## SUMMARY OF SAFETY AND EFFECTIVENESS

## I. GENERAL INFORMATION.

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|---|---|
| DEVICE GENERIC NAME: | Gelatin Matrix Hemostatic Sealant |
| DEVICE TRADE NAME: | FloSeal™ Matrix<br>FloSeal™ Matrix Hemostatic Sealant<br>Proceed™ Hemostatic Sealant |
| APPLICANT: | Fusion Medical Technologies, Inc.<br>1615 Plymouth St.<br>Mountain View, CA 94043 |
| PREMARKET APPROVAL APPLICATION (PMA): | P990009 |
| 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: | October 15, 1999 |
| DATE OF NOTICE OF APPROVAL OF APPLICATION: | December 8, 1999 |
| STREAMLINED REVIEW: | Streamlined processing was authorized on April 14, 1999, based on the fact that FDA had reviewed more than 5 previous applications for similar devices. |

## II. INDICATIONS FOR USE:

FloSeal™ Matrix Hemostatic Sealant is indicated in surgical procedures (other than in neurosurgical, ophthalmic, and urological) as an adjunct to hemostasis when control of bleeding by ligature or conventional procedures is ineffective or impractical.

## III. CONTRAINDICATIONS:

Do not inject FloSeal™ Matrix into blood vessels or allow it to enter blood vessels. Extensive intravascular clotting and even death may result.

Do not use FloSeal™ Matrix in the closure of skin incisions because it may interfere with the healing of the skin edge due to mechanical interposition of gelatin.

Do not use FloSeal™ Matrix in patients with known allergies to materials of bovine origin.

See Contraindications in the Package Insert for Thrombin-JMI®.

## IV. WARNINGS AND PRECAUTIONS:

The warnings and precautions can be found in the FloSeal™ labeling (Attachment 1).

## V. DEVICE DESCRIPTION.

FloSeal™ Matrix Hemostatic Sealant is an absorbable hemostatic agent which is packaged as a kit containing a gelatin matrix component and a thrombin component. The thrombin is reconstituted with saline diluent. A proprietary sterile dispersion needle is used to add the reconstituted thrombin to the gelatin matrix component prior to use. The FloSeal™ Matrix results from the combination of the gelatin matrix and the reconstituted thrombin solution. FloSeal™ Matrix may be extruded directly from the syringe, or applicator tips of various lengths can be attached to the syringe to facilitate delivery.

The gelatin matrix component consists of cross-linked gelatin, which is sterile and non-pyrogenic. The gelatin is derived from bovine corium through heat denaturation and is subsequently crosslinked. The cattle from which the corium is taken are of US origin. The gelatin matrix exists as small granules that are supplied hydrated in a syringe intended for single use. The gelatin matrix component is terminally sterilized by irradiation.

The thrombin is supplied to Fusion Medical Technologies, Inc. by Gentrac, Inc. (distributed by Jones Pharma Incorporated ), and is commercially available in the United States. The thrombin component is supplied as *Thrombin, Topical, USP (bovine origin); Thrombin-JMI®*, a sterile, freeze-dried powder. It is provided with sterile diluent consisting of sodium chloride USP 0.9%. The thrombin is reconstituted with the saline diluent and added to the gelatin matrix component in the operating suite prior to use. FloSeal™ Matrix is supplied in packaging that maintains its sterility and is intended for single use only.

Because of its particulate nature, FloSeal™ Matrix (the combination of the gelatin matrix with thrombin) may be easily extruded from a syringe for delivery to the bleeding site. An applicator tip may be attached to the syringe to facilitate delivery of FloSeal™ Matrix

