SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION.

DEVICE GENERIC NAME:	Absorbable Gelatin Sponge, USP
DEVICE TRADE NAME:	SURGIFOAM™ Absorbable Gelatin Sponge, USP
APPLICANT:	Ferrosan A/S 5 Sydmarken 2860 Soeborg, Denmark
APPLICANT'S US REPRESENTATIVE:	ETHICON, Inc. P.O. Box 151 Somerville, NJ 08876-0151
PREMARKET APPROVAL APPLICATION (PMA):	P990004
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:	August 13, 1999
DATE OF NOTICE OF APPROVAL OF APPLICATION:	September 30, 1999
STREAMLINED REVIEW:	Streamlined processing was authorized on March 22, 1999, based on the fact that FDA had reviewed more than 5 previous applications for similar devices.

II. INTENDED USE/INDICATIONS.

SURGIFOAM™ Absorbable Gelatin Sponge, USP is indicated for use in surgical procedures (other than neurological, urological and ophthalmological surgery) as an adjunct to hemostasis when control of capillary, venous and arteriolar bleeding by pressure, ligature and other conventional procedures is ineffective or impractical.

III. DEVICE DESCRIPTION.

The SURGIFOAM Sponge is a sterile, water-insoluble, malleable, porcine gelatin absorbable sponge intended for hemostatic use by applying to a bleeding surface. The sponge is off-white and porous in appearance. The sponge is available in 6.25 cm x 8 cm x 10 mm (thickness); 8 cm x 12.5 cm x 10 mm and 8 cm x 25 cm x 10 mm sizes for the standard sponges and 8 cm x 12.5 cm x 2 mm size for the compressed sponge.

IV. CONTRAINDICATIONS.

Do not use SURGIFOAM Sponge 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 SURGIFOAM Sponge in intravascular compartments because of the risk of embolization.

Do not use SURGIFOAM Sponge in patients with known allergies to porcine collagen.

The warnings and precautions can be found in the SURGIFOAM 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, 142 patients received SURGIFOAM gelatin sponge and 139 patients received another legally marketed absorbable gelatin sponge. The most common adverse events recorded during and after the application of the device were fever, tachycardia, and asthenia (a general feeling of weakness). Table 1 lists those adverse events that occurred in greater than 5% of the SURGIFOAM patients. The control patients are included for comparison.

Table 1: Incidence of Treatment Emergent Adverse Events by Treatment Group.			
Term	SURGIFOAM (n=142)	Control Sponge (n=139)	Total (n=281)
Fever	28 (19.7%)	34 (24.5%)	62 (22.1%)
Tachycardia	27 (19.0%)	28 (20.1%)	55 (19.6%)
Asthenia	25 (17.6%)	17 (12.2%)	42 (14.9%)
Peripheral Edema	20 (14.1%)	20 (14.4%)	40 (14.2%)
Hypertonia	20 (14.1%)	12 (8.6%)	32 (11.4%)
Anemia	19 (13.4%)	11 (7.9%)	30 (10.7%)
Nausea	18 (12.7%)	22 (15.8%)	40 (14.2%)
Constipation	17 (12.0%)	17 (12.2%)	34 (12.1%)
Hypertension	16 (11.3%)	12 (8.6%)	28 (10.0%)
Insomnia	16 (11.3%)	13 (9.4%)	29 (10.3%)
Pain	13 (9.2%)	17 (12.2%)	30 (10.7%)
Pharyngitis	13 (9.2%)	11 (7.9%)	24 (8.5%)
Vomiting	13 (9.2%)	8 (5.8%)	21 (7.5%)
Edema	12 (8.5%)	10 (7.2%)	22 (7.8%)
Pruritus	12 (8.5%)	10 (7.2%)	22 (7.8%)
Rash	12 (8.5%)	19 (13.7%)	31 (11.0%)
Headache	11 (7.7%)	9 (6.5%)	20 (7.1%)
Hypokalemia	11 (7.7%)	10 (7.2%)	21 (7.5%)
Hypomagnesemia	11 (7.7%)	11 (7.9%)	22 (7.8%)
Infection	11 (7.7%)	6 (4.3%)	17 (6.0%)
Paresthesia	11 (7.7%)	7 (5.0%)	18 (6.4%)
Dyspepsia	10 (7.0%)	4 (2.9%)	14 (5.0%)
Hypotension	10 (7.0%)	10 (7.2%)	20 (7.1%)
Diarrhea	9 (6.3%)	8 (5.8%)	17 (6.0%)
Hypocalcemia	9 (6.3%)	9 (6.5%)	18 (6.4%)
Cough Increased	8 (5.6%)	9 (6.5%)	17 (6.0%)
Edema General	8 (5.6%)	5 (3.6%)	13 (4.6%)
Hematoma	8 (5.6%)	9 (6.5%)	17 (6.0%)

