SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name: SURGICAL SEALANT

Device Trade Name: FOCALSEAL-L SYNTHETIC ABSORBABLE SEALANT

Applicant's Name and Address: Focal, Inc.
Four Maguire Road
Lexington, MA 02421

Date of Panel Recommendation: May 8, 2000

Date of GMP Inspection: March 6-10, 2000

Premarket Approval Application Number: P990028

Date of Notice of Approval to the Applicant: May 26, 2000

Expedited Review: Expedited review was granted on March 25, 1999 based on the potential public health benefit from reducing the number of patients experiencing air leaks through hospital discharge following pulmonary resection.

II. Indications for Use

FocalSeal-L Sealant is intended for use as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection.

III. Device Description

The FocalSeal-L Surgical Sealant system is comprised of synthetic absorbable sealant and primer solutions, two syringe/applicators, a light source, light wand and a PowerCap® light tester. The Sealant is formed via chemical and photochemical polymerization processes. The Sealant solution is provided in frozen form packaged in a red syringe and two primer vials. The two syringe applicators are used to deliver the primer and sealant solutions to the target tissue site. The FocalSeal reusable light source and light wand, ordered separately, photopolymerize the sealant solution to a thin film hydrogel. FocalSeal-L primer and sealant are aqueous solutions of poly (ethylene glycol) that have been modified with short segments of acrylate-capped poly (L-lactide) and poly (trimethylene carbonate). These solutions also contain buffers, initiators, and stabilizers.

8

FocalSeal-L Surgical Sealant solutions (i.e., primer and sealant) are applied to the target tissue site as liquids. Upon exposure of the photo-initiator, Eosin-Y, to blue-green light, the primer and sealant solutions polymerize to form a crosslinked, clear, flexible, adherent hydrogel network. The sealant expands upon contact with body fluids and reaches its equilibrium swell volume within 24 hours. Over time the poly (L-lactide) and poly (trimethlyene carbonate) segments of FocalSeal-L Surgical Sealant degrade by hydrolysis, causing loss of mass and structural integrity. This results in the eventual dissolution and clearance of the Sealant via water-soluble molecules that are cleared through the kidneys or locally metabolized.

IV. Contraindications

- FocalSeal-L Sealant is contraindicated for patients undergoing pneumonectomy or application over open or closed defects in main stem or lobar bronchi, due to an increased incidence of broncho-pleural fistulae observed in clinical study patients undergoing sleeve resection or bronchoplasty.
- FocalSeal-L Sealant is contraindicated for application on oxidized regenerated cellulose and absorbable gelatin sponges, as adherence will be compromised.

V. Warnings and Precautions

Warnings and Precautions can be found in the product labeling.

VI. Alternative Practices or Procedures

Surgical procedures for airleak cessation with and/or without use of autologous tissue, for example, air leak oversew or overlay with pleural tent. Products made of glutaraldehyde-crosslinked bovine pericardium or collagen are applied as patches or strips over tissue sites to reduce or eliminate air leaks.

VII. Potential Adverse Effects of the Device on Health

Adverse events which occurred in the FocalSeal-L cohorts at an incidence of 1% or greater in the US study and 2.9% or greater in the European study are listed in Tables 1 and 2, respectively. The adverse events are listed in descending order according to frequency. These tables list all adverse events reported in the study including those attributed and not attributed to treatment.

