

- Primary Effectiveness Endpoint

The primary effectiveness endpoint was the percent of patients who remained air leak (AL)-free following surgery without post-operative air leak (POAL) through one month post-operatively or the duration of hospitalization, whichever was longer.

- Secondary Effectiveness Endpoints were:

- The proportion of intra-operative air leaks (IOAL) in each group that were sealed or reduced, as demonstrated by the air leak (AL) test, prior to the completion of lung surgery;

- The proportion of subjects in each group who were free of air leaks immediately following surgery as measured by the presence of ALs from the chest tube (CT) at the first post-operative time point once the subject was in the recovery room (RR);

- The duration of post-operative air leaks measured from the time of surgery until the air leak was sealed. For patients discharged with a Heimlich Valve (HV) for out-patient management of ongoing air leak, air leak duration was the number of days

elapsed from surgery until the subject returned to the clinic with no evidence of an air leak;

- The duration of chest tube placement. This endpoint included the time that the Heimlich Valve was in place; and the duration of hospitalization (i.e., post - operative hospital days (POD)).

    - Safety Analyses included:

- Adverse events observed during the study; and

- Changes in the pre- and post-surgery cellular and humoral immune responses.

C. Patient Information

- Patient accounting

Information on subject accounting is presented below.

Table 1. Patient Accounting (Ref: p4529)

Patient Status	Number	
Total Enrolled	275	
Not Randomized	114	
No intra-operative air leak	70	
Surgery cancelled	8	
Withdrew consent	7	
Non-resectable lesion	6	
Device not available	5	
Video-Assisted Thoracoscopic Surgery	5	
Exclusion criteria not met	1	
Other	10	
Not specified	2	
	Surgical Sealant	**Control**
Randomized: 161	103	58
Completed Study	95	53
Death	5	4
Post-Sealant lung transplant	1	0
Post-sealant lobectomy	1	0
Lost-to follow-up	1	1

- Baseline Subject Demographics

Information on the demographics of the two study groups is presented below:

Table 2. Baseline and Demographic Characteristics (Ref: p4532, 4533)

	Surgical Sealant	Control
Number	103	58

		Surgical Sealant	Control
Number		103	58
Gender:	Male	66 (64.1%)	36 (62.1%)
	Female	37 (35.9%)	22 (37.9%)
Age, years:	Mean	63.6	65.9
	SD	13.6	11.1
Percent predicted FEV1:	≤ 40%	3 (2.9%)	3 (5.2%)
	> 40%	94 (91.3%)	53 (91.4%)
	Missing	6 (5.8%)	2 (3.4%)
Immunosuppression:	No	98 (95.1%)	55 (94.8%)
	Yes	5 (4.9%)	3 (5.2%)
Diabetes:	No	90 (87.4%)	51 87.9%)
	Yes	13 (12.6%)	7 (12.1%)
COPD:	No	68 (66.0%)	42 (72.4%)
	Yes	35 (34.0%)	16 (27.6%)
	Previous Thoracic Surgery: No	88 (85.4%)	48 (82.8%)
	Yes	15 (14.6%)	10 (17.2%)
	Radiation Exposure – Chest: No	94 (91.3%)	53 (91.4%)
	Yes	9 (8.7%)	5 (8.6%)
Chemotherapy:	No	94 (91.3%)	56 (96.6%)
	Yes	9 (8.7%)	2 (3.4%)
Steroid Use:	No	99 (96.1%)	55 (94.8%)
	Yes	4 (3.9%)	3 (5.2%)
Smoking:	Never	20 (19.4%)	11 (19.0%)
	Current	18 (17.5%)	11 (19.0%)
	Former	65 (63.1%)	36 (62.1%)

None of the differences between the Sealant and Control groups for the reported demographic and risk variables were statistically significant per Wilcoxon Rank Sum Test. The enrollment of patients with percent predicted FEV1 ≤ 40% was less than 6% of each cohort which limited clinical assessment of outcomes for this cohort. There were no clinically notable or statistically significant differences in pre-operative pulmonary function test results.

- Procedure Variables:

Information on patient condition prior to device application is presented below.

Table 3. Patient Baseline Condition (Ref. page 4535)

		Surgical Sealant	Control
N		103	58
Primary Diagnosis			
	Primary Tumor	70 (68.0%)	42 (72.4%)
	Metastatic Tumor	19 (18.4%)	8 (13.8%)
	Benign Tumor	6 (5.8%)	3 (5.2%)
	COPD/Bronchitis/Emphysema	3 (2.9%)	0 (0.0%)
	Other	5 (4.9%)	5 (8.6%)
Type of Surgery			

Bilobectomy	4 (3.9%)	1 (1.7%)
Lobectomy	55 (53.4%)	34 (58.6%)
Segmentectomy	5 (4.9%)	4 (6.9%)
Single Wedge	12 (11.7%)	7 (12.1%)
Multiple Wedge	8 (7.8%)	2 (3.4%)
Lobectomy with Wedge(s)	10 (9.7%)	5 (8.6%)
Lobectomy/Segment./Other	5 (4.9%)	2 (3.4%)
Lung Volume Reduction	1 (1.0%)	1 (1.7%)
Other	3 (2.9%)	2 (3.4%)
Surgical Approach		
Median Sternotomy	1 (1.0%)	1 (1.7%)
Posterolateral Thoracotomy	85 (82.5%)	45 (77.6%)
Anterolateral Thoracotomy	3 (2.9%)	6 (10.3%)
Mini-thoracotomy	13 (12.6%)	6 (10.3%)
Other	1 (1.0%)	0 (0.0%)
Lymphadenectomy		
Not done	30 (29.1%)	11 (19.3%)
Partial	30 (29.1%)	14 (24.6%)
Complete	43 (41.7%)	32 (56.1%)
IOAL actual distribution, p = 0.0051		
1	33 (32.0%)	30 (51.7%)
2	46 (44.7%)	14 (24.1%)
3	16 (15.5%)	6 (10.3%)
4	2 (1.9%)	5 (8.6%)
5	4 (3.9%)	0 (0.0%)
>5	2 (1.9%)	3 (5.2%)
IOAL statistical distribution		
Mean	3.0	2.0
SD	9.7	1.4
Median	2.0	1.0
Minimum	1	1
Maximum	100	7
Pleural Adhesions		
Missing	1 (1.0%)	1 (1.7%)
No	49 (47.6%)	27 (46.6%)
Yes:	53 (51.5%)	30 (51.7%)
Unspecified	3 (5.7%)	1 (3.3%)
Minimal	28 (52.8%)	14 (46.7%)
Extensive	22 (41.5%)	15 (50.0%)

These data indicate that the baseline distribution of IOAL was statistically different between treatment groups, albeit the mean and median values were not. Other variables were not statistically different as powered.

IOAL and percent FEV1 were statistically significant co-variates.

D. Clinical Results

- Number of Sealant Applications in the Treatment Group

Information concerning the amount of device applied to each patient is presented below.

Table 4. Amount of ProGel Surgical Sealant Applied

Number of Sealant Applications Ref: p4537	**Number of IOALs (%)**
1	125 (59.5%)
2	70 (33.3%)
3	9 (4.3%)
Missing	4 (1.9%)
N/A*	2 (1.0%)
Number of Sealant Units per Patient P010047a1p6	**Number of Patients, (%)**
1	29 (28.2%)
2	37 (35.9%)
3	22 (21.4%)
4	7 (6.8%)
5	4 (3.9%)
6	2 (1.9%)
9	1 (1.0%)
15	1 (1.0%)
Number of Units Used (volume, cc) Ref: p4604	
mean	2.5 (4.8cc)
Median	2.0 (4.0cc)
minimum	1 (2.0cc)
maximum	15 (30cc)

*One subject in the Sealant group had 2 IOALs where no Sealant was applied.

- Effectiveness Evaluations
  - Clinical Review of the Primary Effectiveness Endpoint

The primary study endpoint was the percent of patients without post-operative air leak (POAL) through one month post-operatively or the duration of hospitalization, whichever was longer. The results of the study are presented below:

Table 5. Air Leak Status throughout the Study (Ref. p5344)

Assessment Time	**Air Leak (AL) Status at Various Times after Closure in OR**[a] **N, number of patients**					
Sealant	101					
Control	57					
Intraoperative	**No AL on Final Leak Test**			**With AL on Final Leak Test**		
Sealant	72			29		
Control	6			51		
Recovery Room	**No AL present**		**AL present**	**No AL present**		**AL Present**
Sealant	47		25	9		20
Control	2		4	16		35
During Follow-up	**Success**	**Failure**	**Failure**[b]	**Success**	**Failure**	**Failure**[b]

Sealant	31	16	25	5	4	20
Control	0	2	4	7[c]	9	35

[a]AL status in the recovery room was missing for two subjects in the Sealant group and missing for final intra-operative assessment for one subject in the Control group. Therefore they are not included in this table which tracks the subject's AL status at different points during the operative and postoperative period of follow-up.
[b]Subjects with ALs in the recovery room were considered "FAILURES", regardless of their AL status during the follow-up period.
[c]For one control patient, data on air leak status for the final intra-operative air leak assessment was missing; however, this patient did not have any post-operative air leaks and was considered a success in the primary endpoint analysis.

Of the 72 subjects in the Sealant group who did not have any air leaks present based on their final leak test in the operating room, 31 (43.1%) were treatment successes and remained leak-free through their 1 month follow-up. Of the 6 subjects in the Control group who did not have air leaks on their final leak-test in the operating room, none (0%) were leak-free following surgery. A Fisher's Exact Test comparing these results was not significant at p=0.076, potentially due to the sample size in the Control group.

