SUMMARY BASIS FOR APPROVAL

Reference Numbers: **87-0508 and 87-0509**

Biological Product Name: **Fibrin Sealant**

Manufacturer: **Österreichisches Institut Für Haemoderivate Ges.m.b.H. Subsidiary of IMMUNO AG (ÖIH)**

Trade Name: **TISSEEL® VH Kit**

I. INDICATIONS FOR USE

The TISSEEL® VH Kit (TISSEEL) is indicated as an adjunct to hemostasis in patients undergoing cardiopulmonary bypass, including those patients who have been fully heparinized.

TISSEEL® is also indicated for the sealing of anastomoses in the closure of temporary colostomies to prevent anastomotic complications (leaks, infections, abscesses, reoperations and death). TISSEEL® is also indicated for use in surgery for injuries to the spleen due to blunt or penetrating trauma to the abdomen.

TISSEEL® is an adjunct to surgical methods of hemostasis, such as suture, ligature, and cautery; it is not indicated for the treatment of massive and brisk arterial bleeding. TISSEEL® is intended only for topical administration.

The use of TISSEEL® in combination with biocompatible carrier materials such as collagen felt, fleece or foam (e.g., Gelfoam®) has not been studied directly. It appears, however, that oxycellulose preparations (e.g., Surgicel®) may reduce the efficacy of Fibrin Sealant because of their low pH.

Use in Pediatric and Geriatric Patients: The safety and effectiveness of TISSEEL® has not been systematically studied in pediatric and geriatric patients.

Pregnancy Category C: Animal reproduction studies have not been conducted with TISSEEL®. It is also not known whether TISSEEL® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The TISSEEL® VH Kit should be used to treat a pregnant woman only if clearly needed.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

The TISSEEL® VH Kit comes in four different package sizes: 0.5, 1.0, 2.0, and 5.0. Each package contains the following in four separate vials:

- Sealer Protein Concentrate (Human), Vapor Heated, TISSEEL® VH, dried powder
- Fibrinolysis Inhibitor Solution (Bovine)
- Thrombin (Human), Vapor Heated, dried powder
- Calcium Chloride Solution

The above substances give two components: the Sealer Protein Solution and the Thrombin Solution. To obtain the Sealer Protein Solution, freeze-dried, vapor heated Sealer Protein Concentrate is dissolved in the accompanying Fibrinolysis Inhibitor solution. Upon reconstitution, 1 mL of the Sealer Protein Solution contains at least 70 mg of fibrinogen. Freeze-dried, vapor heated Thrombin is reconstituted by adding the 40 millimolar Calcium Chloride Solution to yield Thrombin Solution at 500 I.U. of Thrombin per mL.

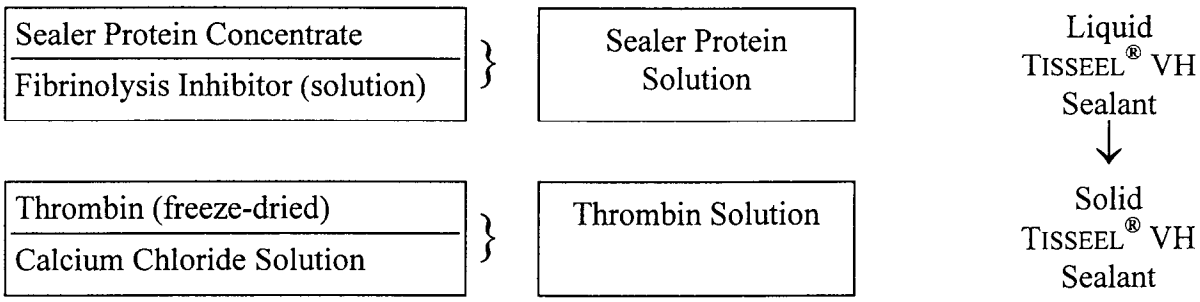
Freeze-Dried Sealer Protein Concentrate when reconstituted contains:

Total protein	100–130 mg/mL
Fibrinolysis Inhibitor (Aprotinin)	3,000 KIU Aprotinin/mL

Freeze-Dried Thrombin (Human), Vapor Heated when reconstituted contains:

Thrombin (Human)	500 I.U./mL
Calcium Chloride	40 μmol/mL

When the Sealer Protein and Thrombin solutions are combined, such as by simultaneous application via a Duploject® syringe, a fibrin clot is formed through the cleavage of fibrinogen by thrombin.