Summary of Adverse Events for U.S. Study
Table 1

	FocalSeal-L (n=125)		*Control (n=55)*	
Event	**#**	**%**	**#**	**%**
Arrhythmia	29	23.2	17	30.9
Fevers	15	12.0	8	14.5
Cancer Progression	13	10.4	4	7.3
Pneumothorax	10	8.0	4	7.3
Thoracic Wound Infection	9	7.2	2	3.6
Pneumonia	9	7.2	5	9.1
Death	7	5.6	4	7.3
Confusion	7	5.6	0	0
Upper Respiratory Infection	7	5.6	3	5.5
Anemia	6	4.8	5	9.1
Ileus / Intestinal Obstruction	5	4.0	2	3.6
Urinary Tract Infection	4	3.2	3	5.5
Empyema	4	3.2	0	0
Persistent Atelectasis	4	3.2	0	0
Pulmonary Emboli	3	2.4	0	0
Deep Vein Thrombosis	3	2.4	0	0
Pleural Effusion	3	2.4	0	0
Residual Space	3	2.4	0	0
Colitis / Gastroenteritis	3	2.4	0	0
Hemoptysis	2	1.6	0	0
CHF	2	1.6	0	0
COPD	2	1.6	0	0
Anxiety	2	1.6	2	3.6
Hypotension	2	1.6	0	0

In the U.S. clinical trial, 7/125 FocalSeal-L and 4/55 Control patients died during the time patients were on study. All deaths were judged as not related to treatment by the investigators. Regarding the severity of non-fatal adverse events, there were 66 severe events in 43 (34%) patients, 90 moderate events in 72 (58%) patients and 27 mild events in 13 (10%) of the 125 FocalSeal-L patients. In the 55 control patients there were 30 severe events in 17 (31%) patients, 41 moderate events in 28 (51%) patients and 15 mild events in 4 (7%) patients.

Summary of Adverse Events for European Study
Table 2

Event	*FocalSeal-L (n=34)*	*Control (n=26)*
Bronchial Fistulae [associated events included infection (4) and pneumothorax (2)]	8 (23.5%)	0 (0%)
Out of Range Lab Values	6 (17.6%)	2 (5.9%)
Pneumonia	5 (14.7%)	1 (3.8%)
Bronchial Infection	5 (14.7%)	0 (0%)
Superficial Phlebitis	4 (11.8%)	0 (0%)
Death	2 (5.9%)	1 (3.8%)
Metastatic Disease	2 (5.9%)	1 (3.8%)
DVT	2 (5.9%)	0 (0%)
Pneumothorax	2 (5.9%)	1 (3.8%)
Respiratory Depression / Insufficiency	2 (5.9%)	1 (3.8%)
Fever and Leukocytosis	1 (2.9%)	2 (7.7%)
Urinary Tract Infection	1 (2.9%)	2 (7.7%)
Pulmonary Infiltrates	1 (2.9%)	1 (3.8%)
Cardiac Failure	1 (2.9%)	1 (3.8%)
Cardiac Tamponade	1 (2.9%)	1 (3.8%)
Hematoma	1 (2.9%)	1 (3.8%)
Pulmonary Embolism	1 (2.9%)	1 (3.8%)
Anemia	1 (2.9%)	1 (3.8%)
Sepsis	1 (2.9%)	1 (3.8%)

The following events occurred in one FocalSeal-L patient, but no control patients: pulmonary erosion, post-thoracotomy syndrome, effusion, atelectasis, bronchitis, pulmonary edema, arrhythmia, lymphedema, intestinal obstruction, visual field defect, CVA, and vomiting.

In the European clinical trial, 2/34 FocalSeal-L and 1/26 Control patients died during the time patients were on study. All deaths were judged by the investigator as not related to treatment.

The only remarkable clinical event finding in the European study was the higher than expected (23.5%) incidence rate of bronchial fistulae (8/34 treated patients). Other relevant details were that the fistulas all occurred at the bronchial stump and that 7/8 of the bronchial fistulas occurred in patients who had FocalSeal-L Sealant applied to the bronchial stump. Analysis concluded that the FocalSeal-L Sealant, when applied to the bronchial stump site, acted as a mechanical barrier to adjacent tissue overlap and adhesion attachment, thereby eliminating a natural source of revascularization, resulting in slower healing. Since this only occurred in approximately one third of patients who had FocalSeal-L Sealant applied to the bronchial stump, it is believed that application of FocalSeal-L Sealant to the stump was one of several contributing factors which may lead to bronchial fistulae formation. Other known risk factors include: extent of resection; sleeve resections; age greater than 60 years; prolonged post-operative ventilation and diabetes.