Of the 29 subjects in the Sealant group who had an air leaks remaining in the operating room, 5 (17%) did not have an air leak in either the recovery room or during the postoperative period. The results in the Control group were similar with 7 of 51 subjects (14%) not having post-operative air leaks (POALs). A Fisher's Exact Test of these results indicated that this difference was not statistically significant (p=0.749). Air Leak data for the primary effectiveness endpoint is presented as:

Table 6. Primary Effectiveness Outcomes (Ref: p4538)

		Surgical Sealant	Control	p-value
No. of patients		103	58	
POAL:	No	36 (35.0%)	8 (13.8%)	0.005
	Yes	67 (65.0%)	50 (86.2%)	

Data for the primary endpoint reflects patients with no air leak from intra-operative air leak closure through one month post-operative follow-up (i.e., n = 31 Sealant; n = 0 Control), as well as patients with intra-operative air leak that was found sealed in the Recovery Room and stayed sealed through one month post-operatively (i.e., n = 5 Sealant; n = 8 Control).

Prognostic variables / co-variates

Proportion of intra-operative air leaks (IOALs) in each group that were sealed or reduced prior to completion of the surgery was a secondary endpoint. There were 161/210 (76.7%) of the IOALs that were sealed in the Sealant group as compared to 17/108 (15.7%) in the Control group (p <0.001), when multiple IOALs were counted for each individual patient. The result (p<0.001) was similar when sealed IOALs per patient

were compared (i.e., 73/103 = 70.9% in the Sealant group, and 6/58 = 10.3% in the control group).

When comparing subjects with more than two IOALs to those with one leak, success for the primary endpoint was found to be statistically significantly increased with the use of Sealant, and in subjects with fewer IOALs. There were also trends for a higher probability of success in subjects with no history of smoking, absence of pleural adhesions, and presence of hypertension.

Given the number of subjects enrolled in each treatment group, the Panel will be asked to offer its interpretation of these results.

PMA analysis of the proportion of sealed IOALs indicated that treatment and size of the initial air leak were significantly associated with the proportion of sealed intraoperative air leaks. The source of the IOAL was recorded in the case report form (CRF) as being suture line, bleb, torn lung, staple line, adhesion, fissure, or other. Hence, the PMA also examined the effect of using the Sealant for those air leaks which originated from different sources.

Due to the sparseness of these data, the categories for bleb, suture line, and other sources were combined. A Cochran-Mantel-Haenszel Test stratifying the individual air leaks based on the source was performed. The results indicate that the Sealant was associated with a higher proportion of sealed IOALs regardless of air leak source.

Table 7. IOAL Closure (Ref: Table 16.1.9.4.3A p. 5335)

	Intra - operative Leak Success			
Air Leak	**Sealant**	(N=210)	**Control** (N=102)*	
Source	N / N	%	n / N	%
Torn Lung	12 / 30	40%	3 / 14	21%
Staple Line	44 / 50	88%	7 / 23	30%
Adhesions	6 / 11	55%	1 / 10	10%
Fissure	79 / 97	81%	3 / 43	7%
Other+	20 / 22	91%	3 / 12	25%

*Missing information on source of AL for 5 leaks and missing the status of final AL test for 1 leak in Control group.
+ Suture line, bleb, and other sources.

The odds ratios for sealing air leaks were not homogeneous among the various sources of air leaks. The odds ratio for sealing air leaks associated with torn lung tissue was 2.44 as compared to estimates of 16.77, 10.80, 58.48, and 30.00 for staple lines, adhesions, fissures, and other sources of leaks, respectively.

Data comparing the initial air leak size and use of additional closure methods in sealing or reducing the size of intra-operative air leaks are presented below.

Table 8. IOALs sealed or reduced by air leak size and treatment (Ref. Table 11.4.2.1B p4542)

	Sealant			**Control**		
All IOAL	Number of IOAL	Reduced N (%)	Sealed N (%)	Number of IOAL	Reduced N (%)	Sealed N (%)
< 2 mm	20	16 (80%)	16 (80%)	5	1 (20%)	1 (20%)
2 – 5 mm	132	124 (94%)	112 (85%)	66	18 (27%)	11 (17%)
>5mm	57	52 (91%)	33 (58%)	37	21 (57%)	5 (14%)
All IOAL without sutures / staples						
< 2 mm	17	13 (76%)	13 (76%)	3	0 (0%)	0 (0%)
2 – 5 mm	78	75 (96%)	67 (83%)	38	4 (11%)	2 (5%)
>5mm	8	8 (100%)	8 (100%)	7	1 (14%)	0 (0%)
All IOAL with sutures / staples						
< 2 mm	3	3 (100%)	3 (100%)	2	1 (50%)	1 (50%)
2 – 5 mm	54	49 (91%)	45 (83%)	28	14 (50%)	9 (32%)
>5mm	49	44 (90%)	25 (51%)	30	20 (67%)	5 (17%)

Smaller leaks, (i.e., <2 mm and 2-5 mm), were significantly more likely to be sealed with Sealant when compared to large air leaks (i.e., >5 mm). Leaks that were associated with torn lung were generally larger in size, which may have contributed to the lower proportion of sealed IOALs observed for this source by Sealant compared to Control.

Table 9. Incidence of Intra-Operative Leak (>5mm) Closure by Tissue Defect
(Ref. Table 16.1.9.4.3B p5337)

	Percent of Intra-operative Leaks >5mm			
Air Leak Source	Sealant (N=209)*		Control (N=103) *	
	N / N	%	N / N	%
Torn Lung	20 / 30	67%	13 / 14	93%
Staple Line	12 / 49	24%	6 / 23	26%
Adhesions	0 / 11	0%	4 / 10	40%
Fissure	20 / 97	21%	5/44	11%
Other+	5 / 22	23%	5 / 12	42%

*Missing information on source of AL for 5 leaks in the Control group and missing the initial size of AL for 1 leak in the Sealant group.
+Suture line, bleb, and other sources.

Overall, smaller leaks (< 5mm), not associated with torn lung were more often sealed intra-operatively upon treatment with Sealant compared to Control.

Covariate Analyses of the Primary Effectiveness Endpoint

Regarding the effect of other patient covariates on POALs, in the sponsor's stepwise logistic regression analysis, several covariates, including treatment group (called randomization), hypertension, history of smoking, presence of pleural adhesions, and others, were included in the final fitted model. The only statistically significant patient covariate was treatment group effect ($p = 0.001$) adjusted for other fitted covariates; i.e., the Sealant group shows statistically significantly improved probability of success for

POALs when compared to the Control group (odds ratio = 5.0, with 95% confidence limits, 1.88 to 13.43).

The clinical results for the primary efficacy endpoint by investigational site (i.e., 5 clinical sites, with multiple investigators within each site) and treatment group (i.e., Sealant versus Control), generally showed the same direction; (i.e., the Sealant group appeared to be superior to the Control group in (no POALs)), except for investigator 02-Millar, from the Mayo Clinic, where the Sealant group showed a worse "no POAL" value of 1/10 = 10%) compared to the Control group (1/6 = 16.7%). However, due to limitation of sample size in each clinical site, statistical power for testing clinic-to-clinic heterogeneity in POALs was very low. Since the direction of success was consistent amongst sites (see below), the analysis justifies the pooling of multi-clinic data.

Table 10. Distribution of POAL-free among five centers (Ref. p 4539)

Center	**Sealant (Success/Total, %)**	**Control (# Success/Total, %)**	**Odds Ratio (OR)***
CSMC	7/13 (53.8%)	0/8 (0%)	Undefined
DUMC	4/19 (21%)	1/8 (12.5%)	1.9*
MAYO	13/36 (36%)	5/20 (25%)	1.7
MDACC	7/17 (41%)	1/9 (11%)	5.6
UWMC/VA	5/18 (28%)	1/13 (7.7%)	4.6
Total	36/103 (35%)	8/58 (7.7%)	3.36 (Overall)

Two-sided Fisher's exact test to compare two success proportions (35% versus 7.7%): p = 0.005

* OR = {[P(Success)/P(Failure)] for Sealant}/{[P(Success)/P(Failure)] for Control};
1.9 = [(4/15)/ (1/7)]
STATXACT software: OR = 3.34 [95% CI: (1.4, 9.1)]

The estimated OR values are all larger than one among all centers, which indicates that all centers are in favor of Sealant over Control in terms of odds ratio. For example, an estimated OR of 1.9 for center DUMC indicates that the Sealant patients show approximately 90% chance better in Success/Failure odds than those in the Control group. No qualitative treatment by center interaction (i.e., treatment effect shows opposite direction among centers) was found.

Pulmonary function subgroups - The actual number of patients analyzed in the Sealant and Control groups is presented below in the "Sample size by predicted FEV_1" Table.

Table 11. Sample size by predicted (Ref: p4532, 4533)

		Sealant	**Control**	**p-value**
Percent Predicted FEV_1	≤40%	3 (2 .9%)	3 (5.2%)	NS*
Percent Predicted FEV_1	>40%	94 (91.3%)	53 (91.4%)	
Missing		6 (5.8%)	2 (3.4%)	
	Total	103	58	

NS* = Non-significant

Due to small sample sizes for patients whose predicted $FEV_1 \leq 40\%$ (i.e., three patients for each group), no statistically valid analysis can be performed between Sealant and Control patients for this subgroup.