to difficult-to-reach sites. FloSeal™ Matrix conforms well to irregular bleeding surfaces. It is hydrophilic and adheres well to wet tissue, including vertical and moving surfaces. The particles swell upon contact with fluids, allowing the material to restrict the flow of blood. The particles of FloSeal™ Matrix are not readily displaced by blood flow prior to hemostasis being achieved. The particles of FloSeal™ Matrix swell approximately 20% upon contact with blood or other fluids. Maximum swell volume is achieved within about 10 minutes. As blood percolates through the bed of FloSeal™ Matrix particles, the thrombin converts the fibrinogen in the patient's blood to fibrin. The fibrin clot that forms incorporates the FloSeal™ Matrix particles, resulting in a FloSeal™ Matrix-clot composite that seals the bleeding site. The particulate nature of FloSeal™ Matrix allows excess material not incorporated into the clot to be removed by gentle irrigation, if desired, without disturbing the hemostatic seal. Since FloSeal™ Matrix is biocompatible and is bioresorbed within 6 – 8 weeks, it may be left *in situ* at the discretion of the surgeon.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES.

Conventional procedures used to control bleeding include the use of direct pressure, sutures and/or electrocautery. In addition, absorbable hemostatic agents such as bovine gelatin powder and sponges, and hemostats made from bovine collagen and oxidized cellulose are commercially available and are used for stopping bleeding. Bovine thrombin may be used alone for hemostasis, but thrombin is also often used in conjunction with bovine gelatin hemostatic agents.

## VII. MARKETING HISTORY:

FloSeal™ Matrix Hemostatic Sealant received CE Mark certification in April, 1999, and has been used commercially in the European Union, Canada, Hong Kong and Switzerland. FloSeal™ Matrix has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

## VIII. POTENTIAL ADVERSE EFFECTS:

A total of 309 patients received FloSeal™ Matrix or the Control (Gelatin Sponge + Thrombin). The most common adverse events recorded during and after the application of the hemostatic agents were anemia, atrial fibrillation, infection, and hemorrhage. Table 1 is a complete list of adverse events reported in greater than 1% of patients that were observed in the pivotal clinical trial for the FloSeal™ Matrix group. The corresponding adverse events for the Control group are listed for comparison. None of the adverse events that occurred were judged by the surgeon to be "Probably Related" to the use of FloSeal™ Matrix.

| **Table 1: Adverse Events Reported in Greater than 1% of Patients in the FloSeal™ Matrix Group** | | |
|---|---|---|
| **Adverse Event** | **FloSeal™ Matrix** | **Control (Gelatin Sponge + Thrombin)** |
| Anemia | 12 (8%) | 7 (4%) |
| Fibrillation Atrial | 10 (6%) | 8 (5%) |
| Infection | 10 (6%) | 11 (7%) |
| Hemorrhage | 6 (4%) | 6 (4%) |
| Pneumonia | 6 (4%) | 2 (1%) |
| Urinary Tract Infection | 6 (4%) | 3 (2%) |
| Rash | 5 (3%) | 3 (2%) |
| Edema | 5 (3%) | 1 (<1%) |
| Hypotension | 4 (3%) | 2 (1%) |
| Respiratory Distress | 4 (3%) | 3 (2%) |
| Confusion | 4 (3%) | 0 (0%) |
| Dural Tear | 4 (3%) | 4 (3%) |
| Fibrillation Ventricular | 4 (3%) | 3 (2%) |
| Arrhythmia | 4 (3%) | 0 (0%) |
| Heart Failure Right | 3 (2%) | 2 (1%) |
| Thrombosis Arterial | 3 (2%) | 8 (5%) |
| Fever | 3 (2%) | 2 (1%) |
| Atelectasis | 3 (2%) | 1 (<1%) |
| Pleural Effusion | 3 (2%) | 5 (3%) |
| Counts reflect number of patients in each treatment group reporting one or more adverse events that map to a Modified COSTART 5th edition body system. At each level of summarization (Adverse Event), patients are only counted once. | | |

Other adverse events observed in 1% or less of the FloSeal™ Matrix patients were myocardial infarction, cellulitis, pneumothorax, pain, cerebrovascular accident, hallucination, paresthesia, bradycardia, abscess, diarrhea, urinary retention, dehiscence, skin ulcer, transfusion reaction, dyspnea, heart arrest, lung edema, back pain, ventricular tachycardia, neuropathy, acute kidney failure, kidney tubule necrosis, gastritis, nausea, nausea and vomiting, skin rash, hyperglycemia, and heel ulcer.