VIII. Marketing History

FocalSeal-L Sealant was granted the CE Mark for commercial distribution throughout the European Union in December, 1997. Sales have commenced in the European Union countries as well as in Canada, Australia, New Zealand, South Africa, Egypt, Hong Kong, Israel and Switzerland. FocalSeal-L Sealant has not been withdrawn from any market for reasons relating to the safety and effectiveness of the device.

IX. Summary of Preclinical Studies

The preclinical studies with FocalSeal-L demonstrated that device extracts are non-cytotoxic and a moderate irritant. The genotoxicity studies indicated that under some circumstances mutation of mammalian cells (mouse lymphoma mutation assay) was observed. Implantation studies indicated that the device degrades very slowly. A chronic inflammatory response was observed with macrophages and giant cells and palpable tissue site in 90 day studies. At the last test time point of 600 days, the device was almost completely resorbed. In this same long-term study in rats, tumors were observed in treated and historical control animals with a similar frequency and time course. Summaries of the preclinical tests performed on FocalSeal-L Sealant are presented in the following Tables: biocompatibility testing (Table 3), laboratory performance testing (Table 4) and animal performance testing of FocalSeal-L Sealant (Table 5).

Table 3 - Biocompatibility Testing Summary for FocalSeal-L Sealant[1]

Type of Test	Method	Result
Cytotoxicity	USP <87> Agar Diffusion (*in vitro*); MEM extract	Non-cytotoxic
Sensitization	Kligman Maximization Test (guinea pig); saline extract	Non-sensitizing
Irritation	USP Intracutaneous Injection (rabbit); saline extract	Moderate irritant

Acute Systemic	Systemic Injection (mouse); saline extract	Non-toxic
Subchronic Toxicity/ Implantation	Intra-Peritoneal Implant (rat) for 8 Days, 30 Days and 14 Weeks	Non-toxic, but chronic inflammation observed at 30x the clinical dose
Chronic Toxicity/ Implantation	Intra-Peritoneal Implant (rat) for 26 Weeks	Non-toxic, but chronic inflammation observed at 50x the clinical dose
Genotoxicity	Ames Mutagenicity (*in vitro*); DMSO extract	Non-mutagenic
	Mouse Lymphoma Cell Mutation Assay (*in vitro*); saline and DMSO extracts[2] (in accordance with ASTM E1280-97)	Non-mutagenic after 4 hrs Weak mutagen after 24 hrs incubation
	Chinese Hamster Ovary (CHO) Chromosomal Aberrations Assay (*in vitro*); saline and DMSO extracts[2]	Non-mutagenic
Implantation	Intramuscular (rat) for 601 days[2]	Encapsulation; small amount of material remaining; local macrophage response
	Application to Resected Lung Tissue (dog) for 8 Months[2]	Encapsulation; localized macrophage response
	Application to Resected Lung Tissue (dog) for 16 Months[2]	Encapsulation; localized macrophage response
Hemocompatibility	Hemolysis Study in Rabbit Whole Blood (*in vitro*); saline extract	Non-hemolytic
Pyrogenicity	USP<151> Pyrogen Test (rabbit); saline extract	Non-pyrogenic

[1] Testing was performed on polymerized and non-polymerized samples unless otherwise noted.
[2] Testing was performed on polymerized samples.

Table 4 – Laboratory Performance Testing of FocalSeal-L Sealant

Test	Methodology	Results

Seal Pressure	FocalSeal-L Sealant was applied to a latex substrate containing a 2 mm diameter hole. The latex sustrate was pressurized to failure.	Mean seal pressure of 257 cm H_2O
Elongation	Polymerized FocalSeal-L Sealant samples were placed into Instron test fixture and stretched to failure.	Mean elongation of 1568 % strain

Table 5 – Animal Performance Testing of FocalSeal-L Sealant

No. of Studies	Methodology	Results
3	Thoracotomy procedure and apical amputation of the cranial, middle and caudal lobes in dogs. FocalSeal-L Sealant was applied over each staple line and lung was inflated to confirm sealing effectiveness. Tissue adherence was assessed 2 weeks following surgery using a predefined 0 – 4 scoring system. The acceptance criterion was a score of ≥ 2.5.	Study 1 - all scores ≥ 3.0 Study 2 - all scores ≥ 3.0 Study 3 - all scores ≥ 3.0

X. Summary of Clinical Studies

The following is a summary of the large-scale study designed to support approval. At the conclusion of this description is a brief summary of an uncontrolled clinical study performed in Europe.