Proportion of intra-operative air leaks in each group that were sealed or reduced, as demonstrated by the air leak test, prior to the completion of lung surgery are presented in Table 8 above.

The proportion of subjects in each group who were *free of air leaks immediately following surgery* as measured by the presence of air leaks from the chest tube at the first post-operative time point once the subject was in the recovery room is presented below.

Table 12. Proportion of Subjects Without AL Immediately After Surgery (Ref: p. 4544)

	In Recovery Room		p-value
POAL (bubbles)	Surgical Sealant	Control	
N (%)			
Missing	1 (1.9%)	0 (0.0%)	0.002
None	56 (54.4%)	19 (32.8%)	
Occassioanl	30 (29.1%)	20 (34.5%)	
Frequent	7 (6.8%)	16 (27.6%)	
Continous	8 (7.8%)	3 (5.2%)	

The *duration of post-operative air leaks* measured from the time of surgery until the air leak sealed is presented below. Patients were allowed to go home with a Heimlich valve, which affected the accuracy of recording the duration of post-operative air leaks, since a patient was not in the hospital for daily observation, but instead returned for a weekly air leak assessment. In these cases, air leak duration was the number of days elapsed from surgery until the subject returned to the clinic with no evidence of an air leak.

Table 13. Duration of Post-Operative Air Leaks (Ref: p4544)

	Post-op		
Duration POAL	Surgical Sealant	Control	P*
N (%)			
Missing	2 (1.9%)	2 (3.4%)	0.410
0-2 days	54 (52.4%)	29 (50.0%)	
3-4 days	18 (17.5%)	14 (24.1%)	
5-6 days	7 (6.8%)	6 (10.3%)	
7-9 days	6 (5.8%)	1 (1.7%)	
10-11 days	3 (2.9%)	3 (5.2%)	
> 11 days	13 (12.6%)	3 (5.2%)	
Mean	4.7	3.6	
SD	6.8	3.9	
Median	2.0	2.0	
Minimum	0.5	0.5	
Maximum	42	22	
N	101	56	

*p-value is associated with Wilcoxon Rank Sum Test.

Analysis of the duration of POALs measured from the time of surgery until the air leak (AL) sealed showed no statistically significant difference in the mean duration of POALs

(p = 0.41 by Wilcoxon rank sum test) between the Sealant group (101 patients analyzed, mean = 4.7 days, standard deviation = 6.8 days) and the Control group (56 patients analyzed, mean = 3.6 days, standard deviation = 3.9 days). The Kaplan-Meier time-to-event survival analysis showed that the log rank test fails to show a significant difference (p = 0.816) in POAL duration over the entire follow-up period, including all study patients (complete, incomplete or censored, lost to follow-up). These data represent only those subjects for whom an end of air leak could be determined

The *duration of chest tube (CT) placement* is presented below.

Table 14. Duration of chest tube placement
(Ref. pp. 47-62, from Amendment 6, Appendix 3)

CT Duration	Sealant N (%)	Control N (%)	P
N	103	58	
Missing	3 (2.9%)	3 (5.2%)	0.57[a]
N	100	55	
0-2 days	2 (1.9%)	0 (0.0%)	
3-4 days	34 (33.0%)	19 (32.8%)	
5-6 days	37 (35.9%)	21 (36.2%)	
7-9 days	11 (10.7%)	9 (15.5%)	
10-11 days	3 (2.9%)	3 (5.2%)	
> 11 days	13 (12.6%)	3 (5.2%)	
Mean	6.97	6.7	
SD	5.5	3.5	
Median	5.0	5.0	
Minimum	2	3	
Maximum	42	22	

[a] Determined by Wilcoxon test

These data indicate no statistically significant difference between Sealant and Control treated groups for duration of chest tube placement. The data also indicate that 7.4% more Sealant than Control patients had a chest tube duration longer than 11 days. The endpoint of chest tube duration included the time that the Heimlich valve was in place.

The *duration of hospitalization* is presented below.

Table 15. Duration of Hospitalization
(Ref: pp. 47-62, from Amendment 6, Appendix 3)

Hospital stay, days	Sealant N (%)	Control N (%)	p-value
N	103	58	
Missing	5 (4.9%)	3 (5.2%)	0.04[a]
N	98	55	
3-4 days	11 (10.7%)	4 (6.9%)	
5-6 days	49 (47.6%)	23 (39.7%)	
7-9 days	22 (21.4%)	16 (27.6%)	
10-11 days	7 (6.8%)	5 (8.6%)	
> 11 days	9 (8.7%)	7 (12.1%)	
Mean	7.4	9.3	
SD	3.4	5.6	
Median	6.0	7.0	

Minimum	3	4	
Maximum	23	38	

[a]p-value determined by log-rank test

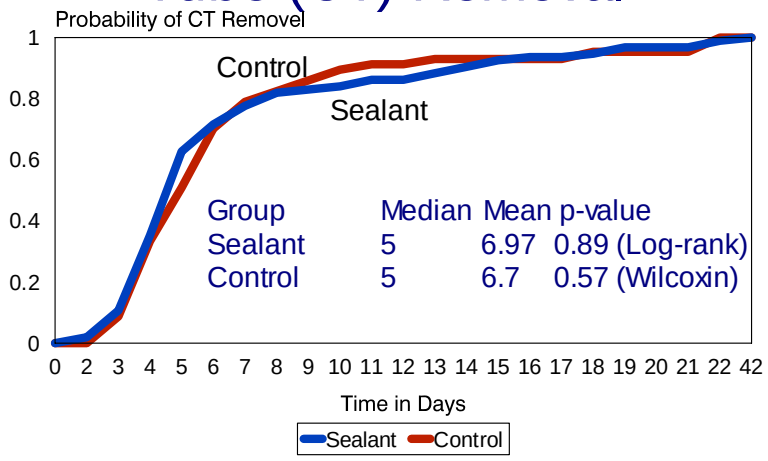
These data indicate that the duration of hospital stay was shorter in the Sealant than Control group. These data also reflect the 10 Sealant and one Control subject discharged home with Heimlich valves to treat an ongoing air leak. Therefore, the parameter of 'hospital stay' for these patients may not completely reflect total time of care for air leak.

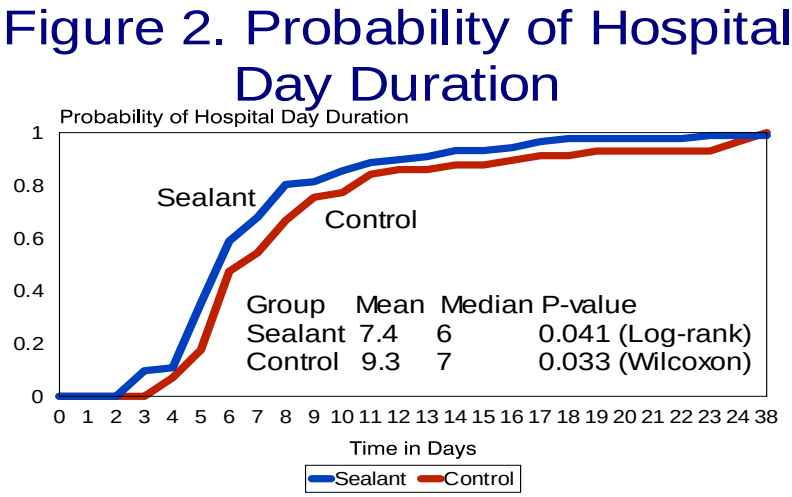
Figures illustrating the time-to-event [Duration of chest tube (CT) placement and duration in days of hospitalization] survival data are below. The distributions of censored observations are described in Table 16.

Table 16. Distribution of censored observations

Group	**CT Removal**	**Hospital Discharge**
Sealant	3, 6, and 7 days	3, 6, 7, 11, and 29 days
Control	1, 13, and 20 days	1, 20, and 23 days

Figure 1. Probability of Chest Tube (CT) Removal





Heimlich valve use -

Twelve subjects received Heimlich valves (HV) (i.e., 10 Sealant and 1 Control patients were discharged with an HV; one patient with unspecified treatment had a HV placed and removed during the hospital course). Concerning Heimlich valve use and air leaks lasting greater than 5 days:

- There were 22 Sealant and 11 Control patients with in-hospital air leaks greater than 5 days. Four Sealant and no Control patients with air leaks greater than 5 days experienced pneumothorax as an adverse event. 16 of 21 (76.2%) Sealant and 5 of 11 (45.5%) Control subjects' hospital stay was prolonged due to post-operative air leak.

- Of the 22 Sealant and 11 Control subjects with air leaks greater than 5 days, there were 11 (50%) Sealant and 1/10 (10%) Control patients identified as 'sealed' with an air leak time greater than 5 days. Conversely, 11/22 (50%) Sealant and 10/11 (91%) Control patients failed to have intra-operative air leaks sealed and an air leak time greater than 5 days.

- 11 Sealant and 1 Control patients with a post-operative air leak greater than 5 days received a Heimlich Valve for: 1) an air leak, 2) with and / or without fluid drainage, and / or 3) an adverse event. 5/21 (23.8%) Sealant and 1/11 (9.1%) Control subjects received an HV for air leak alone. As discussed above Heimlich valve use resulted in potentially inconsistent determinations of when air leaks terminated. This potentially contributed to the proportion and number of subjects with air leaks greater than or equal to 11 days being higher in the Sealant than the Control group.