The following adverse events, all rated "mild," were deemed by the surgeon to be "Possibly Related" to the use of FloSeal™ Matrix: anemia (2 patients, 1%), mild post-operative bleeding (1 patient, <1%), and local inflammation (1 patient, <1%). No other adverse events were deemed by the surgeon to be related to the use of FloSeal™ Matrix.

Allergic reactions may be encountered in people known to be sensitive to bovine materials.

**Other Gelatin-Based Hemostatic Agents: Reported Adverse Events:**

- 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.

- The use of absorbable gelatin-based hemostatic agents during the repair of dural defects associated with laminectomy and craniotomy operations, has 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 has 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.

**Adverse Reactions to Thrombin:**

See Adverse Reactions in Package Insert for Thrombin-JMI® enclosed in the FloSeal™ Matrix Hemostatic Sealant kit.

## IX. SUMMARY OF PRE-CLINICAL STUDIES.

This section provides summaries of important preclinical tests performed on FloSeal™ Matrix Hemostatic Sealant. The studies reported here include assessments of biocompatibility (including testing according to ISO 10993), preclinical efficacy, and bioresorption.

**Biocompatibility:** FloSeal™ Matrix has been tested for biocompatibility by applying appropriate toxicity testing. The test results are summarized in Table 2. These studies

were conducted under Good Laboratory Practices.

**Table 2: Biocompatibility Testing Summary**

| Test | Test Article | Result |
|---|---|---|
| Cytotoxicity ISO Agarose Overlay Method | Gelatin Matrix + Thrombin | Pass |
| Acute Systemic Toxicity | Gelatin Matrix + Saline* | Pass |
| Acute Intracutaneous Reactivity | Gelatin Matrix + Thrombin | Pass |
| Genotoxicity: Ames Mutagenicity (Saline Extract) | Gelatin Matrix + Thrombin | Pass |
| Genotoxicity: Ames Mutagenicity(DMSO Extract) | Gelatin Matrix + Thrombin | Pass |
| Genotoxicity: Ames Mutagenicity (Saline Extract) | Gelatin Matrix + Saline* | Pass |
| Genotoxicity: Sister Chromatid Exchange | Gelatin Matrix + Thrombin | Pass |
| Genotoxicity: Chromosomal Aberration | Gelatin Matrix + Thrombin | Pass |
| Sensitization (Maximization Method) | Gelatin Matrix + Thrombin | Pass |
| Hemolysis (*In-vitro* Direct Contact Method) | Gelatin Matrix + Saline* | Pass |
| Rabbit Muscle Implantation (13 week) | Gelatin Matrix + Saline* | Pass |
| Pyrogenicity: Material Mediated | Gelatin Matrix + Saline* | Pass |
| Mucosal Irritation | Gelatin Matrix + Thrombin | Pass |

* Tests were conducted without the addition of Thrombin to avoid interference of Thrombin with the test.

Biocompatibility of FloSeal™ Matrix was also evaluated in rabbits. Thirty rabbits (15 control animals and 15 animals treated with FloSeal™ Matrix) underwent surgery to mimic splenic injury and bleeding. FloSeal™ Matrix was applied to the bleeding sites at the time of surgery in the treated animals and it was applied to the bleeding sites 7.5 minutes later in the control animals to prevent exsanguination. The rabbits were survived for 14, 28, 42, and 56 days postoperatively. On gross observation, the material was absent in two of the ten animals sacrificed at Day 14. At all other time points, it was not possible to identify the FloSeal™ Matrix in any animals upon gross observation. No postoperative adhesions associated with the FloSeal™ Matrix material were noted in any animal.