U.S. Study

The study was open label, prospective, randomized, multi-center study comparing standard tissue closure techniques (control) to standard tissue closure techniques plus the FocalSeal-L Sealant (treatment) in patients scheduled to undergo elective pulmonary resections via an open thoracotomy procedure. Application of FocalSeal-L Sealant to the bronchial stump was contraindicated in this study. The study enrolled patients in a 2:1 randomization scheme of treated to control patients. There were 125 FocalSeal-L and 55 control patients in the safety cohort. Because the first two FocalSeal-L patients were prospectively identified as pilot patients and not included in the effectiveness analysis, there were 172 subjects in the effectiveness cohort (i.e., 117 FocalSeal-L and 55 control patients). Patient enrollment was also stratified with respect to a high or low risk for adverse events based on pre-operative and intraoperative risk factors.

FocalSeal-L Sealant was applied after patients had received standard surgical management with or without an attempt to close air leaks with conventional sutures

and/or staples. The device was applied by first brushing the primer solution onto the tissue site. Second, the sealant solution was brushed onto the target tissue with the sealant applicator mixing the primer and sealant solutions. The combination of the sealant and the primer solutions resulted in a free radical chemical reaction between the primer and sealant solutions that caused partial polymerization. Third, the sealant solution was dripped onto the target tissue and then illuminated to further photo-polymerize the device.

Control Therapy:
Patients randomized to the control group received standard surgical management, with or without attempted additional closures of air leaks, per surgical routine, i.e., conventional suture and/or staple closure.

Study Endpoints:
The primary efficacy endpoint was the proportion of patients determined to be air leak free at the end of the surgical procedure and who remained air leak free through hospital discharge. The secondary efficacy endpoints were mean time to air leak cessation and the proportion of patients air leak free at the end of the surgical procedure. Data concerning the time to chest tube removal and the time to hospital discharge were also collected. Device safety was evaluated by comparing the incidence and severity of clinical events during the hospitalization period and at 1, 3 and 6 months post-operatively.

Listing of Study Centers and Patient Treatment Group Assignment:
The study enrolled and treated 125 FocalSeal-L and 55 control patients. The study results from all of these patients were included in considerations of product safety. The product effectiveness cohort excluded the first two FocalSeal-L patients enrolled at each center. Thus, the dataset for effectiveness includes 172 patients (i.e., 117 FocalSeal-L and 55 control patients).

Study Results:

Baseline Demographics:
The study population primarily consisted of cancer patients undergoing surgery for tumor resection. The most common primary indication for surgery in both groups was pulmonary cancer, (see Table 6). The majority of the demographic factors were the same for both treatment arms (e.g., gender, race, and age). The only demographic factor approaching a statistically significant difference was the incidence the FEV/FVC% < 65%, (i.e., FocalSeal-L 26/125 (21%) versus Control 19/55 (35%) p = 0.064). The surgical resection procedures for both groups were also similar.

Table 6 - Patient and Baseline Characteristics[1]

		FocalSeal-L (n=125)	Control (n=55)
Gender	Female	73 (58%)	24 (44%)
	Male	52 (42%)	31 (56%)
Age at Surgery (yrs)	Mean	62.1	62.1

	Range	31 – 75	21 – 75
	Std. Dev.	9.7	10.0
Primary Surgical Diagnosis	Pulmonary Cancer	90 (72%)	43 (78%)
	Pulmonary Metastasis	16 (13%)	7 (1%)
	Benign Neoplasis	8 (7%)	2 (4%)
	Other	11 (9%)	3 (5%)
Types of Surgery	Single Lobectomy	83 (66%)	28 (51%)
	Single Wedge	18 (14%)	7 (13%)
	Segmentectomy	8 (7%)	6 (11%)
	Bi-Lobectomy	8 (7%)	4 (7%)
	Other	8 (7%)	10 (18%)
Number of Patients with Air Leaks Prior to Randomization		95 (76%)	39 (71%)

[1]No statistically significant ($p<0.05$) differences were detected between groups.

