P990037

I. General Information

Device Generic Name:	Vascular hemostasis device
Device Trade Name:	Vascular Solutions DUETT™ sealing device
Applicant's Name and Address:	Vascular Solutions, Inc. 2495 Xenium Lane North Minneapolis, Minnesota 55441
PMA Number:	P990037
Date of Panel Recommendation:	See Section XIII
Date of Notice of Approval to Applicant:	JUN 22 2000

II. Indications for Use

The DUETT is indicated for sealing femoral arterial puncture sites and reducing time to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures using a 5F - 9F introducer sheath with an overall length not exceeding 15.2 cm.

III. Device Description

The Vascular Solutions DUETT sealing device is used to stop bleeding at the femoral artery puncture site after a patient has undergone an angiographic or interventional endovascular procedure. The DUETT utilizes a sterile, single-use peripheral intravascular catheter to temporarily stop bleeding and to deliver a procoagulant material, which is a mixture of bovine-derived thrombin and collagen, and sodium phosphate buffered water. At the time of use, the procoagulant is prepared to yield a formulation that is 50 mg/ml collagen and 2000 units/ml thrombin suspended in approximately 5 ml of diluent.

A. Materials and Configuration

Each DUETT includes the following components:

- Single-use, disposable catheter
- Foil pouch containing 10ml collagen syringe (250mg collagen) with attached mixing luer
- Vial of thrombin (10,000 units)
- Vial of diluent (5 ml)
- Procoagulant mixing accessories (syringe (10ml) and 20 gauge needle)

The catheter is a sterile, sub-4 French balloon catheter with a floppy tip, distal sealing balloon and moveable core wire. The catheter protective sleeve is made of lubricious thermoplastic tubing. The purpose of the catheter is to temporarily seal the arterial puncture site and to serve as a backstop for delivery of the procoagulant.

The thrombin is a protein substance produced through a conversion reaction in which prothrombin of bovine origin is activated by tissue thromboplastin of bovine-origin in the presence of calcium chloride. It is supplied as a sterile powder that has been freeze-dried in the final container. Also contained in the thrombin vial are mannitol and sodium chloride. Mannitol is included to make the dried product friable and more readily soluble. The material contains no preservative and has been chromatographically purified. Thrombin requires no intermediate physiological agent for its reaction. It converts fibrinogen directly to fibrin.

The collagen is an absorbable hemostatic agent prepared as a dry, sterile, fibrous, partial hydrochloric acid salt of purified bovine corium collagen. It is prepared in a loose fibrous form. In its manufacture, swelling of the native collagen fibrils is controlled by ethyl alcohol to permit non-covalent attachment of hydrochloric acid to amine groups on the collagen molecule and preservation of the essential morphology of native collagen molecules. Dry heat and sterilization causes some cross-linking which is evidenced by reduction of hydrating properties, and a decrease of molecular weight which implies some degradation of collagen molecules. However, the characteristics of collagen which are essential to its effect on the blood coagulation mechanisms are preserved. Collagen attracts platelets which adhere to the fibrils and undergo the release phenomenon to trigger aggregation of platelets into thrombin in the interstices of the fibrous mass. The effect on platelet adhesion and aggregation is not inhibited by heparin in vitro. The purpose of the procoagulant collagen is to initiate platelet adhesion and activation, and serve as a matrix to maintain thrombin at the puncture site.

The diluent is a sterile buffered solution of sodium phosphate and water. Both the thrombin and collagen are reconstituted with the diluent prior to use. The diluent is used to make the procoagulant suitably fluid for delivery and to maintain the desired pH and osmolarity of the DUETT procoagulant.

The procoagulant mixing accessories are a mixing syringe and its attached needle. Both of these components are currently marketed, sterile, single-use, disposable medical devices.

B. Principles of Use

As early as 1 hour before device use, the DUETT procoagulant is prepared following the mixing steps outlined in the *Instructions for Use*. Following completion of a diagnostic or interventional endovascular procedure, the DUETT catheter is prepped and the distal end is inserted through the hemostasis valve and into the existing introducer sheath. The catheter sleeve is then pulled back, exposing the floppy spring tip and puncture site sealing balloon. The catheter is further advanced through the introducer sheath to position the sealing balloon in the artery. The sealing balloon is inflated using a sterile, 10-ml syringe filled with 3-5 ml of saline. The inflated sealing balloon is pulled into position to initiate hemostasis and to serve as a backstop for delivery of the procoagulant. Markings on the catheter and sleeve facilitate positioning. The procoagulant is then delivered through the sidearm of the existing introducer sheath to the extra-vascular surface of the puncture site. The introducer sheath is gradually withdrawn from the access site as the procoagulant is delivered. Occlusive pressure is then applied 3-5 cm proximal to the access site as the sealing balloon is deflated. The sealing balloon is elongated using the moveable core wire, covered with the catheter sleeve, and the catheter and sleeve are then removed from the site. Finally, light pressure is applied directly to the access site for a short time (2-5 minutes) to complete hemostasis.

