SUMMARY OF SAFTEY AND EFFECTIVENESS

I. GENERAL INFORMATION

DEVICE GENERIC NAME:	Absorbable Hemostatic Agent
DEVICE TRADE NAME:	GELFOAM® Sterile Powder
APPLICANT:	Pharmacia & Upjohn 7000 Portage Rd. Kalamazoo, MI 49001
PREMARKET APPROVAL APPLICATION (PMA)	N18-286/S12
DATE OF PANEL RECOMMENDATION:	In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.
DATE OF GMP INSPECTION:	No inspection was required.
DATE OF NOTICE OF APPROVAL OF APPLICATION:	October 16, 2000

II. INTENDED USE/INDICATIONS.

GELFOAM™ Sterile Powder, saturated with sterile sodium chloride solution is indicated in surgical procedures including those involving cancellous bone bleeding as a hemostatic device when control of capillary, venous, and arterial bleeding by pressure, ligature and other conventional procedures is either ineffective or impractical.

III. DEVICE DESCRIPTION.

GELFOAM™ Sterile Powder is a sterile, water insoluble, malleable, porcine derived gelatin powder intended for hemostatic use by mixing with sterile sodium chloride solution and applying the paste to the bleeding surface. The powder is a fine, dry, heat-sterilized light powder prepared by milling gelatin sponges.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Do not use GELFOAM™ sterile powder in closure of skin incisions because it may interfere with the healing of skin edges. This interference is due to mechanical interposition of gelatin and is not secondary to intrinsic interference with wound healing.

Do not use GELFOAM™ Powder in intravascular compartments because of the risk of embolization.

Do not use GELFOAM™ Powder in patients with known allergies to porcine collagen.

The warnings and precautions can be found in the GELFOAM™ Powder labeling.

V. ALTERNATIVE PRACTICES AND PROCEDURES.

Hemostasis involves the interaction of blood vessels, platelets, and the coagulation cascade to form a localized mechanical seal. A variety of adjunctive methods exist to achieve hemostasis. During a major hemorrhage, direct pressure or clamps may result in hemostasis. Minor bleeding can be controlled and stopped by ligation, pharmacological agents (topical thrombin and tissue sealants), laser, cautery (heat, electric current, or a caustic substance) or topical agents such as oxidized cellulose, collagen, and gelatin sponges.

VI. POTENTIAL ADVERSE EFFECTS.

In a clinical study, 108 patients received GELFOAM™ Sterile Powder on the cut surface of the sternum during cardiopulmonary bypass surgery, while 107 patients received no treatment on the cut surface of the bone. Table 1 is a summary of medial events reported by at least 1.0% of patients in a treatment group. The most frequently reported events were atrial fibrillation, perioperative event, and wound infection. Events occurring in less than 1.0% of the patients were as follows: anaphylaxis, cardiogenic shock, delirium tremens, infection at the vascular catheter site, unevaluable reaction, sepsis, angina pectoris, atrial arrhythmia, nodal arrhythmia, arteriosclerosis, cardiac insufficiency, cardiac tamponade, cardiomyopathy, deep vein thrombosis, mitral valve disorder, endocarditis, ventricular extrasystoles, heart arrest, hypotension, mesenteric occlusion, superventricular tachycardia, thrombophlebitis, thrombosis, gastrointestinal disorder, gastrointestinal bleeding, increased serum creatinine, dehydration, anemia, thrombocytopenia, abnormal healing, hypovolemia, hypoxia, metabolic acidosis, cerebral infarction, visual hallucinations, stupor, aspiration pneumonia, chest congestion, pleural effusion, pulmonary infiltration,

retinal artery occlusion, anuria, UG disorder, abnormal kidney function and menorrhagia.