Other adverse events observed in less than 5% of the SURGIFOAM patients were chest pain, somnolence, anorexia, anxiety, dizziness, ecchymosis, oliguria, abdominal pain, thrombocytopenia, agitation, bradycardia, confusion, depression, dyspnea, back pain, urine retention, abdominal enlargement, dry mouth, GI discomfort, dehydration, lung edema, flatulence, abnormal healing, hematuria, hiccups, hyperventilation, ileus, infection of the urinary tract, leukocytosis, vertigo, amblyopia, arrhythmia, cardiomegaly, cellulitis, chills, dysphagia, hyperglycemia, urinary incontinence, melena, mucous membrane discharge, eye pain and pneumonia.

In general, the following adverse events have been reported with the use of absorbable porcine gelatin-based hemostatic agents:

- 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 have 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.

- The use of absorbable gelatin-based hemostatic agents during the repair of dural defects associated with laminectomy and craniotomy operations, have been associated with fever, infection, leg paresthesias, neck and back pain, bladder and bowel incontinence, cauda equina syndrome, neurogenic bladder, 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 hematoma 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.

Ferrosan A/S has been marketing this product in Europe since January 1, 1999. Ferrosan A/S has never marketed this gelatin sponge within the United States. Previously, a similar product containing one-percent surfactant had been marketed for over 50 years under the product name of SPONGOSTAN. Currently, these products are marketed in approximately 60 countries worldwide. The generic absorbable gelatin product is defined in both the United States and British Pharmacopoeia.

VIII. SUMMARY OF PRE-CLINICAL STUDIES.

This section provides brief summaries of important preclinical studies performed on SURGIFOAM™ Absorbable Gelatin Sponge, USP. Toxicological evaluations were conducted in vitro in L929 mouse fibroblast cells and rabbit blood, and in vivo in mice,

rabbits, and guinea pigs, with durations of treatment ranging from a single implant or single dose of extract to repeat dosing over a two-week period. The results of the toxicity and biocompatibility studies conducted on SURGIFOAM Absorbable Gelatin Sponge, USP are listed in Table 2.

Table 2. Toxicity and Biocompatibility Studies Performed on SURGIFOAM Absorbable Gelatin Sponge, USP.

Toxicity and Biocompatibility Studies	
***In vitro* Cytotoxicity:**	SURGIFOAM is non-cytotoxic.
Dermal Sensitization:	SURGIFOAM is non-sensitizing.
Intracutaneous Reactivity:	No reactivity. SURGIFOAM is non-irritating.
Acute Systemic Toxicity:	No reactivity. SURGIFOAM is non-toxic.
Material-Mediated Pyrogenicity:	No temperature increase detected. SURGIFOAM is non-pyrogenic.
***Salmonella typhimurium* Reverse Mutation Assay (Ames Test):**	No excess reverse mutations were detected. SURGIFOAM is non-mutagenic.
Chromosomal Aberrations in Chinese Hamster Ovary Cells:	No significant increase in cells with chromosomal aberrations was observed. SURGIFOAM is non-clastogenic.
Sister Chromatid Exchange (SCE) Assay in Chinese Hamster Ovary Cells:	No significant increase was seen in the number of SCEs/cell. SURGIFOAM does not cause DNA damage.
Intramuscular Implant Study:	Macroscopically no reaction was seen, however, microscopically, SURGIFOAM was a moderate irritant, but within acceptable limits.
Hemolysis Test:	No reactivity. SURGIFOAM is non-hemolytic.
Vaginal Implant Study with Histopathology:	No significant reactivity was noted microscopically or macroscopically. SURGIFOAM was non-irritating.
Limulus Amebocyte Lysate Assay:	Endotoxin levels were acceptable.

The hemostatic properties of the SURGIFOAM™ Absorbable Gelatin Sponge, USP were evaluated in a female swine model in two studies.