- An imbalance existed between the Sealant (S) and Control (C) groups with regard to: 1) the use of Heimlich valves (i.e., 10S / 1C), 2) the number of subjects with prolonged air leak greater than 11 days (i.e., 13S / 3C), and 3) the number of subjects with chest tube duration greater than 11 days (i.e., 13S / 3C). A high degree of correlation exists amongst these three measurements with many of the same subjects accounting for the differences between the groups. Because the clinical protocol did

not provide guidelines and indications for HV use, these data may reflect differences in standard of care among different practioners.

Therefore, the conclusion that "the median LOS (length of stay) was significantly (p-value <0.05) shorter for subjects in the Sealant group compared to Control patients" may have been affected by the use of Heimlich valves in 10 Sealant and one Control patients, which facilitated an earlier discharge of these patients and hence a difference in hospital stay.

Evaluation of this potential bias was limited as air leak per Heimlich valve was assessed via subsequent weekly office visits, rather than daily during outpatient use of the Heimlich valve. Data and chest X-ray reports for patients with Heimlich valves show that at discharge all patients had pneumothorax; 3 Sealant patients also had subcutaneous emphysema. At 30 days after surgery, clinical and CXR assessments of patients with Heimlich valves revealed: 7/11 Sealant patients experienced operative-side scarring, 7/11 Sealant patients continued to have a pneumothorax and 3/11 Sealant patients had some degree of hydropneumothorax. There was no report of operative side scarring, pneumothorax or hydropneumothorax in the Control patient implanted with a Heimlich valve. These data indicate scarring in the Sealant group, potentially an inflammatory response to the Sealant.

The association of Sealant use with persistent pneumothorax as well as hydrothorax is a topic the panel should consider in their deliberations. Additional information on patients experiencing pneumothorax is presented in Safety Outcomes Section. The Panel is also asked to consider the potential of bias due to lack of uniformly applied prospective criteria as to Heimlich Valve use in this clinical trial.

- Learning curve effect on intraoperative leak closure

While evaluation of the *Learning effect on intraoperative leak closure* was not a secondary endpoint, analyses of these outcomes may have value. The Table below (i.e., Percentages of Intra-operative Air Leak (IOAL) Success) summarizes the air leak success (closure)/failure results by treatment group and number of prior surgeries:

Table 17. Percentages of intraoperative air leak (IOAL) success
(Ref: Table 16.1.9.4.2A, p5334)

# of prior surgeries	Sealant (n = 103)	Control (n = 57*)	p-value**
0-2	20/30 = 67%	1/25 = 4%	<0.0001
3-5	15/24 = 63%	2/19 = 11%	<0.0001
6-8	17/19 = 89%	3/10 = 30%	0.0021
>8	21/30 = 70%	0/3 = 0%	0.04
Total	73/103 = 70.9%	6/57 = 10.5%	<0.001

*Missing final intra-operative leak assessment for one subject in the Control group.
** two-tailed Fisher's exact test; no multiple testing adjustment is used)

The learning curve effect on intra-operative leak closure was presented in P010047 with IOAL outcomes presented in sequential order of subjects enrolled within the Sealant and Control groups by each participating investigator. The actual number of prior surgeries for each investigator was used as a covariate in a logistic regression analysis of the probability of successfully sealing all intra-operative leaks. This analysis was performed using the results of the Sealant group since the investigators were already very experienced in the standard procedures for AL closure. Intra-operative leak data were also summarized across all investigators according to the number of prior surgeries using the categories of 0-2, 3-5, 6-8, and >8 prior surgeries as above.

Table 17 illustrates that the Sealant group has statistically superior percentages of success versus the Control group over four learning effect subgroups, with the Breslow-Day homogeneity test failing to detect any difference in odds ratios or success proportions among these four subgroups. There was no trend in success percentages by learning effect subgroup for both Sealant and Control groups. The sponsor's stepwise logistic regression confirmed that, for the Sealant group, the learning effect is not statistically significant.

The presented learning curve data for Sealant use is clinically consistent with plateau in the success of intra-operative leak closure as a function of the number of cases performed. However, data presented for Control patients may indicate continued increases in the success of intra-operative leak closure, without plateau during this clinical trial and only 3 cases in the >8 number of prior surgeries, may preclude assessment of this cohort due to the small number of cases compared to other cohorts in Sealant or Control categories.

Individual investigator data demonstrate generally consistent or a trend toward consistent intra-operative outcome success with Sealant use for most of the ten investigators. The evaluation of consistency is limited for the investigator who enrolled a total of three patients, all of who were randomized to Sealant. Individual investigator data indicate a trend to consistent intra-operative outcome success with Control use for one investigator, who treated 13 Sealant and 8 Control patients, who had 100% intra-operative success with Sealant, and contributed 4 of the 6 intra-operative successes with Control during the trial. A single intra-operative success with Control was achieved by two other investigators at different centers, yielding intra-operative success in a total of six patients in this clinical trial.

Reasons for the lack of plateau for intra-operative success of leak closure with Control were not discussed, but may be associated with device performance, surgeon experience, or smaller sample size due to two to one randomization.

The Panel will be asked to consider the impact of prior surgeries on patient outcome and whether such experience may have affected clinical outcomes that suggested the superiority of Sealant compared to Control treatments. In addition, what appropriate education and training might assist the surgeon in becoming skilled in effectively delivering the sealant?

- **Safety Outcomes**

  - Clinical Review of Safety Outcomes

Deaths

There were 5 deaths in the Sealant group and 4 deaths in the Control group. None of these deaths were judged by investigators as device-related. A summary of deaths in the clinical study and contributing factors are presented below.

Table 18. Patient Deaths and Contributing Factors (Ref. P010047a6, p44-5 Appendix 1)

Age / Gender	POD of' Death	Cause of Death*
Sealant		
69/Male	POD 7	ARDS
82/Male	POD 28	Pneumonia
61/Male	POD 10	Acute airway obstruction or pulmonary embolism
66/Male	POD 6	ARDS, multi-system failure
65/Male	POD 23	ARDS, multi-system failure
Control		
80/Female	POD 19	Pneumonia
71/Male	POD 22	Atrial fibrillation
82/Male	Day of Surgery	Ventricular fibrillation
67/Male	POD 38	Anoxic brain injury

These data indicate a pulmonary cause of death in five Sealant patients (who died during clinical study), and various, (i.e., pulmonary, cardiac and neurologic) causes of death in four Control patients.

Adverse events reported in greater than 1% of subjects

The total adverse event profile recorded in the clinical study is presented below. None of the adverse events occurring at greater than 1% were found to be statistically significantly different between Sealant and Control groups by the Fisher's exact test. However, no multiplicity adjustment on type II error (false negative rate) was employed for all of these significance tests. The most frequently occurring adverse events were: fever (21.4% for Sealant and 20.7% for Control subjects), atrial fibrillation (11.7% for Sealant and 12.1% for Control subjects), and dyspnea (11.7% for Sealant vs. 17.2% for Control subjects).

Table 19. Incidence of AEs Reported by > 1% of Subjects by Treatment Group
(Ref. pp. 6 – 7 Tab 1 Volume 1 Original PMA)

Adverse Event	**Sealant (N=103)**	**Control(N= 58)**	p-value
Fever	22(21.4%)	12(20.7%)	NS
Fibrillation, Atrial	12(11.7%)	7(12.1%)	NS
Dyspnea	12(11.7%)	10(17.2%)	NS
Constipation	11(10.7%)	6(10.3%)	NS
Nausea	10(9.7%)	7(12.1%)	NS
Confusion	8(7.8%)	5(8.6%)	NS

Pneumothorax	9 (8.7%)	5(8.6%)	NS
Hypotension	8(7.8%)	6(10.3%)	NS
Anemia	8(7.8%)	6(10.3%)	NS
Pain	7(6.8%)	4(6.9%)	NS
Subcutaneous Emphysema	7(6.8%)	5(8.6%)	NS
Tachycardia	7(6.8%)	6(10.3%)	NS
Oliguria	5(4.9%)	1(1.7%)	NS
Vomiting	5(4.9%)	7(12.1%)	NS
Pneumonia	5(4.9%)	7(12.1%)	NS
Pulmonary Infiltration	4(3.9%)	0(0.0%)	NS
Chest Pain	4(3.9%)	1(1.7%)	NS
Pleural Effusion	4(3.9%)	3(5.2%)	NS
Urinary Retention	3(2.9%)	0(0.0%)	NS
Ileus	3(2.9%)	0(0.0%)	NS
Tachycardia, Supraventricular	3(2.9%)	0(0.0%)	NS
Abdominal Pain	3(2.9%)	0(0.0%)	NS
Arrhythmia	3(2.9%)	0(0.0%)	NS
Extrasystoles	3(2.9%)	0(0.0%)	NS
Coughing	3(2.9%)	1(1.7%)	NS
Hypoxia	3(2.9%)	1(1.7%)	NS
Renal Failure, Acute	3(2.9%)	1(1.7%)	NS
Hyperkalemia	2(1.9%)	0(0.0%)	NS
Hyponatremia	2(1.9%)	0(0.0%)	NS
Cardiac Arrest	2(1.9%)	0(0.0%)	NS
Ecg, Abnormal Specific	2(1.9%)	0(0.0%)	NS
Renal Function, Abnormal	2(1.9%)	0(0.0%)	NS
Asthenia	2(1.9%)	0(0.0%)	NS
Influenza-Like Symptoms	2(1.9%)	0(0.0%)	NS
Somnolence	2(1.9%)	1(1.7%)	NS
Abdomen, Enlarged	2(1.9%)	1(1.7%)	NS
Atelectasis	2(1.9%)	2(3.4%)	NS
Post-Operative Wound Infection	2(1.9%)	2(3.4%)	NS
Anxiety	1(1.0%)	1(1.7%)	NS
Withdrawal Syndrome	1(1.0%)	1(1.7%)	NS
Gi Hemorrhage	1(1.0%)	1(1.7%)	NS
Hypokalemia	1(1.0%)	1(1.7%)	NS
Arrhythmia, Atrial	1(1.0%)	1(1.7%)	NS
Respiratory Disorder	1(1.0%)	1(1.7%)	NS
Respiratory Insufficiency	1(1.0%)	1(1.7%)	NS
Sepsis	1(1.0%)	1(1.7%)	NS
Adult Respiratory Stress Syndrome	1(1.0%)	1(1.7%)	NS
Bronchial Obstruction	1(1.0%)	1(1.7%)	NS