Table 1: Summary of Medical Events for Gelfoam Sterile Powder

Medical Event	GELFOAM N=108		Control N=107		Total N=215	
	n	%	n	%	n	%
Atrial Fibrillation	14	(13.0)	12	(11.2)	26	(12.1)
Wound Infection	6	(5.6)	1	(0.9)	7	(3.3)
Perioperative Event	4	(3.7)	5	(4.7)	9	(4.2)
Congestive Heart Failure	4	(3.7)	0	(0.0)	4	(1.9)
Ventricular Tachycardia	2	(1.9)	3	(2.8)	5	(2.3)
Atrial Flutter	2	(1.9)	0	(0.0)	2	(0.9)
Peripheral Vascular Disorder	2	(1.9)	0	(0.0)	2	(0.9)
Pneumothorax	2	(1.9)	3	(2.8)	5	(2.3)
Respiratory Failure	2	(1.9)	2	(1.9)	4	(1.9)
Respiratory Arrest	2	(1.9)	1	(0.9)	3	(1.4)
Fever	1	(0.9)	2	(1.9)	3	(1.4)
Heart Block	1	(0.9)	2	(1.9)	3	(1.4)
Prolonged Wound Drainage	0	(0.0)	1	(0.9)	1	(0.5)
Cellulitis	0	(0.0)	2	(1.9)	2	(0.9)
Dyspnea	0	(0.0)	2	(1.9)	2	(0.9)
Pneumonia	0	(0.0)	2	(1.9)	2	(0.9)

In general, the following adverse events have been reported with the use of absorbable hemostatic agents based on animal collagen or gelatin:

- Gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.
- Giant cell granulomas have been observed at implant sites when used in the brain.
- Compression of the brain and spinal cord resulting from the accumulation of sterile fluid has been observed.
- Multiple neurologic events were reported when absorbable gelatin-based hemostatic agents were used in laminectomy operations, including cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence and paresis.
- The use of absorbable gelatin-based hemostatic agents have been associated with paralysis, due to device migration into foramina in the bone around the spinal cord, and blindness due to device migration in the orbit of the eye, during lobectomy, laminectomy and repair of a frontal skull fracture and lacerated lobe.

- Foreign body reactions, "encapsulation" of fluid, and hemotoma have been observed at implant sites.

- Excessive fibrosis and prolonged fixation of a tendon have been reported when absorbable gelatin-based sponges were used in severed tendon repair.

- Toxic shock syndrome was reported in association with the use of absorbable gelatin-based hemostats in nasal surgery.

- Fever, failure of absorption, and hearing loss have been observed when absorbable hemostatic agents were used during tympanoplasty.

VII. MARKETING HISTORY.

Gelfoam Sterile Powder was first marketed by Pharmacia & Upjohn in 1952 and remained on the market until April 1992 when it was withdrawn pending the approval of the bone hemostasis indication. Later in September 1993, Pharmacia & Upjohn was given approval from FDA to market GELFOAM Sterile Powder for the same clinical use as other Gelfoam presentations provided we remove the bone hemostasis indication from the label until further clinical work could be performed to support this use. For over thirty years, Gelfoam Sterile Powder has enjoyed a history of safe use by the medical community and is currently marketed in over 50 countries worldwide.

VIII. SUMMARY OF PRE-CLINICAL STUDIES.

No pre-clinical studies were performed for this PMA Supplement, since this submission was for a new indication and no pre-clinical studies were necessary.

IX. SUMMARY OF THE CLINICAL STUDY.

A. Study Design

Two randomized open-label clinical studies were conducted at separate investigative sites. The objectives were as follows:

- To evaluate the effectiveness of GELFOAM™ Sterile Powder as a hemostatic agent in the treatment of sternal bone bleeding during cardiopulmonary bypass surgery.

- To identify any deleterious effects of GELFOAM™ Sterile Powder on interference with bone healing.

- To determine any systemic or local wound side effects from leaving GELFOAM™ Sterile Powder *in situ*.

- Patients between the ages of 18 to 74 years old undergoing cardiopulmonary bypass surgery were randomly assigned to either a GELFOAM™ group or a Control group. The GELFOAM™ group (composed of 108 patients) had a paste made up of Sterile saline solution and GELFOAM™ sterile powder applied to the cut sternal surface immediately following sternotomy. The Control group (composed of 107 patients) received no treatment applied to the cut surface.

Blood loss was monitored both during surgery and postoperatively. Blood loss during surgery was determined by measuring the weight of a gauze pad before and after application to the cut edge of the sternum. Postoperative blood loss was collected from the mediastinal drainage tubes. The total blood loss (in milligrams) over 72 hours was determined for each patient.