The first study evaluated the ability of SURGIFOAM Standard thickness sponge to achieve hemostasis of freely bleeding spleen incisions compared to another commercially available absorbable gelatin sponge. Hemostasis incision wounds were made 1 cm apart on the surface of the spleen using a scalpel blade. Wounds were approximately 1.5 cm long and 2 mm deep. After each incision, gauze (for the negative control) or the test/control article under gauze was applied with gentle pressure. At the end of two minutes the pressure was released. This procedure was repeated at 30 second intervals until the hemorrhage was controlled, which was defined as no renewed hemorrhage for 30 seconds. There was no significant difference between the time to hemostasis for three lots of SURGIFOAM (233.3, 233.8, and 232.7 seconds) and the control sponge (233.3 seconds). In contrast, none of the untreated wounds stopped bleeding within 720 seconds (when timing was terminated).

In a second study, SURGIFOAM standard sponge was compared to SURGIFOAM compressed sponge using a similar swine spleen bleeding model. An analysis of the results indicated that the time to hemostasis for the SURGIFOAM Compressed sponge

was comparable to the SURGIFOAM Standard sponge.

In summary, these studies demonstrated that the SURGIFOAM standard and SURGIFOAM compressed sponges proved to be comparable to the control sponge in achieving hemostasis in the swine spleen-bleeding model.

IX. SUMMARY OF THE RESULTS OF THE CLINICAL INVESTIGATION.

The following is a summary of the clinical study designed to evaluate safety and effectiveness of SURGIFOAM™ Absorbable Gelatin Sponge, USP. The primary objective of this study was to compare the safety and effectiveness of SURGIFOAM™ Absorbable Gelatin Sponge to another legally marketed hemostatic agent as measured by hemostasis within 10 minutes of application in routine surgical procedures. Hemostasis was defined as the complete control of bleeding and demonstration of a "dry" site. Statistical equivalence for achieving hemostasis for the two study groups was predefined as the interval (–0.125, 0.125). The safety profiles for the two devices were evaluated by collecting and comparing the incidence of adverse events (AEs) between the two products.

A. Study Design:

The clinical trial was a randomized, concurrently controlled study designed to compare SURGIFOAM™ Absorbable Gelatin Sponge, USP and another marketed absorbable sponge. The study population included patients undergoing orthopedic cardiovascular and general surgical procedures. Each patient was randomly assigned to either SURGIFOAM sponge or the Control sponge at a 1:1 ratio. The target site was the site of most intense bleeding of all evaluable sites in the operative field. Evaluable sites included bleeding sites of capillary, venous, arteriolar, or arterial origin of mild to moderate intensity that were not controlled by other standard hemostatic modalities such as ligature, cautery, or other convenient procedures. Patients had follow-up visits at 2 to 4 weeks and at 6 to 8 weeks postsurgery.

B. Study Endpoints:

Device effectiveness was determined by examination of the proportion of patients achieving hemostasis within 3, 6, and 10 minutes. Safety was evaluated by comparing adverse events for both products.

C. Listing of Study Centers and Patient Treatment Group Assignment:

The clinical trial was performed at seven centers. A list of the centers and the numbers of patients enrolled at each center is supplied in Table 3.

Table 3: Number of Patients Enrolled at Each center				
Site	Investigator	SURGIFOAM	Control	Total
1- UNTHSC: Fort Worth, TX	Smith	44	45	89
2- Galveston, TX	Hunter	21	22	43
3- Birmingham, AL	Knott	14	14	28
4- San Diego, CA	Moossa	37	35	72
5- Columbia: Fort Worth, TX	Guinn	13	12	25
6- Raleigh, NC	Stocks	8	9	17
7- Indianapolis, IN	Mercho	5	2	7
	TOTAL	142	139	281

D. Results:

All 281 enrolled patients were randomized and included in the safety and effectiveness analyses.

1. Baseline Demographics:

The baseline demographics in both the SURGIFOAM™ and Control groups were comparable for gender, race, age, and bleeding intensity. Enrollment was balanced between the SURGIFOAM and control patients for the three types of surgeries: cardiovascular, orthopedic, and general surgical.