Infection Staphylococcal	1(1.0%)	1(1.7%)	NS
Pruritus	1(1.0%)	2(3.4%)	NS
Delirium	1(1.0%)	2(3.4%)	NS
Hypertension	1(1.0%)	2(3.4%)	NS
Angina Pectoris	1(1.0%)	2(3.4%)	NS
Hemoptysis	1(1.0%)	3(5.2%)	NS
Arthropathy	0(0.0%)	1(1.7%)	NS
Gall Bladder Disorder	0(0.0%)	1(1.7%)	NS
Cachexia	0(0.0%)	1(1.7%)	NS
Dehydration	0(0.0%)	1(1.7%)	NS
Npn Increased	0(0.0%)	1(1.7%)	NS
Edema Dependent	0(0.0%)	1(1.7%)	NS
Edema Generalised	0(0.0%)	1(1.7%)	NS
Fibrillation Ventricular	0(0.0%)	1(1.7%)	NS
Cardiac Failure	0(0.0%)	1(1.7%)	NS
Hypoventilation	0(0.0%)	1(1.7%)	NS
Thrombocytopenia	0(0.0%)	1(1.7%)	NS
Allergic Reaction	0(0.0%)	1(1.7%)	NS
Death	5 (4.9 %)	4 (6.9 %)	NS
Fatigue	0(0.0%)	1(1.7%)	NS
Rigors	0(0.0%)	1(1.7%)	NS
Infection, Fungal	0(0.0%)	1(1.7%)	NS
Healing, Impaired	0(0.0%)	1(1.7%)	NS
Cramps, Legs	0(0.0%)	1(1.7%)	NS
Acidosis, Respiratory	0(0.0%)	1(1.7%)	NS
Multiple Organ Failure	0(0.0%)	1(1.7%)	NS
Chyle, Leak	0(0.0%)	1(1.7%)	NS

[a] P-value associated with Fisher's Exact Test for categorical data

Systemic Complications - Renal Function

Pharmacokinetic studies in rats suggest that device clearance occurs rapidly (i.e., < 14 days) with urine as the primary route of clearance (70%). For this reason (and the human serum albumin and polyethylene glycol crosslinker components) evaluation of renal complications is important.

The details on the individual subjects with adverse events related to renal function are provided in the Table below. Three of the nine subjects in the Sealant group and one of the two subjects in the Control group who experienced an adverse event related to renal function, had pre-existing renal disease.

Table 20. Subjects with adverse events related to renal function

(Ref: P010047, p4652-3; 4646, 4649; P010047a6, p39)

Treatment	Adverse Event	BUN	Creatinine	Sealant	Severity
		Pre-op; 1MFU	Pre-op; 1MFU	ml used	
Sealant	Abnormal renal function (RF)	25; 26	1.1; 1.8	6	Severe
Sealant	Abnormal RF, oliguria	23; 84**	0.7; 1.8**	4	Severe, Moderate
Sealant	Acute renal failure	21; 24	1.4; 1.7	2	Severe
Sealant	Acute renal failure*	54; 14	3.8; 5.0	2	Severe
Sealant	Acute renal failure.	8; ***	1.0; ***	6	Severe
Sealant	Oliguria*	13; 11	1.1; 1.3	4	Moderate
Sealant	Oliguria*	33; 39	1.7; 2.2	8	Moderate
Sealant	Oliguria	12; 8	0.9; 1.0	6	Mild
Sealant	Oliguria	10; 11	0.9; 0.8	2	Mild
Control	Acute renal failure*	15; ***	1.0; ***	na	Severe
Control	Oliguria	12;11****	1.2; 1.1****	na	Mild

*Pre-existing renal disease
**at discharge; no 1MFU as patient died
***no discharge or 1MFU as patient died
****at discharge; no 1MFU data

The occurrence of post-operative renal dysfunction (i.e., oliguria, acute renal failure, and abnormal renal function) observed in Sealant and Control patients was 9/103 (8.7%) and 2/58 (3.4%), respectively, a difference that was not statistically significant. The reasons for the disparity in the incidence of total adverse events associated with renal function are unclear; the potential of Sealant to exacerbate renal dysfunction in patients with pre-existing renal disease is unknown.

While there were no statistically significant differences in the incidence of adverse events observed by the two treatment groups, the clinical significance of these differences should be considered by the panel when providing their input.

Local Complications - Late air leaks

Late (delayed) air leaks were defined as an air leak that first occurred on or after POD2. The incidence of late air leaks was 8/102 (8%) in Sealant and 1/58 (2%) in Control patients and not significant (p = 0.157).

Local Complications - Prolonged air leaks

Prolonged air leaks were defined as any air leak that was present in the recovery room on post operative day (POD) POD0 or on POD1 and still present after POD7. The incidence of prolonged air leaks was 14/103 (14%) for Sealant and 7/58 (12%) for Control-treated patients was not significant (p = 0.813). Information on the specific patients with prolonged air leaks is presented below.

Table 21. Subjects with Prolonged Air Leaks (>/ 11 days)
(Ref. P010047a1, Attachment 13a.1, p558)

Subject	Age	Diagnosis	Surgical Proc.	FEV, (% Pred)	FVC (% Pred)	FEV_1 / FVC Ratio	COPD (Y/N)	Adhesions	Date of Discharge	With HV (Y/N)	# Sealant Units Used (mls)	# of IOAL	Largest IOAL (mm)	Air Leak Duration (days)
Sealan	63	Primary tumor	Lobe RUL	2.35 L 58	3.43 L 65	69	N	Extensive	02/20/00	Y	2(4)	1	2-5	15
	69	Primary tumor, COPD	Lobe LLL	1.31 L 36	2.81 L 61	47	Y	No	03/01/00	Y	3(6)	2	2-5	14
	54	Primary tumor, COPD	Segment RLL Other (a)	1.861, 70	2.961- 92	63	Y	No	03/01/00	Y	3(6)	2	>5	13
	60	Primary tumor, COPD Emphysema	Lobe RUL	3.231, (78)	4.58 L (86)	71	Y	Extensive	04/05/00	Y	2(4)	2	>5	19
	75	Metastatic Tumor	Wedge RML	3.05 L 99	4.12 L 102	74	N	Minimal	09/24/00	N	1 (2)	1	2-5	13
	50	Metastatic Tumor	Wedge RUL, RLL	3.07 L (73)	4.021, (75)	76	N	Extensive	02/19/01	Y	4(8)	TNTC	2-5	22
	64	Primary tumor	Lobe RILL	3.3 L (92)	4.52 L (98)	73	N	Minimal	02/22/01	Y	3(6)	3	2-5	18
	78	Primary tumor	Lobe RUL	3.49 L 86	4.84 L 93	72	N	No	02/29/00	N	2(4)	2	>5	14

	28	Metastatic Tumor	Wedge LUL, LLL	L26 L 45	1.29L 40	98	N	Extensive	02/27/00	N	6(12)	5	>5	29
	59	Primary tumor	Lobe RUL	1.9 L 81	2.681, 92	71	N	No	08/19/00	Y	2 (4)	2	2-5	19
	72	Primary tumor	Lobe RLL, Wedge RUL	3.181, (98)	3.92 L (93)	.81	Y	No	05/25/00	N	2(4)	2	>5	15
	59	Primary tumor	Lobe RUL Other'	2.83 L (103)	4.27 L (126)	66	N	Extensive	06/17/00	Y	3(6)	3	2-5	42
Control	53	Primary tumor _	Lobe RLL	2.36 L 59	3.97 L 79	59	N	Minimal	10/27/00	Y _	2(4)	3	2-5	22
	70	Primary tumor	Segment RLL,	2.43 L 79	3.61 L 92	67	N	No	03/23/00 Pt. died	N	NA	2	2-5	11
	73	Primary tumor Emphysema	Lobe RUL Wedge RUL	1.271, (59)	2.27 L (84)	56	Y	No	10/10/00	Y	NA	2	>5	22
	81	Primary tumor Emphysema	Lobe RUL	3.14 L (91)	4.541, (98)	69	N	No	07/29/00	N	NA	f74	>5	16

a. Resection of giant bullae,
b. Pneumothorax 21 days after discharge
c. Chest wall resection; sleeve resection, prosthetic reconstruction
d. RML enbloc resection
Abbreviations: FEV1 - forced expiratory volume at 1 sec; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease; HV - Heimlich Valve; IOAL - Intraoperative air leak; AL- air leak; 1 – liters; RUL: right upper lobe; RLL: right lower lobe; RML - right middle lobe; LUL left upper lobe; LLL- left lower lobe.