The required dose of TISSEEL® VH Sealant depends on the size of the surface to be covered.

Maximum Size of Area to be Sealed	Required Package Size TISSEEL® VH Kit	Total Available Volume: TISSEEL® VH & THROMBIN Solutions
4 cm^2	TISSEEL® VH Kit 0.5	1.0 mL
8 cm^2	TISSEEL® VH Kit 1.0	2.0 mL
16 cm^2	TISSEEL® VH Kit 2.0	4.0 mL
40 cm^2	TISSEEL® VH Kit 5.0	10.0 mL

Application of TISSEEL® VH Sealant

The manufacturer recommends the following precautions when using the TISSEEL® VH Kit:

- The product should only be applied under direct visualization.
- The product should not be applied by injection into mucosal areas (which may result in inadvertent intravascular administration) unless the potential risk is outweighed by clinical benefit.
- The product should not be administered intravascularly as this has previously resulted in thromboembolic complications.
- The adequate training of surgical and nursing staff prior to the clinical use of the product is recommended.
- Application must be completed within 4 hours of reconstitution.

A set for reconstitution and application is included in each TISSEEL® VH Kit. It consists of four syringes, four needles, one Duploject®, two joining pieces, and four blunt application needles.

In order to maintain a temperature of 37°C, the components of the TISSEEL® VH Kit may be reconstituted by using a heating and stirring device, the Fibrinotherm®, or a water-bath, or an incubator,. Once reconstituted, the Sealer Protein and Thrombin solutions may be applied, such as by means of a Duploject® syringe. The Duploject® consists of a clip for two identical disposable syringes and a common plunger which provides for the delivery and mixture of equal volumes of the two solutions through a common joining piece and application needle.

III. MANUFACTURING and CONTROLS

A. MANUFACTURING

Source Plasma for use in the production of Sealer Protein Concentrate (Human), and Thrombin (Human) is collected at U.S.-licensed establishments located in the United States according to the requirements of 21 CFR § 640.60 (Source Plasma). See also **Section V.A, Plasma Safety**.

The human albumin, stabilized with sodium caprylate and sodium acetyltryptophanate, used in the manufacture of Sealer Protein Concentrate (Human), and Thrombin (Human), meets all requirements for Albumin (Human) in 21 CFR §§ 640.80-640.83.

a) Sealer Protein Concentrate (Human), Vapor Heated

Cryoprecipitate is obtained from frozen plasma by thawing at 2 - 6°C and is separated from the cryosupernatant by centrifugation at 2 - 6°C. The cryoprecipitate is then washed with buffer (glycine, sodium citrate, sodium chloride, aprotinin and heparin, pH 6.5) and frozen (≤ -30°C) and stored at or below -20°C. The washed cryoprecipitate is subsequently formulated in buffer (glycine, sodium citrate, aprotinin, Polysorbate 80 (of plant origin), and 4.5 g/l human albumin, pH 7.3). The resulting solution is filtered (70 µm) and then freeze-dried.

The vapor heated bulk powder is reconstituted with water for injection (WFI) to give a concentration of 47 g protein/l. This solution is clarified (20 µm/0.8 µm/0.2 µm) and sterilized (0.2 µm) by filtration.

Following sterile filtration, the Sealer Protein Concentrate (Human) is filled into sterilized glass vials, equipped with a stainless steel stirring propeller and subjected to freeze-drying.

The final containers are quarantined at 2 - 8°C until released by Quality Control for labeling and packaging.

b) Manufacture of Thrombin (Human), Vapor Heated

The starting material for Thrombin is Vapor Heated FEIBA® (Factor Eight Inhibitor Bypassing Activity) Bulk Powder. Final product, FEIBA® VH IMMUNO, which is manufactured by ÖIH from the same bulk powder, is licensed and distributed in the United States for the control of spontaneous bleeding episodes or to cover surgical interventions in hemophilia A and B patients with inhibitors.

For the manufacture of Thrombin, Vapor Heated, FEIBA® Bulk Powder is reconstituted with WFI.

Thrombin bulk power is reconstituted with sodium chloride and glycine dissolved in WFI and a solution of human albumin (17.5-70 g/l, depending on fill size).

Following sterilizing filtration (0.2 µm), Thrombin (Human) Vapor Heated is immediately filled into sterilized glass vials and subjected to freeze-drying.