IV. Contraindications

The DUETT is contraindicated in patients with known sensitivity to bovine-derived materials.

V. Warnings

Thrombin must not be injected. The thrombin is for use only with the DUETT.

The use of topical bovine thrombin preparations has occasionally been associated with abnormalities in hemostasis ranging from asymptomatic alterations in laboratory determinations, such as prothrombin time (PT) and partial thromboplastin time (PTT), to severe bleeding or thrombosis which rarely have been fatal. These hemostatic effects appear to be related to the formation of antibodies against bovine thrombin and/or factor V which in some cases may cross react with human factor V, potentially resulting in factor V deficiency. Repeated clinical

applications of topical bovine thrombin increase the likelihood that antibodies against thrombin and/or factor V may be formed. Consultation with an expert in coagulation disorders is recommended if a patient exhibits abnormal coagulation laboratory values, abnormal bleeding, or abnormal thrombosis following the use of topical thrombin. Any interventions should consider the immunologic basis of this condition. Patients with antibodies to bovine thrombin preparations should not be re-exposed to these products.

The DUETT should not be used in patients with suspected arterial puncture distal to the common femoral artery bifurcation, clinically severe peripheral vascular disease (refer to Individualization of Treatment section), or a common femoral artery estimated to be less than 6 mm in diameter. Use of the DUETT in these situations may lead to inadvertent intravascular delivery of the procoagulant. The acute onset of severely diminished or absent peripheral pulses in the limb treated with the DUETT may indicate that inadvertent intravascular delivery of the procoagulant has occurred. If this is suspected, immediately perform appropriate diagnostic and therapeutic procedures for thrombus dissolution/removal.

The DUETT should not be used if posterior arterial wall puncture is suspected, as this may lead to incomplete sealing and bleeding complications.

VI. Precautions

The DUETT deployment procedure should be performed by physicians or physician-directed allied health care professionals with adequate training in the use of the device.

To minimize the risk of puncture site infections:

- observe sterile technique at all times when using the DUETT
- do not use the DUETT if the sterile packages (barrier bag and collagen foil pouch) have been damaged or opened
- do not proceed with DUETT deployment in potentially contaminated puncture sites

The DUETT should be kept dry; it contains materials that are degraded by heat and moisture.

The DUETT is for single use only. Do not resterilize.

A limited femoral angiogram should be performed prior to DUETT deployment to confirm that:

- the arteriotomy is above the common femoral artery bifurcation
- the femoral artery is ≥ 6mm in diameter
- no significant plaque is present in the vicinity of the arterial sheath

In the event that proper positioning of the DUETT balloon prior to procoagulant delivery cannot be achieved, remove the device and proceed with an alternate method of puncture site closure.

In the event that hemostasis is not achieved with the DUETT, apply manual or mechanical compression until bleeding is controlled.

Individualization of Treatment

As noted in the warning section, the DUETT should not be used in patients with severe peripheral vascular disease. Severe peripheral vascular disease is defined as:

- severe claudication when ambulating < 100 feet
- weak or absent pulses in the affected limb
- ABI < 0.5 at rest
- known stenosis ≥ 50% in the iliac or femoral artery on the affected side
- prior vascular bypass surgery involving the affected femoral artery

- prior stent placement in the vicinity of the arterial puncture site

Note that the safety and effectiveness of the DUETT have not been established in the following patient populations:

- patients younger than 18 years of age
- women who are pregnant or lactating
- patients with a suspected posterior femoral artery puncture
- patients with an antegrade femoral artery puncture
- patients with a hematoma ≥ 6 cm prior to sheath removal
- patients with a known bleeding disorder, including thrombocytopenia (platelet count <100,000), thrombasthenia, hemophilia, or von Willebrand's disease
- patients with significant anemia (Hgb < 10 g/dL, Hct < 30)
- patients with a baseline INR > 1.5 (e.g. coumadin therapy)
- patients who received thrombolytic therapy (streptokinase, urokinase, t-PA) in the preceding 24 hours
- patients with an ACT > 400 seconds at the conclusion of the endovascular procedure
- patients with an elevated blood pressure (SBP >180 or DBP >110 mm Hg) despite medical therapy
- patients in whom continued heparin or other anticoagulant therapy (with the exception of Glycoprotein IIb/IIIa receptor blockers) is planned following completion of the endovascular procedure

VII. Alternative Practices and Procedures

Alternative practices for achieving hemostasis of the femoral artery puncture site post-catheterization include manual compression, mechanical compression, collagen hemostasis devices and percutaneous delivery of sutures to the femoral artery access site. Pressure dressings and sandbags are routinely used in combination with compression methods to control oozing.