Histologically, an acute inflammatory response and fibrosis were seen in all the animals. Scores for inflammation were highest in 14 and 28-day animals, significantly reduced in animals sacrificed at 42 days, and mostly resolved in Day 56 animals. Likewise, the fibrotic reaction was most pronounced in rabbits from the earliest time points, with the fibrosis at the 42 and 56 day time points being characterized as mild. This type of acute inflammatory response and fibrosis is typical of the normal wound healing response of the spleen to injury. These results demonstrated the biocompatibility of FloSeal™ Matrix.

**Preclinical Effectiveness:** Thirty rabbits (15 control animals and 15 animals treated with FloSeal™ Matrix) underwent surgery to mimic splenic injury and bleeding. The bleeding for each animal was quantified over a 15 minute period. In the treated animals FloSeal™ Matrix was applied to the lesion immediately after the lesion was created. Control animals were not treated during the first 7.5 minutes to demonstrate the amount of bleeding resulting from the lesion. All control animals received FloSeal™ Matrix after the initial 7.5 minutes to prevent exsanguination. FloSeal™ Matrix was effective in providing hemostasis, resulting in a complete cessation of bleeding at the wound site in all animals. Moreover, the amount of bleeding after application of FloSeal™ Matrix during the initial 7.5 minutes in the treated animals was significantly less than that for the untreated controls.

**Bioresorption:** In the rabbit spleen efficacy study described above, FloSeal™ Matrix was absent histologically in tissue from two out of ten animals sacrificed at the 14 day time point. At 28 days post-implant, FloSeal™ Matrix was completely absent in five out of ten rabbits examined and present in minimal amounts in the remaining animals, showing that FloSeal™ Matrix was essentially biodegraded by 28 days. FloSeal™ Matrix was completely absent in all five animals examined at 42 days post-implant and found in very small amounts in one of four animals examined at 56 days post-implant. Healing of the splenic lesion was proceeding in a normal fashion in all cases.

Additional data that support the biodegradation time for FloSeal™ Matrix were generated in a Muscle Implant study. This study consisted of 12 rabbits implanted with the gelatin matrix component of FloSeal™ Matrix. Three animals each were evaluated at the following time points: two, four, six and thirteen weeks. Four implantation sites each for the gelatin matrix from each animal were evaluated at each time point. The implanted test material was observed histologically in all implant sites at 2 weeks. At four weeks, minimal test article was observed histologically in 2 of 12 implant sites, and was absent histologically from 10 of 12 implant sites. The test article was absent from all implant sites at both the six and thirteen week time points.

## X. SUMMARY OF THE RESULTS OF THE CLINICAL INVESTIGATION.

The following is a summary of the large scale study designed to support PMA approval, "Protocol C98-001: Evaluation of FloSeal™ Matrix (now known as FloSeal™ Matrix Hemostatic Sealant), a Novel Hemostatic Sealant, for Stopping Intraoperative Bleeding".

## A. Study Objectives:

The objectives of the clinical study were to evaluate the safety and effectiveness of FloSeal™ Matrix compared to a control gelatin hemostat sponge plus thrombin in controlling intraoperative bleeding.

## B. Study Design:

A prospective, randomized, controlled, multi-center, multi-specialty study was conducted to evaluate the safety and effectiveness of FloSeal™ Matrix, compared to a control gelatin sponge plus thrombin in controlling intraoperative bleeding. This study was designed to show that the FloSeal™ Matrix success rate was equivalent to the success rate for the Control. If during surgery, the surgeon encountered a bleeding site that he or she was unable to control because of the failure or impracticality of conventional methods (sutures and/or cautery), the patient was enrolled and randomly assigned to a treatment group. Patients assigned to the FloSeal™ Matrix group were treated according to the Instructions for Use. For Control group patients, the control treatment was applied directly to the bleeding site and held there with light pressure, as per standard practice. In all cases, multiple bleeding sites in each patient were treated with the hemostat to which the patient was randomly assigned. In the case of treatment failure, the surgeon could use any treatment of the surgeon's choice, except FloSeal™ Matrix, to control the bleeding.