The final containers are quarantined at 2 - 8°C until released by Quality Control for labeling and packaging.

c) Manufacture of Fibrinolysis Inhibitor (Aprotinin) Solution

Aprotinin Solution, manufactured by Bayer, is a purified polypeptide with a molecular weight of 6,500, and is obtained from frozen bovine lungs. Aprotinin Solution contains approximately 50,000 KIU/mL in compliance with the European Pharmacopoeia, 2nd Edition, p. 579, 1994. (One (1) European Pharmacopoeia Unit (E.P.U.) corresponds to 880 Kallidinogenase Inactivator Units (KIU)). Aprotinin is purchased as a bulk solution from Bayer and is identical to that used by Bayer to manufacture its final U.S.-licensed product Trasylol®.

For manufacture of Aprotinin Solution, the bulk solution is sterile filtered and then formulated by dilution with WFI to a final concentration of 3,000 KIU/mL. The solution is sterile filtered once more and filled into sterilized glass vials.

The final containers are quarantined at 2 - 8°C until released by Quality Control for labeling and packaging.

d) Calcium Chloride Solution ($CaCl_2 \cdot 2H_2O$)

The calcium chloride solution used complies with USP 23, page 250, 1995. $CaCl_2 \cdot 2H_2O$, 40 mmol, per liter is dissolved in Water for Injection in a stainless steel pressure tank, sterile filtered (0.2 µm), and filled into sterilized glass vials.

The final containers are steam sterilized and then quarantined at room temperature until released by Quality Control for labeling and packaging.

Sterile Filling and Lyophilization:

A newly constructed filling suite at the location is dedicated to the sterile filling and lyophilization of Sealer Protein Concentrate and Thrombin, as well as the sterile filling and sealing of Fibrinolysis Inhibitor, Bovine (Aprotinin) and Calcium Chloride Solution, all contained in the TISSEEL® VH KIT.

Manufacture of Double Syringe Holder Duploject®

The Duploject® is a plastic device consisting of two parts, the double syringe clip and the plunger which are manufactured by injection moulding. The plastic granulate used is which complies with 21 CFR § 177.1520 "Olefin polymers". The color master batch complies with 21 CFR, § 177.1680 or 178.3970.

The manufacturer of the Duploject® is The injection moulding, assembly, and packaging is performed under US Federal Standard 109, Class conditions. The device is sterilized by ethylene oxide and has a shelf life of five years.

The Duploject® received clearance from the Center for Devices and Radiological Health as a Class I Medical Device (General Controls) under section 510(k) of the Federal Food, Drug, and Cosmetic Act on December 8, 1997.

Fibrinotherm®, Heating/Stirring Device

The Fibrinotherm® is a combination heating and stirring device and may be used to reconstitute the components of the TISSEEL® VH Kit. Alternatively, the components may be reconstituted in a water-bath or in an incubator. In all cases, the object is to maintain a temperature of 37°C in order to assure complete dissolution of the components, particularly the Sealer Protein.

The Fibrinotherm® is considered to be an article of general laboratory equipment and not subject to regulation as a Medical Device. A Fibrinotherm® unit was provided to CBER with the conformance samples and was used during potency testing of those samples. The device appeared to be appropriate for its intended purpose and its operation was satisfactory.

The Fibrinotherm® is not supplied with the TISSEEL® VH Kit, but is available separately from the manufacturer.

Final Container Testing

Final product release tests are performed on every lot of each component of the TISSEEL® VH kit. In addition to tests (as required) for general safety (CFR 21 § 610.11), pyrogen (CFR 21 § 610.13b), and sterility (CFR 21 § 610.12), these tests include:

a) Sealer Protein Concentrate (Human): Total and clottable protein, pH, moisture, solubility, albumin, Polysorbate 80, NaCl, sodium citrate and glycine.

b) Thrombin (Human): Potency, total protein, pH, moisture, solubility, albumin, NaCl, $CaCl_2$, and glycine.

c) Fibrinolysis Inhibitor (Bovine) and Calcium Chloride Solutions: Potency and extractable volume.

B. VALIDATION

Validation of Systems and Equipment: Utility systems, manufacturing equipment, manufacturing processes and analytical methodologies used in the production of Fibrin Sealant have been validated according to established written procedures. Procedures are in place to ensure the regular maintenance of equipment and the regular monitoring of environmental conditions within the production facilities.