VIII. Marketing History

The DUETT sealing device is commercially marketed in Germany, England, Ireland, Norway, Denmark, Finland, Sweden, Switzerland, Italy, Greece, Cypress, Belgium, Holland, Austria, Spain, and China. The DUETT has not been subject of regulatory action in any country for safety or effectiveness-related issues.

IX. Adverse Effects of the Device on Health

The DUETT sealing device was evaluated in a randomized, controlled clinical investigation involving 695 patients, a non-randomized U.S. Continued Access Registry (n=236), a U.S. Phase I clinical investigation (n = 43) and three European clinical investigations, including a single-site prospective clinical investigation (n = 24), a two-site prospective clinical investigation (n = 48) and a European Multi-center Registry (n = 1587).

A. Randomized Multi-center Clinical Investigation

The randomized multi-center clinical investigation compared the DUETT sealing device to Standard Compression (i.e., manual or mechanical) methods. Sixty-five (65) of the patients enrolled in this investigation were non-randomized DUETT run-in patients. Of the 630 randomized patients, 392 (62%) were randomized to DUETT and 238 (38%) were randomized to Standard Compression. Of the patients randomized to DUETT, 266 (68%) were post-intervention and 126 (32%) were post-diagnostic angiography. Of the patients randomized to Standard Compression, 155 (65%) were post-intervention and 83 (35%) were post-diagnostic angiography.

A total of 5 deaths (4 DUETT, 1 Standard Compression) were reported during the randomized investigation. None of these deaths were determined to be device-related.

Table 1 summarizes the adverse events reported within the randomized investigation's 30-day follow-up period. Events are summarized by percentage of randomized patients experiencing the event during the clinical investigation.

Table 1: Incidence of All Complications:
Percentage/Number of Patients With An Event (N=630)

Description of Event	DUETT N = 392	Standard Compression N = 238†	Mean Difference [95% C.I.] (a)
Major Complications			
Vascular Repair			
Surgery for Vascular Complication	2.0% (8/392)	0.8% (2/237)	
Ultrasound Guided Compression	1.5% (6/392)	0.4% (1/237)	
PTA or Other Percutaneous Procedure	0.5% (2/392)	0.0% (0/237)	
Subtotal: Any Vascular Repair	3.1% (12/392)	0.8% (2/237)	
Bleeding Requiring Transfusion	1.5% (6/392)	1.3% (3/237)	
Infection Requiring Extended Hospitalization (with antibiotics)	0.5% (2/392)	0.0% (0/237)	
*Total: Any Major Complication	3.6% (14/392)	1.7% (4/237)	1.9% [4.97%] (c)
Vascular Complications			
Hematoma ≥ 6 cm	5.9% (23/392)	3.0% (7/237)	
Pseudoaneurysm	2.3% (9/392)	0.8% (2/237)	
AV Fistula	0.3% (1/392)	0.0% (0/237)	
Retroperitoneal Bleed	0.3% (1/392)	0.0% (0/237)	
Peripheral Arterial Occlusion or Peripheral Nerve Injury	0.8% (3/392)	0.4% (1/237)	
Total: Any Vascular Complication	7.1% (28/392)	3.8% (9/237)	3.3% [-1.3%, 7.8%] (b)
Device Malfunctions	5.4% (21/392)	NA	NA
Failure to Deploy	2.3% (9/392)	NA	NA

(a) C.I.: Confidence Interval for Difference in rates
(b) two-sided 95% confidence interval
(c) one-sided 95% upper confidence limit
Difference = DUETT – Standard Compression
*Primary endpoint for the trial was constructed using a 1-sided hypothesis (Blackwelder)
† The number of patients is less than the total patients studied due to missing data for some patients.

B. U.S. Continued Access Registry

In the Registry, patients received the DUETT sealing device following diagnostic and interventional endovascular procedures and were monitored up to hospital discharge for device-related complications. Of the initial 236 patients, 69 (29%) were post-intervention and 167 (71%) were post-diagnostic angiography.

One death was reported during the Registry, which was determined not to be device-related.

Table 2 summarizes the adverse events reported during the Continued Access Registry.

Table 2: Principal Safety Results:
Percentage/Number of Patients With An Event (N=236)

Safety Measures	All patients
Vascular Repair	0.8% (2/236)
Transfusion	0.4% (1/236)
Infection	0.0% (0/236)
Hematoma ≥ 6 cm	1.7% (4/236)
Pseudoaneurysm	0.8% (2/236)
Periph. Arterial Occlusion Or Periph. Nerve Injury	0.4% (1/236)
Any Complication	2.5% (6/236)
No Major Complication	98.7% (233/236)
Device Malfunctions	6.8% (16/236)
Failure to Deploy	5.5% (13/236)

C. U.S. Phase I and Three European Clinical Investigations

A U.S. Phase I clinical investigation (n = 43) and three European clinical investigations were conducted to examine the safety and performance of the Vascular Solutions DUETT sealing device in achieving hemostasis of the femoral artery puncture site following diagnostic and interventional endovascular procedures. Table 3 summarizes the adverse events reported during these studies.