All patients were required to provide blood samples at Baseline (up to 24 hours prior to surgery), and at the follow-up periods (12 – 36 hours post-surgery and 6 – 8 weeks post-surgery) for measurement of hematology, coagulation parameters, and metabolic panel. In addition, serum samples from the Baseline and 6 – 8 week follow-up period were used to measure anti-bovine thrombin and anti-bovine Factor $V_a$ antibodies. Any adverse events that occurred post-surgery were recorded and analyzed to determine safety.

## C. Study Endpoints:

The primary effectiveness endpoint was the cessation of bleeding within 10 minutes of application of the assigned product to the first treatment site in each patient. A failure was defined as persistence of bleeding for more than 10 minutes after application of the assigned product. The study also assessed time to hemostasis. The surgeon determined the time to hemostasis by checking each treatment site at 1, 2, 3, 6, and 10 minutes after application of the assigned product to the bleeding site.

## D. Product Safety:

Product safety was determined by evaluating adverse events that occurred post-surgery and their relationship, if any, to use of the assigned product, by comparing the number of out-of-reference-range blood test results (hematology, coagulation tests, and blood chemistry tests) at 24 hours (12 – 36 hours) post-surgery and 6 – 8 weeks post-surgery between the FloSeal™ Matrix and Control groups and by comparing the

number of patients in the FloSeal™ Matrix group and the Control group that developed anti-bovine thrombin and anti-bovine Factor $V_a$ antibodies.

**E. Study Sites:**

The study enrollment for each of the Investigational Sites is presented in Table 3.

**Table 3: Patient Enrollment by Investigational Site**

| Investigational Site | Total No. of Patients Enrolled | No. of Patients in FloSeal™ Matrix Group | No. of Patients in Control Group |
|---|---|---|---|
| 1. California Pacific Medical Center, San Francisco, CA | 16 | 9 | 7 |
| 2. Mercy Medical Center, Redding, CA | 23 | 12 | 11 |
| 3. USC School of Medicine, Los Angeles, CA | 27 | 14 | 13 |
| 4. Methodist Hospital, Indianapolis, IN | 53 | 27 | 26 |
| 5. Rush Presby. St. Luke's Medical Center, Chicago, IL | 22 | 12 | 10 |
| 6. Columbia Presby. Medical Center, New York, NY | 33 | 17 | 16 |
| 7. Cleveland Clinic Foundation, Cleveland, OH | 26 | 12 | 14 |
| 8. Washington Hospital, Fremont, CA | 21 | 11 | 10 |
| 9. St. Agnes HealthCare, Baltimore, MD | 56 | 27 | 29 |
| 10. Univ. California at San Francisco, San Francisco, CA | 32 | 15 | 17 |
| TOTAL | 309 | 156 | 153 |

**F. Study Demographics:**

The Baseline demographics in both the FloSeal™ Matrix and Control groups were comparable for gender and age. The distribution of males and females in the 2 study groups was as follows: FloSeal™ Matrix group - 91/156 (58%) males and 65/156 (42%) females; Control group – 88/153 (58%) males and 65/153 (42%) females. Of the 309 patients enrolled in the study, 6 patients were lost to follow-up at the 6 – 8 week period. These included 2 patients in the FloSeal™ Matrix treated group and 4 patients in the Control group. A total of 16 patients expired during the course of the

study. Of these, 13 patients expired before the final follow-up was completed, and 3 patients expired of complications that had started within the 6 – 8 week period following surgery after exiting from the study. Of the patients that expired, 5 patients were in the FloSeal™ Matrix group and 11 patients were in the Control group. The causes of all the deaths were determined by the surgeon to be "Not Related" to the use of either product.

## G. Intent-To-Treat Analysis:

Intraoperative data were collected for all 309 patients enrolled in the study. The percent of successful applications, defined as the percent of bleeding sites in which hemostasis was achieved in less than or equal to 10 minutes is shown in Table 4. Analysis of equivalence using the method of Blackwelder and Chang showed the two products to be equivalent ($p < 0.001$). The difference between Treatment and Control was shown to be statistically significant using the Cochran-Mantel-Haenszel Test ($p < 0.001$).