Viral Inactivation/Removal Studies: Virus inactivation/removal studies have been performed for each of the two human plasma-derived components of the TISSEEL® VH Kit (Sealer Protein and Thrombin)

Removal of viruses by various manufacturing steps, as well as inactivation of viruses by the two-stage vapor heating process were quantified. A summary of results (expressed as $\log_{10}$ reduction factors) are provided in the following two tables.

Viral Clearance: Sealer Protein Concentrate

	Log Reduction Factors for Indicated Viruses				
Manufacturing Step	**HIV-1**	**TBEV**	**PRV**	**ERV-1**	**HAV**
Cryoprecipitation and Washing	2.6	1.3	1.5	1.8	nd
Freeze-Drying	1.2	1.3	2.1	3.2	3.0
Vapor Heating	≥4.7	≥5.6	≥4.8	≥4.0	≥3.0
Cumulative	≥8.5	≥8.2	≥8.4	≥9.0	≥6.0

Viral Clearance: Thrombin

	Log Reduction Factors for Indicated Viruses				
Manufacturing Step	**HIV-1**	**TBEV**	**PRV**	**ERV-1**	**HAV**
Cryoprecipitation and Washing	1.4	≤1.0	1.1	≤1.0	nd
DEAE-Sephadex	2.0	3.0	3.1	≤1.0	nd
Freeze-Drying	2.0	≤1.0	2.6	1.9	2.7
Vapor Heating	≥4.6	≥7.0	≥4.8	≥4.7	≥2.7
Cumulative	>10.0	>10.0	>11.6	>6.6	>5.4

C. STABILITY STUDIES

Stability studies have been performed on all four substances included in the TISSEEL® VH Kit: Sealer Protein Concentrate (Human), Thrombin (Human), Fibrinolysis Inhibitor, and Calcium Chloride Solution.

The studies on freeze-dried Sealer Protein Concentrate (Human) comprise: (1) real-time stability; (2) accelerated stability at elevated temperature; and (3) short-term stability after reconstitution. The real-time studies at 8 - 12°C are on-going and will be completed after a period of 30 months. Interim results for 12 months revealed no deviations from the product specifications. The accelerated studies at 28 - 32°C for 12 months have been completed. The product remained within specifications during this period, except for solubility which was exceeded in several instances. Therefore, a shelf life of 2 years at 2 - 8°C is justified, contingent upon the satisfactory completion of the real-time studies. Updates of the ongoing stability studies are to be submitted to CBER as they become available. After reconstitution and storage for 6 hours at 37°C there was no significant loss of activity. A maximum holding time of 4 hours following reconstitution is recommended in the Package Insert.

The studies on freeze-dried Thrombin (Human) also comprise: (1) real-time stability; (2) accelerated stability at elevated temperature; and (3) short-term stability after reconstitution. All studies have been completed. The real-time studies (at 8 - 12°C for 36 months) and accelerated study (at 28 - 32°C for 12 months) included one lot each of the 0.5 mL, 1.0 mL, 2.0 mL, and 5.0 mL package size. The studies after reconstitution and storage for 6 hours at 37°C were performed on two lots of the 1.0 mL and one lot of the 2.0 mL package size. There were no deviations from the product specifications during any of the studies, supporting a 2 year shelf life at 2 - 8°C, and a maximum holding time of 4 hours following reconstitution, as above.

The studies on Fibrinolysis Inhibitor cover: (1) real-time stability and (2) accelerated stability at elevated temperature on one lot of each package size. The real-time studies at 8 - 12°C for 48 months and accelerated study at 28 - 32°C for 12 months showed no deviations from the defined product specifications during the entire storage period. These data support a shelf life of 3 years at 2 - 8°C.

Long-term stability studies on 4 lots of Calcium Chloride Solution held at 20 - 25°C for 6 years showed unimpaired potency and safety in all lots during the 6 year storage period.

D. LABELING

The package insert and container and package labels are in compliance with 21 CFR §§ 201.57, 610.60, 610.61 and 610.62. The tradenames, TISSEEL®, TISSEEL® VH, TISSEEL® VH Kit and similar combinations are not known to be in conflict with the trademark of any other biological product. A copy of the package insert is attached.