B. Study Endpoints

Patients were evaluated upon admission (preoperative), during surgery (intraoperative), after surgery (postoperative), upon hospital discharge (7 to 10 days after surgery), and at the 3-month follow-up visit. An additional post study follow-up was required if a patient reported an ongoing medical event at the 3-month follow-up visit.

C. Listing of Study Centers and Patient Treatment Group Assignment

Table 2 shows the investigators and center locations for each of the two studies along with the number of participating patients.

Table 2: Number of Patients Enrolled at Each Center

Study	Study Site	Location	Investigator	GELFOAM	Control
001	Duke University Hospital	Durham, NC	J.E. Lowe, MD	54	55
002	Medical College of Virginia	Richmond, VA	R. Damiano, MD	54	52

D. Study Results

Blood Loss

In both studies, the amount of blood loss was significantly less in the GELFOAM group than in the control group. In Study 001, the mean blood loss in the GELFOAM group was 13727.7 mg while the mean blood loss in the Control group was more than double at 27712.0 mg. Similar results were found in Study 002, where the mean blood loss in the GELFOAM group was 9514.8 mg while the mean blood loss in the Control group was 22687.5 mg.

Table 3: Blood Loss in Sternotomy Patients				
	Site 001		Site 002	
	GELFOAM	Control	GELFOAM	Control
Mean Blood Loss (mg)	13727.7	27712.0	9514.8	22687.5
Median Blood Loss (mg)	11561.0	24798.0	6950.0	16900.0
Minimum Blood Loss (mg)	2922.0	10748.0	800.0	900.0
Maximum Blood Loss (mg)	87448.0	61535.0	46000.0	89800.0

Sternal Bone Healing

Patients in the GELFOAM and Control groups were similar with regard to sternal bone healing. At hospital discharge, normal bone healing was reported for 105 patients (97%) in the GELFOAM group and 104 patients (97%) in the Control group. Results for 6 patients (three GELFOAM and three Control) were not known.

At the 3-month follow-up, 103 patients (95%) in the GELFOAM group and 100 patients (93%) in the Control group were healed. Six patients (Two GELFOAM and 4 Control) were not healed. Results for 6 patients (three GELFOAM and three Control) were not known.

Infection Complications

Few patients in either treatment group had sternotomy infection or other postoperative infection complications related to sternotomy. At hospital discharge, two GELFOAM-treated patients had mediastinitis. No Control patients had any infections at hospital discharge. One GELFOAM-treated patient had a non-infection-related complication.

At the 3-month follow-up, one of the original GELFOAM patients who had mediastinitis was still infected. Two additional patients in the GELFOAM-treated group had also developed Mediastinitis.

One patient in the CONTROL group experienced sternal osteomyelitis at the 3-month follow-up but recovered with no residual effects. No patients from the GELFOAM arm of the study had reported complications of sternal osteomyelitis.

There was a total of four patients who had non-infection related complications.

One CONTROL patient had serous/sanguineous wound drainage from the left leg and sternum incisions at hospital discharge. This complication was non-infectious and the patient recovered with no residual side effects.

The remaining three CONTROL patients all experienced chronic pain syndrome, a symptom that can occur following thorasic/cardiac surgery. Evaluation sternal bone healing at the 3-month follow-up for these patients showed no evidence of non-union of the sternum. In all three cases, bone healing at the 3-month follow-up was reported as being normal.

X. CONCLUSIONS DRAWN FROM THE STUDY.

These studies demonstrate that a paste made from GELFOAM™ Sterile Powder is safe and effective in treating intraoperative bleeding when applied to the cut surface of cancellous bone and has shown superior hemostasis versus no treatment at all to the cut bone surface. The benefit to patients is that a reduction in bleeding will make surgery easier to perform by reducing the time the surgeon needs to revisit cut bone surfaces to clean up the bleeding. This study also demonstrated that GELFOAM® Sterile Powder could be left *in situ* without increased risk of bone infection or nonunion of the sternum.

XI. PANEL RECOMMENDATION.

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA Supplement was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CDRH ACTION.

This submission was approved on October 16, 2000.

APPROVAL SPECIFICATIONS.

Directions for use: see the labeling.

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

Postapproval requirements and restrictions: See Approval Order.