Table 3: Summary of Device-Related Complications for Other Investigations

Complication (per event basis)	Incidence rate (%)			
	U.S. Phase I N = 43	European Feasibility N = 24	European Multi-center N = 48	European Registry N = 1587
Ultrasound-guided compression*	2.3	0	0	1.7
Surgical repair*	0	0	0	0.4
Other vascular repair*	0	0	0	0.3
Bleeding event requiring transfusion*	0	0	0	0.2
Infection requiring extended hospitalization and antibiotic administration*	0	0	0	0
Hematoma (≥6cm in diameter)	2.3	0	0	0.6
No major complication	97.7	100.0	100.0	97.4

*Major complication

The following adverse events were NOT observed during the clinical investigation, but are recognized as potential complications associated with balloon catheter, thrombin, or collagen usage. Events are listed in alphabetical order:

- adhesion formation
- allergic reaction
- abscess formation
- foreign body reaction
- wound dehiscence.

A recognized rare potential reaction associated with the use of bovine derived thrombin is the development of inhibitory antibodies which interferes with hemostasis.

Although clinical reports of DUETT-related femoral artery access site infections were very few, tissue necrosis was noted with intramuscular implantation of the mixed procoagulant in a rabbit model.

X. Summary of Non-clinical Studies

A. Bench and In Vitro Device Characterization Testing

1. Biocompatibility

Biocompatibility testing of the DUETT catheter was conducted in accordance with the FDA-modified matrix of the International Standard ISO-10993, *"Biological Evaluation of Medical Devices Part 1: Evaluation and Testing."* The following tests were conducted: cytotoxicity, hemolysis, systemic toxicity, sensitization, intracutaneous injection, and pyrogenicity. The results indicate that the Duett catheter is non-toxic, non-hemolytic, and non-pyrogenic.

The procoagulant thrombin and collagen are each approved for commercial use as hemostasis aids. The following biocompatibility tests were conducted on the mixed procoagulant: cytotoxicity, sensitization, and implantation. The results of the cytotoxicity and sensitization tests demonstrated that the mixed procoagulant was non-cytotoxic, and had a weak allergenic potential.

Two separate ISO 10993-6 compliant rabbit muscle implantation studies were conducted on the procoagulant. These studies evaluated the local implant site response of the rabbit muscle to the procoagulant at 14 and 28 days post implantation. The results indicated that the procoagulant was moderately toxic when implanted for 14 days and slightly toxic when implanted for 28 days when compared to a negative control plastic. The results indicated that the procoagulant material was non-toxic when the collagen component of the procoagulant was used as the control. This result is being further investigated in a post-approval study requirement.

Gross and histopathologic examination of the femoral artery at the puncture site and surrounding tissues 14 days following procoagulant delivery in two dogs revealed normal vessel healing at the puncture site and only a mild inflammatory response present at the site of procoagulant deposition.

2. Functionality

In vitro tests were conducted to characterize the mechanical and biochemical performance of the DUETT sealing device. Results from catheter mechanical tests demonstrated that the performance of the catheter was acceptable. Results from the *in vitro* procoagulant characterization testing demonstrated the hemostatic potential of the procoagulant and that the procoagulant can be mixed at least 1 hour before use.

Catheter Mechanical Tests

As described in the following paragraphs, functional, bond strength, leak and rupture tests were performed on representative samples of catheter assemblies or sub-assemblies made according to established manufacturing procedures. Bench-top design qualification testing was performed to demonstrate that the product specifications were met.

DUETT Catheter Functional Test

This test was performed to demonstrate that under simulated use conditions, the DUETT catheter withstood clinical use forces for the duration of a single procedure. To perform this test, the distal balloon was inflated to a specified pressure. The balloon diameter was measured and recorded. The balloon was then placed in a device and a force was applied on the balloon and shaft for a specified amount of time. The balloon was deflated, the core wire was extended and

the balloon was recaptured. This process was then repeated with an increased force and time. All samples tested passed the force/time test.

Knob Movement Test
This test was performed to demonstrate that the knob movement force was adequate to ensure that the knob remained in the desired position during clinical use. This test was performed using a calibrated industry tensile test machine at a specified compression rate. The proximal face of the knob to be tested was placed in the upper jaw and the distal end of the adapter in the bottom jaw. The compression force was recorded. The average result of the knob movement force was within the specification.