**Table 4: Treatment Success, By Surgical Specialty:**

| **Hemostasis within 10 minutes – First Lesion Only (Intent-to-Treat Patients)** | | |
|---|---|---|
| **Patient Category** | *FloSeal™ Matrix* | **Control** |
| All Patients | 96% (149/156) | 77% (118/153) |
| Cardiac | 94% (45/48) | 60% (27/45) |
| Vascular | 93% (40/43) | 76% (35/46) |
| Spinal/Orthopedic | 98% (64/65) | 90% (56/62) |

In the cardiac cohort, 88 of the 93 patients (95%) underwent surgery with extracorporeal cardiopulmonary bypass. FloSeal™ Matrix was used for hemostasis prior to heparin reversal by the administration of protamine sulfate in 19 of 46 patients. Protamine sulfate reverses the anticoagulative effects of heparin. Results for hemostasis at 10 minutes for the heparinized patients in both the FloSeal™ Matrix and Control groups, before and after protamine sulfate reversal of heparin, are shown in Table 5.

**Table 5: Hemostasis Success**

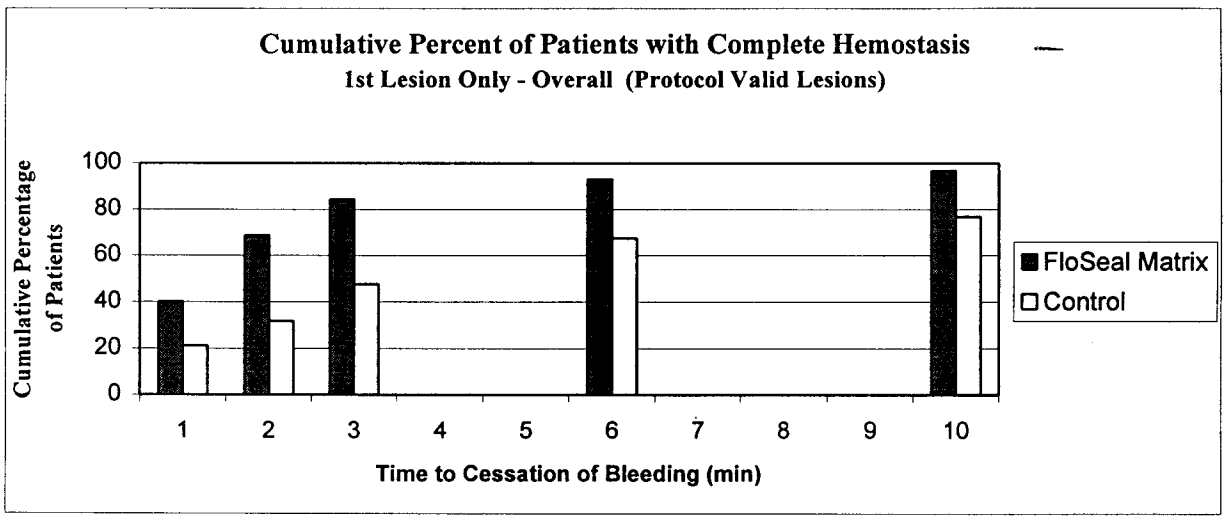
| **Hemostasis Success at 10 Minutes Before and After Protamine Administration (Cardiac Patients Only)** | | |
|---|---|---|
| Group | Before Protamine | After Protamine |
| **FloSeal™ Matrix** | 89% (17/19) | 96% (26/27) |
| Control | 36% (5/14) | 75% (21/28) |

The success rate for FloSeal™ Matrix did not appear to be affected by whether or not the patient had received protamine sulfate administration. This was demonstrated by the fact that the success rate for FloSeal™ Matrix before protamine sulfate inistration was similar to the success rate after protamine sulfate administration whereas the Control hemostat success rate was clearly lower before protamine sulfate reversal of heparin was administered.