E. ESTABLISHMENT

Locations Covered by Establishment License No. 258 and Associated with the Production of TISSEEL® VH Kit

a) [redacted] Frozen plasma storage for three month inventory hold period. There have been no changes made in the locations where frozen plasma is stored as a result of this PLA.

b) [redacted] Storage of released frozen plasma and the manufacture of bulk intermediate plasma products. An ELA Supplement to upgrade the Purified Water System at this location was approved on September 29, 1997 under Ref. No. 97-0491 for products already licensed in the US. The [redacted] change involves the use of additional space for the crude fractionation of Sealer Protein Concentrate.

c) [redacted] Manufacture of purified intermediate plasma products including the virus inactivation processes. The new facility at Benatzkygasse was the subject of an ELA Supplement in November 1995, approved on January 22, 1997 under Ref. No. 95-1841.

d) [redacted] Manufacturing steps include formulation, sterilization, sterilizing filtration, sterile filling, freeze-drying and part of Quality Control testing.

e) [redacted] Quality Control testing: sterility, pyrogen and general safety testing. No changes have been made in this facility.

f) [redacted] Quality Control testing: final filled containers; labeling and packaging. No changes have been made in this facility.

Establishment Inspections

On November 17-21, 1997 a pre-license inspection of the facilities of ÖIH involved in the manufacturing of TISSEEL® was performed by personnel from the Center for Biologics Evaluation and Research and Team Biologics. An FDA Form 483 was issued; the firm responded to all observations and their corrective actions were found to be adequate and complete.

F. ENVIRONMENTAL ASSESSMENT

An environmental assessment was filed, reviewed and found to be acceptable. A Finding of No Significant Impact (FONSI) is attached. The manufacture of the TISSEEL® VH Kit is also subject to applicable Austrian Law.

G. PRODUCT BATCH/LOT IDENTIFICATION

Each lot of each of the four components of the TISSEEL® VH Kit is assigned a unique identifier during manufacture and a unique lot number for the final containers. The expiration dates of the components are determined independently. The four components along with other items are packaged together into the TISSEEL® VH Kit, each lot of which is assigned a unique number: e.g.

IV. PHARMACOLOGY/TOXICOLOGY

The Sealer Protein Concentrate is dissolved in the Fibrinolysis Inhibitor solution, and upon reconstitution, 1 mL of the Sealer Protein Solution contains at least 70 mg of fibrinogen. Thrombin is reconstituted by adding the 40 millimolar Calcium Chloride Solution to yield Thrombin Solution with a concentration of 500 I.U. of Thrombin per mL. The two components, the Sealer Protein Solution and the Thrombin Solution, are mixed and applied topically. The mixture forms a fibrin clot.

The active ingredient of Sealer Protein Concentrate is fibrinogen. The fibrinogen molecule consists of three pairs of chains, i.e. $A\alpha$, $B\beta$, and γ , which are connected by disulfide bridges. Thrombin, a highly specific protease, splits off fibrinopeptides A and B from the $A\alpha$ and $B\beta$ chains of the fibrinogen molecule; the resulting fibrin monomers are insoluble under physiological conditions and aggregate to form the clot. In the presence of free calcium ions, Factor XIII, which is not added to the product but which may be present endogenously in the patient, can be activated by Thrombin. Factor XIII is capable of crosslinking and stabilizing the fibrin that comprises the clot.

The degradation and absorption of solidified Fibrin Sealant occurs through the action of plasmin, which is produced by the activation of plasminogen by tissue plasminogen activator or urokinase. To delay the degradation process, TISSEEL® contains Fibrinolysis Inhibitor (Aprotinin), a polyvalent protease inhibitor capable of inhibiting enzymes such as plasmin.

TISSEEL® contains fibrinogen in a concentration that yields clots with a strength of ≥ 500 pound cm^{-2} and reconstitutes within 20 min. Thrombin is present at a concentration which produces rapid clotting. Sufficient Fibrinolysis Inhibitor is present to delay degradation of the fibrin clot.

The plasma protein dosages present in the Sealer Protein Concentrate and Thrombin amount to small fractions of the corresponding plasma proteins present in the patient and are expected to be eliminated at the same rates and by the same mechanisms as the autologous plasma proteins. Excess Thrombin would normally be inactivated by protease inhibitors present in the blood. Released Fibrinolysis Inhibitor (Aprotinin, a protein of bovine origin) and its metabolites are eliminated by the kidney; its circulatory half-life is known to average between 30 and 60 minutes.