Bond Strength Test
These tests were performed to demonstrate that the device bond strengths withstood the anticipated maximum tensile forces that the joints will encounter during clinical use. All bond strength tests were performed using a calibrated force gauge or a calibrated industry tensile test machine at a specified pull rate. The bond to be tested was placed between the clamps and the joint was pulled until failure. The separation force and the nature of the failure were recorded. The bond strength test results were greater than the anticipated maximum tensile forces that the joints will encounter during clinical use, based on measurements of the force required to position the catheter and balloon during animal studies.

Wire Seal Leak Test
This test was performed to demonstrate that the catheter did not leak under simulated normal clinical conditions. The wire seal was checked for leaking during the functional test. After the tensile force is applied between the hub and inflated sealing balloon the system was checked for leaks. No leaks were found.

Balloon Rupture Test
This test was performed to demonstrate that the sealing balloon withstood 1.5 times the nominal clinical use pressure. To perform this test a catheter was heated by submerging it in a water bath for at least 30 seconds before beginning the balloon inflation. Pressure was increased until the balloon ruptured. The rupture pressure and mode of failure (i.e., longitudinal, lateral, etc.) were recorded. The resulting average burst pressure was approximately three times the nominal operating balloon pressure.

Balloon Inflation/Deflation Time Test
This test was performed to demonstrate that the sealing balloon inflation and deflation times met the same specifications for currently marketed peripheral balloon catheters. This test was performed by recording the time required to pressurize the catheter using the 3/4 cc syringe as directed in the DUETT Instructions for Use. The resulting average inflation and deflation times were within the design specification.

Repeat Performance Test
This test was performed to demonstrate that the integrity of the catheter and balloon were maintained after repeated simulated use. Test assemblies were prepped and balloons inflated according to procedures outlined in the Instructions for Use. The core wire was pulled to shape the balloon, and the balloon was then deflated, the core wire re-extended and the sleeve slid over the deflated balloon. After each major step the catheter and balloon were inspected for leaks. In additional testing, catheter balloon assemblies heated to body temperature were stressed through cycles of inflating to the nominal operating pressure and then deflating. At the end of the test the balloons and balloon joints were inspected for any failures. The results indicated that the balloon and balloon joints were not likely to fail during clinical use of the device, which requires only one balloon inflation.

Catheter Body Maximum Pressure Test
This test was performed to demonstrate that the catheter did not rupture under simulated normal clinical use conditions. To perform this test the distal end of the catheter shaft was closed and the catheter heated to body temperature. The catheter was then pressurized initially in intervals until rupture. The average catheter rupture pressure was approximately 22 times the nominal operating pressure. In all cases the failure mode was separation of tubing from the adapter.

Sleeve Marker Location
This test was performed to demonstrate that the sleeve marker location indicated proper balloon placement for inflation. This test procedure is a method of measuring the location of the black and white sleeve marks on the movable sleeve. The location of the black and white sleeve marks was within the specification.

End Profile Diameter
This test was performed to demonstrate that the diameter of the catheter's end profile was compatible with commonly used 5F introducer sheaths. This procedure measured the diameter end profiles of the deflated balloon, shaft and movable sleeve on the catheter by advancing the balloon portion of the catheter into successively smaller diameter holes until the balloon no longer passed through the profile gauge. The average outside diameter of the sleeve met the specification.

Device/ Introducer Compatibility Test
This test measured the working length of the sleeve assembly to ensure that the catheter assembly accommodated the maximum length of a conventional short (optimal 10 cm) introducer sheath with a maximum overall length of 15.2 cm. The average working length of the sleeve assembly was within the specification.

Balloon-to-Sleeve Gap
This test was performed to demonstrate that the sleeve fully covered the core wire subassembly, and when pulled back, fully exposed the sealing balloon. This test used a scale to measure the distance between the distal end of the movable sleeve when in the retracted position and the proximal end of the balloon. The average measurement was within the specification.

Procoagulant In Vitro Tests

As described in the following paragraphs, procoagulant clotting time, stability, and deliver-ability tests were performed using finished DUETT procoagulant components prepared according to established procedures in the DUETT Instructions for Use. Bench-top design qualification testing was performed to demonstrate that the product specifications were met.

Whole Blood Clotting Test (Hemostatic Potential)
This test was performed to demonstrate that the procoagulant was able to clot heavily anticoagulated whole blood in a reasonable amount of time. To perform this test a specified amount of heparin is added to whole blood and mixed. The activated clotting time (ACT) is then measured using a Hemochron to ensure an ACT of >400 seconds. Calcium chloride is added to a test tube with heparinized whole blood and procoagulant is then added and a timer is started simultaneously. After mixing, the tube is covered and inverted at 3 second intervals until a solid mass had formed. The time from when the procoagulant is added to the tube to when a solid mass formed is considered the clotting time. All of the procoagulant samples met the specification for whole blood clotting.