Local Complications - Pneumothorax

The retrospectively defined criteria for whether or not a pneumothorax was reported as an adverse event included: whether the subject was symptomatic, how large the pneumothorax was, the course of events for that patient, whether the pneumothorax enlarged, required treatment, or prolonged hospitalization. A small pneumothorax per se (or air space as seen on a CXR) was typically not considered an adverse event unless it was unanticipated, occurred late in a patient's course, or altered the patient management due to presenting clinical symptoms that required treatment, (e.g. reinsertion of a chest tube). In cases where the subject was asymptomatic and simply had a persistent air leak, pneumothorax was not reported as an adverse event. A "Summary of Subjects who experienced an Adverse Event as Pneumothorax" is presented in the Table below for the 9 Sealant and 5 Control patients who had pneumothorax reported as an adverse event. Five of nine Sealant patients required intervention such as chest tube or Heimlich valve insertion and one of these patients died. There were no deaths in the Control group and one of five control patients required chest tube reinsertion.

Table 22. Summary of Subjects who Experienced Pneumothorax as an AE
(Ref. P010047a1, p439; Attachment 5c)

Treatment	Date of PTX	POD	Resolution Date	Severity	CT Status[a]	Date CT Out	Actions Taken
Sealant[b]	05/04/00	8	08/07/00	Moderate	Suction	05/06/00	CT reinserted
Sealant[c]	09/14/00	1	09/16/00	Moderate	Suction	09/20/00	DC'd with HV on 9/18/00
Sealant[d]	04/16/00	3	05/02/00	Mild	Water seal	04/16/00	None
Sealant	02/20/01	14	03/01/01	Mild	Removed	02/11/01	CT reinserted, pt. died 03/01/00.
Sealant[e]	02/02/01	1	03/08/01	Mild	Suction	02/22/01	DC'd with HV on 02/10/01
Sealant[f]	02/03/01	6	03/14/01	Mild	Removed	02/03/01	None; DC'd 02/05/01
Sealant[g]	02/13/01	0	03/14/01	Mild	Suction	03/02/01	DC'd with HV on 2/22/01
Sealant	09/23/01	1	09/26/01	Mild	Suction	09/26/00	None
Sealant	03/14/00	20	03/29/00	Severe	Removed	02/27/00	Admitted to ER, CT inserted on 03/15/00
Control[h]	06/10/00	5	06/13/00	Severe	Removed	06/08/00	CT reinserted

							Post-DC.
Control[i]	11/23/00	3	12/07/00	Mild	Water - seal	11/28/00	None
Control	11/24/00	2	11/27/00	Mild	Suction	11/27/00	None
Control[j]	02/23/01	1	03/30/01	Moderate	Suction	02/28/01	None
Control	08/03/00	0	08/04/00	Mild	Suction	08/09/00	None

Abbreviations: POD: post operative day; CT: chest tube; DC'd: discharged; HV: Heimlich valve; PTx: Pneumothorax; ER: Emergency Room.
a. At onset of PTx.
b. 5/6 CXR showed no PTx and should be resolution date; may have transcribed 5/7 date wrong.
c. PTx resolved on 9/16 but subcutaneous emphysema (SQE) persisted until 9/20 so CT remained until 9/20.
d. CXR showed PTx on 4/16, post-CT removal; pt. asymptomatic when DC'd. CXR showed no PTx on 5/20. e. CXR at 1 MFU on 3/8 showed no PTx confirming resolution.
f. Date of PTX mistranscribed on CRF and corrected here. CXR at 1 NB--U on 3/14 showed no PTx.
g. CXR at 1 MFU showed good expansion of lung.
h. Small PTx at discharge (<5%) on 6/9. SQE resolved 6/13/00.
i. Pt had small pneumothorax; emphysema resolved 12/7.
j Patient had multiple complications after surgery due to various problems. Serial CXRs from 2/23/01-3/28/01 revealed loculated hydropneumothorax. Decreased by 03/01/01. Cont. to show hydropneumothorax until 3/30/01 after patient underwent a bronchoscopy with irrigation of his copious secretions and debridement of granulation tissue; stent also replaced. CXR following operation showed all residual air replaced with fluid. By 4/10/01 fluid was resolving. Hydropneumothorax thought due to patients atelectasis.

Local Complications - Partial lung expansion

Partial lung expansion was reported in 32 (33%) of the Sealant and 12 (22%) of the Control patients as determined by the treating investigator and the sponsor's medical monitor's review of the 1 month CXR. To further evaluate the occurrence and 30 day outcome of pneumothorax / partial expansion, a follow-up chest x-ray evaluation protocol was designed by FDA and the sponsor during PMA review. In this analysis, chest x-rays from: 1) the recovery room, 2) within 24 hours of chest tube removal, and 3) 30 day post-op were reviewed for sixty subjects randomly selected at three of five investigational centers. Subjects were selected in a two Sealant to one Control ratio, read by an independent masked radiologist and compared to investigator assessments. The masked case report form for this analysis included standard criteria and check boxes for readings such as: complete expansion; incomplete expansion: pneumothorax; incomplete expansion: not pneumothorax.

Evaluation and comparison was performed for the chest x-rays from 36 Sealant and 20 Control patients or 56/162 (34.6%) of the study population. For this subset of patients the following observations were made:

- A comparable incidence of complete expansion was noted on the recovery room chest X-rays (i.e., 26/36 (72%) for Sealant and 14/20 (70%) for Control subjects).

- The percentage of completely expanded lungs was 20/39 (51%) for Sealant and 8/20 (40%) for Control subjects on the day of chest tube removal.

- The incidence of completely expanded findings for the one-month follow-up chest x-rays was 30/36 (83%) for Sealant and 20/20 (100%) for Control subjects which trended, but was not statistically (p=0.078) significant for this subset of the study population.

- In this subgroup, 17% more Control patients proceeded to complete expansion at the 30 day follow-up than Sealant patients. This trend occurred in the same direction, albeit to a lesser extent, as the study investigators' chest X-ray assessment of the entire study population (i.e., 65% of the Control and 55% of the Sealant patients were completely expanded at the 1 month follow-up).

In the subgroup of 36 Sealant and 20 Control patients, the median size of pneumothorax observed in CXRs assessed by the independent radiologist using an assessment method that was standard for this review was:

- Nearly twice the size for Sealant (n=10) (38mm) compared to Control (n=6) subjects (22mm) in the recovery room (RR). Because the mean values for Sealant (37.6 mm) and Control (45.5 mm) patients differed from the median values, these data may not be normally distributed for this small group of patients.

- The median size of pneumothorax was larger for Sealant than the median value for Control subjects at all time points (i.e., RR, CT-pull, 1 month follow-up).

- The median size of pneumothorax increases from the time of chest tube pull (n= 19) to one month (n= 6) follow up for Sealant patients (i.e., from 21mm to 27mm) while resolving to zero for Control subjects.

In comparison of pneumothorax size observed in all CXRs as assessed by the independent radiologist and assuming that "no pneumothorax" equals zero the following observations may be summarized;

- On the recovery room CXRs, comparable mean pneumothorax size was observed in both groups, albeit the Control group range was broader (i.e., Sealant 0-74mm; control 0 – 106mm).

- At chest tube removal, mean pneumothorax size was comparable, however the median values were not (i.e., Sealant 21 mm; Control 15 mm), while the Sealant range was broader (i.e., Sealant 5-56; Control 5-39mm).

- The change in size for the 6 Sealant patients who had a pneumothorax at 1 month follow-up are presented in Table 23.

Table 23. Pneumothorax Size at Time of CT Pull and 1 Month Follow-up
(Ref. p. 7 A11)

Subject	Type of Procedure	Size at CT Pull	Size at 1 Month
1	Right upper lobectomy	Not measured	28 mm
2	Right upper lobectomy	11 mm	2 mm
3	Bilobectomy (right upper and right middle lobe)	12 mm	35 mm
4	Wedge resection (right upper and right lower lobes)	56 mm	48 mm
5	Right upper lobectomy	45 mm	26 mm
6	Right upper lobectomy	43 mm	25 mm

These data suggest that the mean pneumothorax size was 5.6 mm larger for the Sealant (n=6) patients at one month follow-up (27.3 mm) compared to size observed for Sealant (n=19) patients at CT pull (21.7 mm) and the range of pneumothorax size at one month follow-up was 2-48 mm for Sealant (n=6) patients compared to 0mm for Control (n=20) patients.

The concordance of the independent radiologist and treating investigators was determined. The percent agreement at each time point was within 7% (67-75%) across all time points for the Sealant group; within 5% (60-65%) across all time points for Control patients and within 4% (66-70%) for the entire subgroup. Clinically and statistically significant differences were noted between interpreters for all groups and at various time points.

Comparison of the chest x-ray review on: 1) the day of chest tube removal and 2) the one-month follow-up by the independent radiologist revealed that while no patients were found to have a new pneumothorax, 1/22 Sealant (4.5%) and 0/15 Control patients' pneumothorax increased, 2/22 (9%) Sealant and 0/15 of the control patients' pneumothorax remained the same and 19/22 (86%) Sealant and 15/15 (100%) of the Control patients pneumothorax decreased.

Comparing the baseline characteristics of patients in the CXR study cohort to the overall study cohort, revealed that Control patients had more and larger final IOALs per leak, however, the percentage of patients with no post-operative air leak was comparable in this subgroup (i.e., 32.5% for Sealant and 30% for Control patients). Hence the percentage of patients with post-operative air leak were comparable, which was not consistent with the overall cohort which had a 35.0% incidence of no post-operative air leak in the Sealant and a 13.8% incidence of no post operative air leaks in Control groups.