In order to show that each component of this combination product makes a contribution to its claimed effects, ÖIH performed animal (rabbit) studies showing that a Fibrin Sealant preparation containing Thrombin achieved hemostasis significantly faster and with significantly less blood loss than did a Fibrin Sealant preparation without Thrombin. The manufacturer also demonstrated that in a fibrinolytic environment, a Fibrin Sealant preparation containing Aprotinin reduced blood loss significantly, to about 20 % of levels obtained in its absence. In these studies, the free fibrinolytic activity in rabbits treated with streptokinase or tPA was comparable to that in the human patients undergoing cardiovascular bypass surgery, assessed by area under the fibrinolytic time-curve from onset of surgery to completion of bypass. While the Fibrin Sealant preparation without Aprotinin achieved primary hemostasis, the presence of Aprotinin reduced rebleeding.

The presence of Factor XIII in a Fibrin Sealant preparation was also shown to reduce blood loss in a fibrinolytic rabbit model (2.0 ± 0.3 grams of blood compared to 4.5 ± 0.8 grams). While this difference was statistically significant, the difference was considered too small to be of clinical relevance. As a consequence, Factor XIII, most of which is destroyed during vapor heating (virus inactivation), is not added back to the product.

In patients with a severe congenital deficiency of Factor XIII, hemostasis has been achieved by the infusion of 10 mL of fresh frozen plasma per kg body weight, suggesting that minimal amounts of Factor XIII may be sufficient for ongoing hemostasis.

To examine the risk of bovine sensitization, Fibrinolysis Inhibitor (Aprotinin) was injected intravenously into sensitized guinea pigs. None showed shock symptoms. Furthermore, no case of clinically manifest bovine sensitization was observed in any of the clinical studies conducted, or through postmarketing experience in Europe of an analogous Fibrin Sealant.

The animal models, developed to measure the hemostatic efficacy of Fibrin Sealant by time to hemostasis and blood loss, were used to validate the comparability of the product after manufacturing changes made after the pivotal trials were completed. These changes included: (1) substitution of Human Thrombin for Bovine Thrombin; (2) a change in the viral inactivation process from dry heat to vapor heat treatment in the manufacture of Sealer Protein Concentrate; and (3) elimination of Factor XIII added back to the Sealer Protein Concentrate. These changes were shown not to impair the product's hemostatic efficacy.

With respect to the replacement of Bovine Thrombin by Human Thrombin, two preclinical studies in guinea pigs demonstrated that Human Thrombin is at least as safe as Bovine Thrombin. Human Thrombin was no more likely than Bovine Thrombin to cause anaphylactoid reactions as assessed by their effects on pulmonary inflation pressure and was as well tolerated locally as Bovine Thrombin on the basis of capilliary leakage induction. Human Thrombin has been used as an active ingredient of the formulation of TISSEEL® marketed in Europe since 1991.

V. SAFETY

A. PLASMA SAFETY

a) Donor Program

TISSEEL® is prepared from Source Plasma (Human) obtained exclusively from FDA-licensed plasmapheresis centers located in the United States. Each candidate donor is first subjected to an assessment of risk factors, medical history, and a physical exam performed by a physician or physician substitute. The donor then undergoes laboratory evaluations for hematocrit, total protein, serum protein electrophoresis, and syphilis. In addition, each unit of plasma is tested for antibodies against HIV 1/2 and HCV, for HIV p24 antigen, and for HBsAg; all must be non-reactive. The plasma units are also tested for elevations of ALT.

b) First Time Donors

Donors meeting the above requirements must, in addition, return within six months to donate a subsequent unit in order to become "qualified" donors. Plasma obtained from an otherwise acceptable donor is held in quarantine until that donor returns to the center for repeat participation, including a second panel of virus screening tests. If the donor applicant does not return, the initial plasma donation is destroyed. Any donor who has not donated within the prior six months is not considered to be a qualified donor.

c) Inventory Hold

Plasma obtained from qualified donors is also held in an inventory hold for a minimum of three months. If, on a subsequent donation, a donor seroconverts, as detected by virus testing, or is permanently deferred as a result of elevated ALT levels or risk factor, all previously obtained

units remaining in the inventory hold from this donor during this 3-month period are retrieved and destroyed.

B. POOL SIZE

The plasma donor exposure for each lot of TISSEEL® is calculated to be below the limit of ( ) donors. To assure compliance, Immuno's Production Planning Department will be responsible for scheduling the plasma input and the Quality Assurance Department will be responsible for verifying that the donor upper limit of ( ) has not been exceeded.