Procoagulant Stability Test
The deliver-ability and thrombin activity of the procoagulant over time was evaluated to confirm that the procoagulant could be mixed up to 1 hour in advance of its use. During animal studies the procoagulant was mixed 1.5 hours in advance of use with no negative impact on device performance, including deliver-ability and achievement of hemostasis. Procoagulant thrombin activity over time was also tested following the thrombin supplier's established protocol for evaluating the stability of reconstituted thrombin. The results showed that the procoagulant thrombin activity does not degrade significantly for up to three hours following procoagulant preparation. These results demonstrated that the procoagulant can be prepared 1 hour prior to use as described in the DUETT Instructions for Use without a detrimental effect on device performance.

Procoagulant Deliver-ability Test
This test was performed to demonstrate that an adequate amount of the procoagulant was deliverable through a 5F introducer sheath in a reasonable amount of time. This test was performed by inserting a DUETT catheter into a 5F introducer sheath until the protective sleeve extended past the end of the sheath by 2-3 cm. Procoagulant was then delivered in a manner that simulated clinical practice. The volume of procoagulant delivered through the sheath was measured. The testing configuration represented a conservative, "worst case" scenario; the test method required the use of a 5F sheath. The test results indicated consistent and acceptable procoagulant deliver-ability.

3. Shelf-life
Product stability testing performed for the DUETT sealing device demonstrated that functionality and sterility of the device was maintained for a minimum of 12 months. Based on these results, a shelf-life of 12 months for the DUETT sealing device has been established.

B. Animal (In-Vivo) Studies
Animal studies of the DUETT were conducted to evaluate its performance and to define the operating techniques.

Methods and Results
DUETT prototypes were successfully deployed and hemostasis achieved in 25 of 27 attempts (93%) in both normal and heparinized canine models. In 6 of the 13 heparinized dogs (~150 U/kg), the contralateral femoral artery served as a control. In those tests, hemostasis was achieved in the DUETT-treated arteries at 6.5±3.4 minutes but in none of the controls. In 15% of the heavily anticoagulated dogs, late re-bleeding or hematoma growth was observed. In all of the animal tests there was no evidence (blood pressure, EKG, pedal pulses, temperature, heart rate) of complications, and no evidence of obstruction or distal embolization in tests that included angiographic imaging. In tests that included ultrasound imaging of the groin, no complications were noted on follow-up. Physical, angiographic and histopathologic examination of the animals restudied at 2 weeks showed that there was no interference with normal vessel healing at the puncture site and that only a mild inflammatory response was present at the site of procoagulant deposition.

In three additional tests, failure of the balloon to create a backstop during procoagulant delivery was caused intentionally, to simulate a situation where procoagulant material could be inadvertently injected into the distal femoral vasculature. In those three failure mode tests, physical examinations and laboratory tests for indications of disseminated intravascular coagulation (increases in thrombin anti-thrombin III complex, fibrin D-dimer formation, fibrin/fibrinogen degradation products, or decreasing levels of circulating fibrinogen) showed no evidence of injection of thrombin into the femoral artery.

XI. Clinical Studies

The safety and effectiveness of the Vascular Solutions DUETT sealing device in achieving hemostasis of the femoral artery puncture site following diagnostic and interventional endovascular procedures was evaluated in a randomized, controlled, multi-center clinical investigation involving 695 patients. The safety and effectiveness of the DUETT was also evaluated in a U.S. Continued Access Registry (n=236, to-date), a U.S. Phase I clinical investigation (n = 43) and in three European clinical investigations, including a single-site prospective clinical investigation (n = 24), a European two-center prospective clinical investigation (n = 48) and a European Multi-center Registry (n = 1587).

A. Randomized Multi-center Clinical Investigation

The DUETT sealing device was evaluated in a randomized clinical investigation to evaluate the safety and effectiveness of femoral artery closure using the DUETT sealing device versus Standard Compression (i.e., mechanical or manual) methods following diagnostic angiography and percutaneous interventional procedures. The DUETT sealing device investigation was a multi-center, prospective, randomized, controlled trial. The study was conducted at fifteen institutions (14 U.S. sites and 1 European site) from August of 1998 to February of 1999. Patients were randomly assigned with a five-to-three probability to femoral artery closure with the DUETT or Standard Compression, respectively.

The investigation was designed as an equivalency trial for the 30-day primary safety endpoint of the combined rate of major complications, and as a superiority trial for the primary effectiveness endpoints of time to hemostasis (time from the end of the antecedent procedure to the time that hemostasis is first observed) and ambulation (time from the end of the antecedent to when the patient stands at the bedside and walks 110 feet without re-bleeding). Major complications included: surgery or ultrasound-guided compression for vascular repair, groin-related bleeding requiring transfusion, and groin-related infection requiring antibiotics or prolonged hospitalization.