As illustrated in Table 7, the treatment groups were also balanced with regard to risk stratification.

Table 7 - Risk Factors

	FocalSeal-L	**Control**	**p-value**
Fragile Tissue	28/125 (22%)	10/55 (18%)	0.647
Extent of Surgery	21/125 (17%)	14 (25%)	0.099
Surgical sites ≥ 4	38 (30%)	21 (38%)	0.268
Low risk (Score 0-4)	110 (88%)	46 (84%)	
High risk (score 5-8)	15 (12%)	9 (16%)	
Mean risk score	2.4	2.7	

Effectiveness Analysis:
FocalSeal-L Sealant use as an adjunct to standard surgical management of pulmonary airleaks, i.e., conventional suture and/or staple closure provided a statistically significant increase in the proportion of patients air leak-free from time of skin closure through hospital discharge (the primary study endpoint) as well as: 1) a reduction in the time to air leak cessation and 2) an increase in the proportion of patients air leak free at the end of surgery (i.e., the secondary endpoints). These data are displayed below in Table 8. Analyses of the Time to Chest Tube Removal and the Time to Hospital Discharge revealed no statistically significant differences between the two treatment groups (Table 9).

Table 8
Primary and Secondary
Study Endpoint Data

	FocalSeal-L (n=117)	**Control (n=55)**	**p-Value**
Patients Air Leak-Free through Hospital Discharge	39% (46/117)	11% (6/55)	0.001[1]

Patients Air Leak-Free at Skin Closure	92% (108/117)	29% (16/55)	0.001[1]
Time to Air Leak Cessation (Hrs)			0.006[2]
Mean (SE)	30.9 (4.8)	52.3 (11.6)	
Median	12.1	27.6	

[1] Mantel-Haenszel Test
[2] Generalized Wilcoxon Test comparing time to last air leak distribution

Table 9 - Additional Analyses

	FocalSeal-L (n=125)	Control (n=55)	p-Value[1]
Days to Chest Tube Removal			
Mean (SE)	4.5 (0.2)	5.2 (0.5)	NS[1]
Median	4.0	4.0	
Days to Hospital Discharge			
Mean (SE)	7.4 (0.4)	10.1 (1.8)	NS
Median	6.0	6.0	
Days to Drainage < 125 cc/day			
Mean (SE)	3.4 (0.12)	3.7 (0.25)	NS
Median	3.0	3.0	
Patients with Recurrent Air Leak	62/108 (57%)	10/16 (63%)	NS

[1] NS – Not statistically significant.

Airleak cessation – For the entire effectiveness cohort, the incidence of patients being air leak-free from the end of surgery through hospital discharge (i.e., the primary study endpoint) was 46/117 (39%) for FocalSeal-L and 6/55 (11%) for Control patients, which was statistically significant (p=0.001) by the Mantel-Haenszel Test. For the entire effectiveness cohort, the frequency of patients that were air leak-free at the end of surgery (i.e., a secondary study endpoint) was 108/117 (92%) and 16/55 (29%) for FocalSeal-L and Control patients, respectively, which was statistically significant (p=0.001) by the Mantel-Haenszel Test. For the subset of patients who were airleak free at the end of surgery (see below), the proportion who remained airleak free through hospital discharge was 46/108 (42.6%) for FocalSeal-L and 6/16 (37.5%) for Control patients. This difference was not statistically significant.