**H. Secondary Endpoint (Time to Hemostasis):**

The time to hemostasis for the first lesions treated in each patient, pooled across investigational sites is summarized in Figure 1.

**Figure 1: Cumulative Percent of Patients with Complete Hemostasis**




Median times to hemostasis for the first lesions treated in each patient are summarized in Table 6.

**Table 6: Time to Hemostasis**

| Time to Hemostasis<br>First Lesion Only (Protocol Valid Lesions) | | |
|---|---|---|
| **Patient Category** | **Median Time to Hemostasis in minutes (95% Confidence Interval *)** | |
| | **FloSeal™ Matrix** | **Control** |
| **All Patients** | 2.0 (1.5, 2.5) | 6.0 (5.5, 6.0) |
| **Cardiac** | 2.8 (2.0, 4.0) | 8.0 (6.0, 8.5) |
| **Vascular** | 2.5 (2.0, 4.0) | 6.5 (4.5, 8.0) |
| **Spinal/ Orthopedic** | 1.5 (1.0, 1.5) | 3.0 (2.0, 4.5) |
| *Confidence interval using a Bonferroni correction. | | |

## I. Device Safety:

Six (6) patients were lost to follow-up at the 6 – 8 week period. These included 2 patients in the FloSeal™ Matrix group and 4 patients in the Control group. In addition, 16 patients expired during the course of the clinical study. Of the patients that expired, 5 patients were in the FloSeal™ Matrix group and 11 patients were in the Control group. The causes of all deaths that occurred during the course of the study were determined by the surgeon to be "Not Related" to the use of either hemostat.

A total of 384 adverse events were recorded during the course of the study. Of these, 192 events were reported in 80 patients treated with FloSeal™ Matrix, and 192 events were reported in 85 patients in the Control group. All reported adverse events, regardless of any relationship to the use of FloSeal™ are listed in Table 1, located in **Section VI. Potential Adverse Effects.**

## J. Immunology Results:

Antibody data were available for 139 patients in the FloSeal™ Matrix group and 131 patients in the Control group. Twenty-five (25) patients (18%) in the FloSeal™ Matrix group and 26 patients (20%) in the Control group developed antibodies to bovine Thrombin ($p = 0.757$). Thirty-nine (39) patients (28%) in the FloSeal™ Matrix group and 43 patients (33%) in the Control group developed antibodies to bovine Factor $V_a$ ($p = 0.428$). There was no evidence of any antibody-related coagulopathies, as judged by Prothrombin times, in any patients in the FloSeal™ Matrix or Control groups. At 6-8 weeks, 7 patients (5%) in the FloSeal™ Matrix group and 8 patients (6%) in the Control group, who were positive for either bovine thrombin or bovine Factor $V_a$ antibodies, had elevated Prothrombin times (> 15 seconds). In each of these patients, the elevated Prothrombin time could be attributed to prescribed anticoagulant medications.

Cross-reactivity to human thrombin was observed in five patients in the FloSeal™ Matrix group and three patients in the Control group. There was no statistically significant difference between the two groups ($p = 0.455$, Fischer's Exact Test). There was no cross-reactivity to human Factor $V_a$ in either the FloSeal™ Matrix or Control groups. Prothrombin times for all the patients in either group who tested positive for antibodies to human thrombin were within the normal limits.

## XI. CONCLUSIONS DRAWN FROM THE STUDY.

FloSeal™ Matrix is a topical hemostatic agent that is comprised of bovine gelatin and bovine thrombin. The results of the preclinical and clinical testing demonstrated that there is reasonable assurance of safety and effectiveness for the FloSeal™ Matrix Hemostatic Sealant 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 FloSeal™ Matrix in surgical patients. The control group was treated with a legally marketed absorbable gelatin sponge pretreated with bovine thrombin.

## XII. 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.

## XIII. CDRH ACTION:

A GMP inspection was conducted of the Fusion Medical Technologies facilities in Mountain View, California on October 15, 1999, and they were found to be in compliance with the Device GMP Regulations.

## XIV. 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.