Secondary endpoints included: procedure success rate, and device success rate. Procedure success rate was defined as the number of patients in which hemostasis was achieved with freedom from major complications vs. the number attempted. Device success rate was defined as the number of patients in which hemostasis was achieved using the DUETT sealing device alone with freedom from major complications vs. the number attempted.

1. Subject Selection and Exclusion Criteria

Patients were enrolled in the study if they met the following criteria: the patient was at least 18 years of age; patient agreed to return for a 30 ±7 days follow-up examination; patient or guardian provided written informed consent, and; in a subgroup, patient agreed to ultrasound examination of the femoral artery.

Patients were excluded from the investigation if they met any one of the following criteria: an arterial introducer sheath size of <5F, >9F or longer than 10 cm; a large hematoma (≥ 6 cm in diameter) present prior to vascular sealing; clinically severe peripheral vascular disease; suspected posterior femoral arterial wall puncture or puncture distal to the common femoral artery bifurcation; a known bleeding disorder, including thrombocytopenia (<100,000 platelet count), thrombasthenia, hemophilia or von Willebrand's disease; significant anemia (Hgb < 10 g/dL, Hct < 30); a documented baseline INR > 1.5; heavily anticoagulated (ACT > 400 sec) at the end of the catheterization procedure; women who were known to be or suspected to be pregnant; a life expectancy of less than 1 year; acute Q wave myocardial infarction within the last 72 hours;

uncontrolled severe hypertension (systolic BP > 180 mm Hg or diastolic BP > 110 mm Hg) despite therapy; continued heparin or other anticoagulant therapy (except GPIIb/IIIa platelet receptor blockers) was planned following completion of the interventional or diagnostic procedure; known allergies to bovine derived products; concurrent participation in an investigation when such participation could confound the treatment or outcomes of this investigation; an antegrade puncture; patients receiving thrombolytic therapy (e.g., streptokinase, urokinase, t-PA.) within the last 24 hours, and; a common femoral artery diameter estimated to be < 6 mm during the femoral angiogram.

2. Methodology

The following methodology was adhered to at each of the investigational sites.

- Informed consent and baseline medical histories were obtained prior to the catheterization procedure.
- Following the diagnostic or interventional procedure, femoral angiography was performed to assess eligibility; patients were then randomized to receive the DUETT sealing device or Standard Compression.
- DUETT sealing device-treated patients had immediate sheath removal in the catheterization laboratory; for patients in the compression arm of the study, activated clotting times (ACT) were assessed and sheaths removed using standard institutional protocols, e.g., when the ACT measured 150-180 seconds.
- The times when hemostasis and ambulation occurred were recorded and the elapsed times to hemostasis and ambulation were calculated from the end of the diagnostic or interventional procedure.
- Patients were followed in the hospital and at 30 days (±7 days) following the procedure for evidence of major complications or other vascular complications. Femoral artery ultrasounds were performed at the 30-day follow-up on 193 patients from 5 sites for evidence of pseudoaneurysms and arterio-venous (AV) fistulae.

3. Study Population

A total of 695 patients were enrolled in the DUETT trial, with 392 (62%) randomized to the DUETT sealing device, 238 (38%) randomized to Standard Compression, and 65 non-randomized DUETT run-in patients. Among patients randomized to DUETT, 266 (68%) were post-intervention and 126 (32%) were post-diagnostic angiography. Among patients randomized to Standard Compression, 155 (65%) were post-intervention and 83 (35%) were post-diagnostic angiography. A total of 24% of the patients studied received GPIIb/IIIa receptor blockers.

Arterial sheath sizes used were comparable between treatment arms. There were no significant differences between the two randomized groups with respect to gender, age, risk factors, peri-procedural medications, body size, or blood pressure. Activated clotting times (ACT) at the time of sheath removal were higher in the treatment arms [220.0 ± 74.4 seconds (DUETT) versus 147.6 ± 41.6 seconds (Standard Compression); p=0.001].

4. Gender Bias Analysis

The higher percentage of male patients enrolled in the study (73.3% male vs. 26.7% female) reflects the gender referral pattern for patients undergoing interventional and diagnostic procedures. All differences between the treatment groups with respect to time-to-hemostasis, time-to-ambulation, and complication rates were consistent between the genders.

5. Safety Data

A summary of the adverse events (complications) experienced by patients enrolled in the DUETT clinical investigation is reported in Table 1 (see section IX). Major complications were

experienced by 14 (3.6%) of 392 patients randomized to the DUETT sealing device compared to 4 (1.7%) of 237 patients randomized to compression (p=0.220).