Airleak recurrence - The percent of patients who were air leak free at skin closure, but subsequently developed a post-operative air leak was comparable between the FocalSeal-L (57%) and Control (63%) groups. For both study groups, the majority of the air-leaks developed during the first 24 hours after surgery, i.e., 93% for FocalSeal-L 90% for Control patients.

High/Low Risk Patients - For patients in the low risk stratum, 42/102 (41%) FocalSeal-L and 5/46 (11%) Control patients were air leak-free from the time of skin closure through hospital discharge. For patients in the high risk stratum, 4/15 (27%) FocalSeal-L and 1/9 (11%) control patients were air leak-free from the time of skin closure through hospital discharge.

Device Safety

Study Withdrawals:
No patients withdrawals occurred during the 6 month study. 13 (8%) patients were lost to follow-up. Per treatment arm, the division was 6 (5%) FocalSeal-L and 7 (13%) control patients.

Adverse events: Are displayed in section VI.

There were no reports of unanticipated adverse device effects in the study, (where an adverse device effect was defined as a serious adverse event which was probably or definitely related to the device and which had not been previously identified in the clinical investigation or the study protocol).

Patient Deaths – 7/125 (5.6%) FocalSeal-L and 4/55 Control (7.2%) patients died during the study. All deaths were judged by investigators as not related to treatment. Causes of death are displayed in Table 10.

Table 10
Causes of Death for Patients in the US Study
(All deaths were judged as not related to treatment by investigators)

FocalSeal-L Patients	Control Patients
Pneumonia (before discharge)	Pneumonia (before discharge)
Acute respiratory distress (before discharge)	Respiratory failure (betwx 1-3 mo. visit)
Metastatic disease in spine & liver (betwx 1-3 mo. visit)	Recurrent cancer (betwx 3-6 mo. Visit)
Cardiac disease (betwx 3-6 mo. visit)	Metastatic cancer progression (after 6 month visit)
Metastatic cancer progression (betwx 3-6 month visit)	
Metastatic cancer progression (after 6 mo. Visit)	
Metastatic cancer progression (after 6 mo. Visit)	

European Study

Study Design:
An open-label, prospective, randomized study was conducted in 34 FocalSeal-L and 26 Control patients undergoing lobectomy or segmental lung resection at 2 European clinical sites. Patients were over 18 years old, with SGPT, SGOT and alkaline phosphatase levels < 1.5 ULN; Bilirubin < 1.5 mg/dL; creatinine < 2.0 mg/dL; hematocrit > 25%, PT < 15 sec and a negative pregnancy test. Patients were excluded from study entry if they were: scheduled for pneumonectomy or presented with extensive intrathoracic pathology such as wide spread tumor or extensive adhesions from previous thoracic trauma or surgery; pregnant or lactating; with a history or lab evidence of hemostatic abnormality or failure to achieve adequate hemostasis at surgery; severe congestive heart failure, COR pulmonale and/or renal failure or the patient underwent investigational therapy within 28 days before surgery or planned treatment within next 30 days.

The primary efficacy endpoint was the proportion of patients air leak free at the end of the surgical procedure. The severity of air leaks was scored 0-3 (0= no leak, 1= just detectable in underwater test, 2= easily detectable in underwater test and 3= measurable) by the anesthesiologist. Patients were followed for 2 months. Safety was evaluated by comparing the incidence and severity of clinical events during the hospitalization period and at 1 and 2 months post-operatively.

Study Results:

Baseline Demographics:
The study population was predominantly male (i.e., 70% and 77% for FocalSeal-L and Control groups, respectively) and the primary surgical diagnosis was bronchogenic carcinoma (i.e., 77% and 65% for FocalSeal-L and Control groups, respectively). The primary surgical procedure was single lobectomy (i.e., 83% and 77% for FocalSeal-L and Control groups, respectively).

Effectiveness Analysis:
The proportion of patients air leak free at the end of the surgical procedure was 100% in the treatment group and 27% in the control group (p=0.001).