C. VIRAL SAFETY

See **Sections III.B, Validation, and VII.A, Clinical Safety**.

VII. CLINICAL

A. CLINICAL EFFICACY

1) Efficacy of TISSEEL® as an Adjunct to Hemostasis in Cardiac Surgery Patients Undergoing Resternotomy or Reoperation

Immuno performed a pivotal study of TISSEEL® in reoperative cardiovascular surgery in 489 patients who were randomized to either Fibrin Sealant, or a control group in which any topical agent available to the surgeon of his/her choice was allowed to be used. The primary endpoint was cessation of bleeding within 5 minutes. Investigators were allowed to switch to the alternative regimen after 5 minutes, if bleeding had not stopped.

Per protocol analysis: For the primary endpoint (including only first bleeding episodes), 237 patients were analyzed and 252 excluded. In the analyzed group, 162 patients received fibrin sealant and 75 received a control hemostatic agent. The reasons for exclusion were: (1) violation of group assignment (wrong treatment first); (2) less than 5 minutes allowed to see if treatment failed before an alternative therapy was begun; and (3) clinical information needed to determine treatment success or failure was missing. Absolute time to hemostasis, drainage volumes, blood transfusions, hospital stay, and mortality were also analyzed for all 453 patients except protocol exclusions. Both hemostasis within 5 minutes and absolute time to hemostasis were highly significantly improved in patients on TISSEEL® ($p < 0.0001$, Pearson χ^2 test, Wilcoxon test, two-sided).

Intent-To-Treat Analyses: Primary endpoint of the pivotal study was cessation of bleeding within 5 minutes. The analysis includes all patients who had a bleeding episode: 193 in Group A (Fibrin Sealant), 172 in Group B (Control), for a total of 365 patients. Only first

episodes in patients were considered. All patients were analyzed as randomized, irrespective of the treatment they received first. Endpoint data were available on 342 patients. For 23 patients (10 in Group A, 13 in Group B) endpoint data was missing and 124 patients (53 in Group A, 71 in Group B) did not have bleeding that qualified for treatment. Hemostasis within 5 minutes was significantly more frequent in the TISSEEL® Group than the Control Group ($p < 0.0001$, Pearson χ^2 test, two-sided). Absolute time to hemostasis also showed a significant difference in favor of Fibrin Sealant ($p < 0.0001$, Gehan-Wilcoxon test, two-sided). There were no statistically significant differences between TISSEEL® and control hemostatic agents with regard to post-operative drainage volumes, blood product usage or mortality.

2) Use of Fibrin Sealant to Treat Traumatic Injuries to Spleen and Liver

This historically controlled, prospective study of the effectiveness of as a hemostatic agent was undertaken in patients who underwent laparotomy for injuries to the spleen and/or liver. The results obtained with TISSEEL® in the prospective study were compared with the experience in patients who underwent laparotomy for the same reasons in the period immediately preceding the study. The endpoints of this study were salvage of the spleen and reduction in mortality among liver trauma patients. Additionally, such variables as transfusion requirements, duration of hypotension and overall patient care were reviewed.

There was a 100 % salvage of spleens among patients treated with TISSEEL®for splenic trauma alone, yielding a significant difference of $p < 0.0001$, (Pearson χ^2 test, two-sided) when compared to the control group, in which 64 % of the patients required splenectomies. Among patients who suffered splenic trauma in combination with liver injury, the result was a 96 % salvage rate in the patients treated with Fibrin Sealant, as opposed to 44 % in the historical control, with a significance of $p < 0.0001$ (Pearson χ^2 test, two-sided). TISSEEL® did not result in statistically significantly reduced mortality in patients with blunt or penetrating trauma to the spleen ($p < 0.067$, one-sided).

3) Use of Fibrin Sealant in Closure of Temporary Colostomies

This single center, prospectively controlled, study was conducted at the
to investigate the efficacy of Fibrin Sealant in sealing colonic anastomoses, to decrease the incidence of complications following the closure of temporary colostomies. The patients who underwent colostomy closure with Fibrin Sealant were compared to those who underwent colostomy closure without Fibrin Sealant. The endpoint was prevention of anastomotic leaks as manifested by the occurrence of fistulae, infection at the anastomotic site, intra-abdominal abscess formation, reoperation, septic shock, and death.