While it is recognized that resection may result in an under-filled pleural cavity, it is known that remaining lung expands with intent to fill the residual space, and it is clinically preferred and usually surgically attempted to minimize residual space so as to optimize lung function and decrease risk of complications in the residual space. The risk of long-term complications associated with the incidence of partial expansion associated with device use has not been evaluated.

The incidence of selected adverse events according to chest x-ray results at 1 month follow-up is presented below for Sealant and Control patients in two groups: 1) with complete expansion and 2) with partial expansion. Listed adverse events are fever, dyspnea, subcutaneous emphysema, pneumothorax, and atelectasis.

Table 24. Incidence of Selected AEs According to CXR Results at 1 MFU
(Ref. P010047a6 Appendix 4)

	Patients with Complete Expansion [b]			Patients with Partial Expansion [b]		
Adverse Event Preferred Term	Sealant (N- 62)	Control (N° 41)	P-Value [c]	Sealant (N= 34)	Control (N= 12)	P-Value [d]
Fever	11 (17.7%)	9(22.0%)	0.619	10 (29.4%)	2 (16.7%)	0.472
Dyspnea	8 (12.9%)	6(14.6%)	1.000	3 (8.8%)	1 (8.3%)	1.000
Subcutaneous emphysema	5 (8.1%)	4 (9.8%)	1.000	1 (2.9%)	0 (0.0%)	1.000
Pneumothorax	4(6.5%)	4 (9.8%)	0.710	3 (8.8%)	1 (8.3%)	1.000
Atelectasis	1 (1.6%)	2 (4.9%)	0.562	0 (0.0%)	0 (0.0%)	

[a] AEs selected for the table included fever, dyspnea, subcutaneous emphysema, pneumothorax, atelectasis, respiratory disorder, and sepsis.
[b] based on the chest x-ray results at the one month follow-up visit
[c] 2-sided p-value associated with Fisher's Exact test comparing Sealant and control groups - complete expansion
[d] 2 - sided p-value associated with Fisher's Exact test comparing Sealant and control groups - partial expansion

In this group of patients fever was reported as an adverse event in 10 (29.4%) of Sealant patients with partial lung expansion compared to 2 (16.7%) of Control patients with partial lung expansion. Reasons and sequelae of this clinically notable increase in fever in the Sealant patients with partial lung expansion were not presented.

Subsequent to discussions with FDA, the sponsor provided new data, reanalysis of existing data and additional published literature discussing the clinical significance of partial lung expansion and the relationship between surgical procedure and the incidence of partial lung expansion.

Review of the dataset revealed that in the subset of subjects selected for the independent radiologist CXR review, 6/32 (19%) of all patients who underwent either an upper lobectomy or an upper wedgectomy surgery experienced unresolved pneumothorax at 1 month compared to 0/28 (0%) subjects who underwent other types of surgery. The PMA data showed that an imbalance in cohorts existed for the patients in the independent CXR review with 26/40 (65%) Sealant and 6/20 (30%) Control subjects undergoing either an upper lobectomy or upper wedgectomy surgery. For the entire study population, review indicated that while the types of surgeries were balanced for each treatment group (Tables 3 and 25), an imbalance of 67/103 (66%) Sealant and 29/58 (50%) Control subjects was observed when the incidences of upper lobectomy or upper wedgectomy surgery (page 9 amendment 11) were combined. (In Table 3 of this summary, the incidence of all lobectomy surgeries was 55/103 (53.4%) for Sealant and 34/58 (58.6%)

for Control patients with no statistically significant or clinically notable differences in the type of surgery (lobectomy or other) between the study cohorts.)

Table 25. Incidence of Lobectomy Surgery
(Ref: Appendix 16.2.4.5.1 pp. 7165 – 7187)

	Sealant		Control	
N	103		58	
	N	%	N	%
Right upper lobectomy	32	31.1	15	25.9
Left upper lobectomy	16	15.5	9	15.5
All upper lobectomies	48	46.6%	24	41.4

Based on literature precedent, the PMA suggested that patients undergoing upper lobectomy surgery should be expected to have a greater chance of apical pleural space. In addition, the PMA suggested that for lung lobes remaining after surgery, even though they may be fully expanded, they may not expand sufficiently to fill the apical pleural space following upper lobectomy, thus, it was not surprising that there was a higher rate of partial lung expansion in the subset of Sealant of patients whose CXR were evaluated by independent radiologist, ($p=0.17$, N.S.), (due to the higher proportion of Sealant subjects undergoing upper lobe resection) compared to the Control population. However, combining the outcomes of patients undergoing upper lobectomy and upper wedgectomy surgeries may not be appropriate, because they can represent different surgical patient populations.

The literature analysis provided also examined the clinical significance of partial lung expansion and suggested that prolonged air leak is a risk factor for infection and pneumonia, as well as a cause of extended hospital stay. Because there were no statistically significant differences in these complications between the Sealant and Control groups, (and the Sealant patients demonstrated a shorter hospital stay than the Control group ($p<0.05$)), the PMA data suggests that the observed differences in incidence of partial lung expansion were not clinically significant.

The panel will be asked to comment on the following issues discussed in four publications submitted in the PMA that discussed post-operative residual space (and the risks thereof) as they relate to the patient outcomes in the pivotal clinical trial:

1. 'Trial of a novel synthetic sealant in preventing air leaks after lung resection', Wain et al. *Ann Thorac Surg* 2001; **71**:1623-9, discussed a clinical study assessing the safety and effectiveness of a new synthetic, bioresorbable surgical sealant in preventing air leaks after pulmonary resection, (i.e., FocalSeal). The authors state: "Although not achieving statistical significance, 2% of treated patients did demonstrate residual spaces on follow-up chest roentgenograms without evidence of empyema or fistula. The sealant does serve as an adhesion barrier and a possible explanation for the residual space finding may be that the sealant modifies the expected postoperative reconfirmation of the lung to the thoracic cavity."

2. ‘Postoperative Residual Pleural Space: Characteristics and Natural History’, Misthos et al. *Asian Cardiovasc Thorac Ann* 2007; **15**:54-8, reports on a clinical study to re-define the incidence and natural history of post-resectional residual spaces (PRS) by retrospective analysis of 966 patients who were subject to less that entire lung resection, followed with any cases of PRS recorded. The authors state that “Multiple regression analysis revealed no prognostic factors for PRS development.” Table 2 in this publication lists a higher incidence of PRS associated with upper rather than lower lobectomy, and right compared to left lobectomy, in patients with normal compared to increased wall thickness. However, this retrospective data set also demonstrates a clinically notable imbalance of upper and lower lobectomies (546 (62.5%) compared to 133 (37.5%)), as well as right and left sided surgery (638 (73%): such imbalance may have introduced bias and error as to outcome assessment that is specific to resection location.

3. ‘Residual post-operative pneumothorax: harmless radiologic finding or complication-prone diagnosis?,’ Schmidt et al. *Scheiz Med Wochenschr.* 1995 Jul 22; **125**(29): 1391-5, this abstract summarizes 470 patients who underwent lobectomy, bilobectomy or decortication at their institution between 1980 and 1991. A residual post-operative pneumothorax was observed on 20.7% of patients at discharge after chest removal. The authors state that there was no significant correlation between the development of a residual post-operative pneumothorax and the patient’s age and gender, the type of surgery, and the date of surgery as relates to introduction of stapling devices, and that complete regression was observed in 91% of the patients within one year after the operation and the duration of regression did not correlate with the size of the pneumothorax at discharge.

4. ‘Air leak and Pleural Space Management’, Murthy, S., *Thoracic Surg Clin* **16** (2006) 2611-265 reports that “although air leaks are common following anatomic resection, most resolve within the first 3 post-operative days. …The underlying mechanisms of air leak resolution remain unknown, although the formation of pleural-pleural adhesions at the sites of leaks seems most plausible. This mechanism can be postulated because in the presence of pleural space where pleural apposition cannot occur, management of an air leak is a more formidable problem. …Depending on the volume of air leak, the amount of parenchyma resected, and the compliance of remaining lung, an ipsilateral residual pleural space may result after lung resection. This phenomenon is far more common after lobectomy, although it can accompany extensive wedge resections. Even in the absence of an air leak, a post-operative space may result. This space eventually fills with lung or fluid and early after the operation causes large swings in the water seal chamber (without air breach) during the respiratory cycle. ...Anecdotally, the presence of a pleural space also seems to be a poor prognostic sign.” The author also describes several maneuvers that are useful to optimize lung inflation and minimize unfilled space. These include dividing the inferior pulmonary ligament, temporarily anesthetizing the phrenic nerve, creating a pleural tent, mechanical pleurodesis or pleurectomy, and rarely re-suspension of the diaphragm and thoracoplasty.

The information in these articles suggests noting,: 1) the report of a 2% incidence of residual space was observed during the clinical study of a lung sealant (that was subsequently FDA approved), 2) the report of an inconsistent relationship between the type of surgery and the incidence of post-operative residual space, and 3) a detailed discussion of intra-operative maneuvers to minimize post-operative residual space. The latter publication identifies the importance of efforts to minimize the incidence of residual inter-pleural space.