Safety Results:
13 treatment patients experienced 1 or more clinical events including pneumonia, fistula, empyema, pneumothorax, pleural effusion, lung hematoma, DVT, and sepsis. One FocalSeal-L patient died due to cardiac failure. All clinical events were managed using standard medical and/or surgical therapy. A table of the adverse events in presented in Section VI.

XI. Conclusions Drawn from Study

The results of the U.S. study demonstrated a significantly greater proportion of FocalSeal-L patients were air leak-free at the end of the surgical procedure and remained air leak-free through hospital discharge when compared to Control patients ($p=0.001$). The mean time to air leak cessation was significantly shorter in the FocalSeal-L Sealant group ($p=0.006$) and a statistically significant reduction in intraoperative air leaks was observed in the FocalSeal-L Sealant group when compared to the Control patients.

The FocalSeal-L Sealant group showed trends toward a shorter duration of chest tube placement and a shorter length of hospital stay. These improvements were not statistically significant.

There were no statistically significant differences in the incidence of adverse events between the FocalSeal-L Sealant group and the control group.

These results support the safety and effectiveness of FocalSeal-L Sealant when used as an adjunct to standard closure of visceral pleural air leaks incurred during elective pulmonary resection.

XII. Panel Recommendations

On May 8, 2000, the General and Plastic Surgery Devices Panel recommended approval with conditions for Focal, Inc.'s PMA for FocalSeal-L Sealant. In these discussions the Panel considered the adequacy of the preclinical testing. The Panel voted against requiring additional animal testing to evaluate the carcinogenicity of the device. The Panel also discussed the clinical significance of the elevated incidence of thoracic wound infection and empyema that were observed in the US study. Regarding tumor progression, the Panel stated that the incidence of tumor progression in the study was acceptable. While some Panel members were satisfied with the 6 month follow-up of patients in the US study, other Panel members believed that longer patient follow-up (e.g., 2-5 years) would be appropriate to see if there is an impact on cancer progression. The Panel voted in favor of collecting additional postmarket data on the incidence of infection and cancer progression.

Regarding product effectiveness, the Panel determined that the data in P990028 demonstrate a reasonable assurance that the use of the FocalSeal – L Sealant in a significant portion of the target population will provide clinically significant results. The Panel also commented on the similar incidence of air leak recurrence for FocalSeal-L (62/108 (57%)) and control (10/16 (63%)) patients. The Panel concluded that patients receiving FocalSeal-L displayed statistically significant improvements in the incidence of being air leak-free: 1) from the time of skin closure through hospital discharge and 2) at the end of surgery as well as a 3) reductions in the time to air leak cessation for

FocalSeal-L patients, but statistically significant improvements in the times to Chest Tube Removal, Hospital Discharge or Drainage < 125 cc/day were not observed.

XIII. CDRH Decision

Expedited review was granted on March 25, 1999 based on the potential public health benefit of FocalSeal-L Sealant for reducing the number of patients experiencing air leaks through hospital discharge following pulmonary resection.

Inspection of the sponsor's manufacturing facilities was performed on March 6-10, 2000. The facility was found to be in compliance with the device Good Manufacturing Practice regulations on May 26, 2000.

The FDA reviewed the recommendations provided by the General and Plastic Surgery Devices Panel at the May 8, 2000 Panel meeting. With regard to the impact of device use on the incidence of thoracic wound infection and empyema, FDA determined that the clinical experience from the U.S. and European studies was sufficient to accurately describe these adverse events in separate Warning statements in the product labeling. These statements would clarify the existing knowledge about the incidence of wound infection and empyema. Regarding the impact of device use on the incidence of cancer progression, the FDA determined that the sponsor should continue to evaluate the incidence of cancer emergence or recurrence in all (i.e., both FocalSeal-L Sealant and Control) patients who enrolled in the U.S. clinical study with annual visits up to 5 years post-surgery and FocalSeal-L implantation.

FDA issued an approval order on May 26, 2000.

XIV. Approval Specifications

Directions for Use: See the labeling

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the labeling

Post Approval Requirements and Restrictions: see the Approval Order.