Leakage was significantly less in the Fibrin Sealant Group compared to the Control ($p = 0.0406$, Jonckheere-Terpstra test, two-sided). Reviewed individually, there were significant differences for two variables, intra-abdominal abscess rate ($p = 0.0062$, Pearson χ

^{2} test, two-sided mid-p) and reoperation rate (p = 0.0411, Pearson χ^2 test, two-sided mid-p), both in favor of the Fibrin Sealant Group.

B. CLINICAL SAFETY

Vapor Heated Sealer Protein (Human)

Prior to the introduction of vapor heating, TISSEEL® was subjected to a dry-heating process which likely was a less effective virucidal method. A prospective study evaluated virus transmission by the dry-heated preparation. The study included a subset of patients enrolled in the U.S. cardiovascular surgery study (Rousou et.al.). None of 26 patients evaluated seroconverted for HIV. Of 24 patients evaluated for anti-HBs, all remained negative but one who transiently expressed this antibody. This seroconversion could have been due to passively acquired antibody from transfusion of 103 units of other banked blood products. However, this same patient also had a transient elevation of ALT greater than 2.5 times the upper limit of normal. Otherwise, none of 20 patients evaluated were found to have elevations of ALT.

No prospective studies have been performed with vapor heated TISSEEL® However, to date, there have been no confirmed reports of transmission of HIV, HBV, or HCV resulting from the use of one- or two-step vapor heated TISSEEL®.

Aprotinin (Trasylol; Bayer)

Anaphylactic reactions have been reported in less than 0.5% of patients receiving intravenous Aprotinin (Trasylol®), including first time and re-exposures. Since Aprotinin is a foreign protein, the incidence of hypersensitivity reactions, including anaphylaxis, is considerably higher upon re-exposure. One report (Trasylol® package insert, 1/94) cites an anaphylaxis incidence rate of approximately 1 per 10,000 in patients with no known previous exposure to Trasylol®, and approximately 1 per 1,130 in patients with previous Trasylol® exposure.

A single average 1.0 mL treatment dose of TISSEEL® contains approximately 3,000 KIU of Aprotinin, applied topically. In contrast, the recommended dose of Trasylol® for cardiovascular surgery includes: a 1-2 million KIU intravenous loading dose, a 1-2 million KIU "pump prime" dose, as well as 0.25-0.50 million KIU per hour by intravenous constant infusion. Thus, the total exposure to Aprotinin should be far less by use of Fibrin Sealant than by intravenous infusion.

Thrombin (Human)

According to the adverse event reports since 1991, one patient has been reported to likely have experienced anaphylaxis (which resolved following therapy) after repeated exposure to TISSEEL® containing Human Thrombin. To date, approximately 2,774,000 treatments (average single treatment dose = 1.0 mL) of TISSEEL® with Human Thrombin have been applied. Since 1991, there have been four reports of suspected anaphylaxis following administration of the vapor heated product containing Bovine Thrombin. All recovered following therapy. During this time,

approximately 2,140,000 treatments (average single treatment dose = 1 .0 mL) of vapor heated Fibrin Sealant containing Bovine Thrombin have been applied.

Polysorbate 80

Polysorbate 80 is used in the manufacture of Sealer Protein Concentrate (Human). In compliance with the 97/534/EC Commission Decision of July 30, 1997 on the Prohibition of the Use of Material Presenting Risks as Regards Transmissible Spongiform Encephalopathies, OIH uses Polysorbate 80 of plant origin only in the manufacture of TISSEEL.

VIII. PACKAGE INSERT

28 Apr 98
Thomas J. Lynch, Ph.D. Date
Chair, PLA Review Committee
HFM-340

Laura L. Wood 4/28/98
Laura L. Wood Date
HFM-340

4/28/98
Mark J. Weinstein, Ph.D. Date
HFM-340

Mary P. Padgett 28-APR-98
Mary P. Padgett Date
HFM-3 80

Toby A. Silverman MD 4/29/98
Toby A. Silverman, M.D. Date
HFM-3 80

4.29.98
'Richard M. Lewis, Ph.D. Date
HFM-3 80

6/29/98
Chinying J. Wang, Ph.D. Date
HFM-2 15

Alicia Gilbert 4.29.98
Alicia A. Gilbert Date
Chair, ELA Review Committee
HFM-207

4/29/98
Mary A. Malarkey Date
HFM-207