Therefore, when evaluating device performance in this study, the Panel will be asked to consider whether the comments: 1) 'upper lobe resections are a risk factor for apical pleural spaces that often appear as pneumothorax on a chest x-ray' and 2) 'partial filling of the pleural spaces is of no clinical significance in patients whose air leak has been sealed' are supported by the published literature.

In the clinical trial, patients were followed for only 30 days post-operatively. Because, the residual post-operative spaces were reported as filled with air rather than fluid, it remains unclear whether the remaining space will be expected to change past the 30th day post-operatively.

The panel will be asked to consider the fact that safety outcomes associated with an increased incidence of post-operative residual space in the device and control groups were not evaluated beyond 30 days after surgery, and discuss what data-based comments may be made concerning the rate of adverse events associated with the increased incidence of post-operative space found in the investigational device cohort.

Complete references for these publications are found in the panel pack.

Finally, the PMA also presented information suggesting that the higher rate of pneumothorax in the subgroup of Sealant patients who were evaluated by the independent radiologist may reflect a longer follow-up time in the Control group (as illustrated in the Table below).

Table 26. Time since Surgery & Patients with PTX at CT Pull (Ref: p.9 A 11)

Length of follow-up at 1 Month	**Result**	**Sealant**	**Sealant**	**Control**
		PTX at 1 MFU	No PTX at 1 MFU	No PTX at 1 MFU
Time from surgery	N	6	13	12
	> 5 weeks	2 (33%)	9 (69%)	8 (67%)
	> 6 weeks	0	7 (54%)	3 (25%)
	Mean	29.7	44.6	42.8
	Median	32	44	37

E. Immunology

An unique aspect of this device is that it is derived from a human serum albumin. The significance of immune responses elicited by Sealant implantation was evaluated by

ELISA and lymphocyte proliferation assays. In addition, a review of adverse events that could potentially be immunologically related was also performed. These analyses are described below:

Humoral Immune Response Analysis

Assay Methods – An ELISA was developed to detect antibodies elicited to the polymerized, pulverized Sealant. In this assay the polymerized, pulverized Sealant was coated on a 96 well plate. Serum to be analyzed was incubated with the plate and after rinsing, detection of bound antibodies was achieved by either an enzyme linked anti-human or anti-rabbit IgG secondary antibody.

Sample Collection – Serum samples were collected within 30 days before and 4-6 weeks after device implantation.

Results

Patient Accounting - Pre- and post-treatment blood/serum samples were obtained from 118 of the enrolled subjects, (i.e., 74/103 (72%) of the Sealant and 44/58 (76%) of the Control patients). Taking deaths into account, the percentage of samples collected was 79/98 (81%) for Sealant and 45/54 (83%) for Control patients.

Test Results - 70/71 (98.6%) of the Sealant and 36/37 (97.3%) of the Control subjects did not display a positive ELISA response against Sealant. One subject in each group had a postoperative serum level consistent with the formation of anti-Sealant antibodies. In each case the subject's preoperative serum also showed a high value which indicated that their serum contained antibodies that cross-reacted with the Sealant before device exposure. These results suggest that device use did not elicit a significant immune response against the device.

Lymphocyte Proliferation Assay (LPA)

Assay Methods – The presence of T-cell mediated immune responses against Sealant was assessed in a LPA. In this assay the proliferative response of lymphocytes was assessed with a standard screen of mitogens (i.e., Concanavalin A, Phytohemagglutinin, and Pokeweed mitogen), recall antigens (*Candida albicans* and Tetanus Toxoid) and the Sealant. The cellular response to recall antigens indicated whether device exposure had altered the T-cell's response to antigenic stimuli and tests with the Sealant explored cell sensitization to the device. Analyses of patients' blood before and after device implantation permitted assessment of possible immunosuppressive and immunostimulatory effects related to device exposure.

Sample Collection – Whole blood samples (with sodium heparin) for each patient were collected within 30 days before and 4-6 weeks after device implantation. Samples were kept at room temperature and shipped overnight to the Center Laboratory where cells

were isolated from blood and assayed at 1 or 2 days following collection. When the blood arrived later than 2 days after collection, it was assayed if viable cells could be isolated.

Results

Patient Accounting –

As discussed above, only subjects with pre and post-operative samples were included in comparative analyses, (i.e., 59/103 Sealant and 34/58 Control patients (mitogen analysis) and 69/103 Sealant and 32/58 Control patients (recall antigen and Sealant analyses)).

Test Results -

No significant differences in cell-mediated immunity were found to exist between the Sealant and Control groups. The only significant difference observed was a lower preoperative value for the tetanus toxoid response in the Control group (compared to the mean value calculated for the treatment group). The higher preoperative values detected in the Sealant group were judged to be not clinically significant, because the blood was collected prior to Sealant exposure.

In addition to the comparison of mean treatment group values, the presence of significant differences in the average pre- and post-surgery responses of individuals was assessed. In this analysis a 95% confidence interval (C.I.) was established based on the Control samples so that any post-surgical test results that were unusually high or low in either treatment group were identified. There were 10 Sealant and 5 Control subjects who fell outside the 95% C.I. The clinical outcomes of these patients were evaluated with regard to the emergence of adverse events that could possibly be related to an immune response against the Sealant (see below). From this analysis no evidence was found for a correlation between abnormal LPA results and immune-related adverse events.

Possible Immune-Related Clinical Symptoms

The clinical significance of potential immune responses against the Sealant was evaluated by comparing the incidence of signs and symptoms that could be associated with immune-mediate disease for the two treatment groups. These data were:

Table 27. Incidence of AEs Potentially Related to Immune Responses against Sealant
Ref. p. 14 P010047a1

Signs/symptoms	Sealant	Control	P-value
Abnormal renal function	2 (1.9%)	0 (0%)	0.536
Acute renal failure	3 (2.9%)	1 (1.7%)	1.00
Allergic reaction	0 (0%)	1 (1.7%)	0.360
Anemia	8 (7.8%)	6 (10.3%)	0.573
Arthritis	0 (0%)	0 (0%)	N/A
Fever	22 (21.4%)	12 (20.7%)	1.00
Hypotension	8 (7.8%)	6 (10.3%)	0.573
Multi-organ failure	0 (0%)	1 (1.7%)	0.360

Neutropenia	0 (0%)	0 (0%)	N/A
Oliguria	5 (4.9%)	1 (1.7%)	0.420
Pancytopenia	0 (0%)	0 (0%)	N/A
Pleural effusion (Ty. IV)	4 (3.9%)	3 (5.2%)	0.703
Pruritis	1 (1.0%)	2 (3.4%)	0.295
Rigors (fever)	0 (0%)	1 (1.7%)	0.360
Thrombocytopenia	0 (0%)	1 (1.7%)	0.360

While the incidence of abnormal renal function, acute renal failure and oliguria were consistently higher in the Sealant group, and are clinically notable, their incidence was not found to be statistically significantly higher than the rates found in the Control group.

V. Summary

Based on the data provided in the PMA, the following observations may be made about potential device effectiveness:

- The percent of patients without post-operative air leak (POAL) from recovery room through one month post-operatively or the duration of hospitalization was:
    - Sealant: n = 36 / 103 (35%)
    - Control: n = 8 / 58 (13.8%)
    - P = 0.005
- The percent of patients without post-operative air leak (POAL) from last air leak test in the operating room through one month post-operatively or the duration of hospitalization was:
    - Sealant: n = 31 / 103 (30.1%)
    - Control: n = 0 / 58 (0%)
- The duration of chest tube placement included the time that the Heimlich Valve was in place. The results were not statistically significantly different for Sealant and Control treatment groups. Data indicate that 7.4% more Sealant (i.e., 13/103 – 12.6%) than Control (i.e., 3/58- 5.2%) patients had the chest tube duration longer than 11 days.
- The duration of hospitalization (i.e., post-operative hospital days (POD)) was shorter in the Sealant than the Control group. Data also indicate that 10 Sealant patients compared to 1 Control patient were discharged home with Heimlich valves to treat an ongoing air leak. Hospital stay for these patients may not reflect the total time of active care for air leak with device intervention.

Concerning device safety, the following observations may be made:

- Pneumothorax reported as an adverse event occurred in 9 Sealant and 5 Control patients. At one month follow-up, 65% of the Control and 55% of the Sealant patients were completely expanded as judged by the treating investigator.
- Fever was reported as an adverse event in 10 (29.4%) of the Sealant patients with partial lung expansion, compared to 2 (16.7%) of the Control patients with partial lung expansion.
- The severe renal dysfunction occurred in 5/9 Sealant and 1/2 Control patients who had renal dysfunction reported as an adverse event.

- Death in Sealant treated patients was of pulmonary etiology (i.e., ARDS, n = 3, and 2 of these 3 were associated with multi-organ failure; pneumonia, n = 1; pulmonary embolism or obstruction, n = 1). Death in Control treated patients was of mixed etiology (i.e., pneumonia, n = 1; ventricular fibrillation, n = 1; atrial fibrillation, n = 1; anoxic brain injury, n = 1).

The Panel will be asked to discuss the topics in the Panel Questions, considering the information provided in this summary.

VI. Postapproval Plan

NOTE TO PANELISTS: *FDA's inclusion of a section/discussion on a Post-Approval study in this memo should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether to approve a device or not must be based on the premarket data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding a potential post-approval study should the panel find the device approvable following its discussions and deliberations of the pre-market data.*

The company has not included a post approval study plan in their PMA. Should an approvable recommendation be made by the panel, FDA may at that time, ask some questions about the details of what may comprise an adequate post approval study for this device, should that be appropriate.