2. Efficacy Results:

The primary purpose of this study was to evaluate the comparability of SURGIFOAM™ Absorbable Gelatin Sponge, USP to a control gelatin sponge as measured by hemostasis outcome within 10 minutes of application in routine surgical procedures. The difference in the proportion of patients who achieved hemostasis in each treatment group was also evaluated at two other time points (three and six minutes) to assess the relative performance of the two test articles over time.

The majority of patients in the study achieved hemostasis within ten minutes for both the SURGIFOAM and the control groups. The confidence interval for the difference in proportions for the two groups was (-0.015, 0.071), which was contained within the predetermined equivalence interval (–0.125, 0.125), therefore, it was concluded that the two treatments were equivalent. The results are summarized in Table 4.

Table 4: Summary of Effectiveness Results Comparing SURGIFOAM to Another Absorbable Gelatin Sponge, USP (Percent achieving hemostasis).					
Minutes	Device	General Surgical	Cardiovascular	Orthopedic	Total
		% (Ratio)	% (Ratio)	% (Ratio)	% (Ratio)
3	SURGI-FOAM	65.6 (42/64)	57.4 (39/68)	100.0 (10/10)	64.0 (91/142)
	Control Sponge	66.2 (43/65)	62.9 (39/62)	91.7 (11/12)	66.9 (93/139)
6	SURGI-FOAM	98.4 (63/64)	80.9 (55/68)	100.0 (10/10)	90.1 (128/142)
	Control Sponge	95.4 (62/65)	91.9 (57/62)	100.0 (12/12)	94.2 (131/139)
10	SURGI-FOAM	100.0 (64/64)	89.7 (61/68)	100.0 (10/10)	95.1 (135/142)
	Control Sponge	95.4 (62/65)	96.8 (60/62)	100.0 (12/12)	96.4 (134/139)

3. Safety Results:

Adverse events were reported by 232 of the 281 patients in the trial; 121 in the SURGIFOAM group and 111 in the Control group. A total of 1406 individual events were reported, 713 in the SURGIFOAM group and 693 in the Control group (Table 5).

Table 5: Patients Experiencing At Least One Adverse Event (AE)			
	SURGIFOAM (n=142)	Control Sponge (n=138)*	Total (n=281)
Experienced an AE	121 (85.2%)	111 (79.9%)	232 (82.6%)
Did not experience an AE	21 (14.8%)	27 (19.4.%)	48 (17.1%)
Total number of Aes	713	693	1406

*Adverse event data was not collected on one control patient.

None of the adverse events experienced by patients in this study were considered definitely related to treatment, 34 were considered possibly related (17 each to the treatment and control groups), and none were considered serious. Most of the events were considered by the investigators to be unrelated to treatment with either product. Five of the 281 patients enrolled in the trial died during the study. Three of the deaths were in the SURGIFOAM group and two were in the control group. None of the deaths were considered related to treatment with either product. See Table 1 for a list of adverse events observed during this study.

Wound evaluations were performed for presence of hematoma, breakthrough bleeding, signs of infection or other wound observations at three times: prior to discharge, 2 to 4 weeks post-surgery and 6 to 8 weeks post-surgery.

4. Immune Response:

Patient sera were tested for the presence of anti-porcine collagen immunoglobulins. Sera were collected prior to surgery, at 2 to 4 weeks post surgery and at 6 to 8 weeks following surgery. Two hundred six patients were tested at baseline, 2-4 weeks, and at 6-8 weeks. Only one of the 206 patients had antibodies at baseline and 6 of the 206 patients had antibodies at the 6-8 week time point. Three of the patients were in the SURGIFOAM group and 3 patients were in the control group. The analysis of the immunology data indicated that there was no difference in the ability of the SURGIFOAM to induce anti-porcine collagen immunoglobulins when compared to the control sponge.

X. CONCLUSIONS DRAWN FROM THE STUDY.

The results of the preclinical and clinical testing demonstrated that there is reasonable assurance of safety and effectiveness for SURGIFOAM Absorbable Gelatin Sponge, USP for the stated indication for use. The sponsor performed a randomized, parallel, controlled, comparative, multicenter clinical trial designed to determine the hemostatic ability of the SURGIFOAM sponge in surgical patients. The control group was treated with a legally marketed absorbable gelatin sponge.

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 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.

A GMP inspection was conducted of the Ferrosan A/S facilities on August 13, 1999, and they were found to be in compliance with the Device GMP Regulations.

This submission was approved on September 30, 1999.

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.