Failure to fully deploy the device occurred in 21 (5.4 %) of cases. Patients were successfully treated with a second device with no complications in 12 of those cases, 3 reported successful deployment with the existing device with no complications, 4 were successfully crossed over to Standard Compression with no complications, and 2 crossed over to Standard Compression and later reported a complication (one major hematoma and one pseudoaneurysm requiring surgical repair). Device malfunctions were not associated with any excess risk of major complications as compared to all other DUETT-treated patients.

No deaths were determined to be device-related. Four deaths occurred in the DUETT arm and one in the Standard Compression arm during the 30-day follow-up period and were reported as not associated with the arterial access closure.

6. Effectiveness Data

Thirty day clinical follow-up was performed in 94.8% of patients in accordance with the protocol. In a sub-group of 193 patients, a duplex ultrasound of the femoral artery was performed to rule out pseudoaneurysm and other abnormalities.

In both the diagnostic and interventional groups, use of the DUETT resulted in statistically significant decreases in time to hemostasis and time to ambulation as compared to Standard Compression (Tables 4 and 5).

Table 4: Effectiveness Endpoints for All patients (N = 630)

	Duett (N = 392) †	Standard Compression (N = 238) †	Difference [95% C.I.]
Time to Hemostasis (min) Median (Interquartile) Mean (std. dev.) N	 14.0 (10, 17) 20.4 (41.6) 388	 195.0 (46, 351) 228.4 (206.9) 225	-208.0 [-235.5, -180.5]
Time to Ambulation (min) Median (Interquartile) Mean (std. dev.) N	 337.5 (223, 526) 535.4 (711.2) 366	 705.0 (400, 1120) 834.2 (622.6) 217	-298.8 [-413.2, -184.4]
Device Success (a)	93.1% (365/392)	NA	NA
Procedure Success (b)	96.4% (378/392)	98.3% (233/237)	-1.9% [-5.5%, 1.8%]

(a) Device Success = number of patients in whom hemostasis was achieved using the Duett sealing device alone with freedom from major complications vs. the number attempted.
(b) Procedure Success = number of patients in whom hemostasis was achieved with freedom from major complications vs. the number attempted.
† The number of patients is less than the total patients studied due to missing data for some patients.

Table 5: Endpoint Outcomes for Patient Subgroups (N = 630)

	Diagnostic		Intervention	
	Duett (N = 126) †	Standard Compression (N = 83) †	Duett (N = 266) †	Standard Compression (N = 155) †
Time to Hemostasis (min) Median (Interquartile) Mean (std. dev.) N	 12.0 (9, 16) 12.8 (5.3)) 125	 38.0 (29, 52) 67.1 (171.6) 77	 14.0 (11, 19) 24.0 (50.0) 263	 296.5 (195, 384) 312.3 (171.2) 148
Time to Ambulation (min) Median (Interquartile) Mean (std. dev.) N	 155.0 (121, 262) 349.1 (752.7) 120	 359.0 (285.5, 421.5) 485.3 (646.3) 72	 385.0 (325, 732) 626.2 (673.1) 246	 960.0 (692, 1204) 1007.4 (533.2) 145

† The number of patients is less than the total patients studied due to missing data for some patients.

B. Continued Access Registry

1. Methods

The performance of the DUETT (N=236) in sealing a femoral arterial puncture site following a diagnostic or interventional endovascular procedure was further evaluated in the Continued Access Registry. Primary endpoint data collected included time to hemostasis, time to ambulation, and the composite endpoint of major complications. The treatment protocol for the Registry was nearly identical to that used during the randomized investigation. Follow-up until discharge was performed in all 236 patients in accordance with the protocol.

2. Results

Table 6 summarizes the mean time-to-hemostasis and the mean time-to-ambulation results from the Continued Access Registry. A summary of the adverse events (complications) experienced by patients enrolled in the Registry is reported in Table 2 (see section IX). Patients enrolled in the Registry displayed a 1.3% rate of major complications at the time of hospital discharge.

Table 6: Endpoint Outcomes (N = 236)

	All Duett patients (N= 236) †	Diagnostic patients (N = 167) †	Interventional patients (N = 69) †
Time to Hemostasis (min)			
Median (Interquartile)	11.0 (9, 17)	11.0 (8, 16)	12.0 (10, 17)
	20.0 (51.1)	14.2 (10.2)	35.2 (94.4)
Mean (std. Dev.)	227	164	63
N			
Time to Ambulation (min)			
Median (Interquartile)	199.0 (140, 390)	163.0 (133, 245)	681.0 (289, 1219)
Mean (std. Dev.)	445.9 (782.9)	312.9 (774.4)	801.0 (694.6)
N	224	163	61
Device Success (a)	89.0% (210/236)	92.2% (154/167)	81.2 % (56/69)
Procedure Success (b)	98.7 % (233/236)	99.4% (166/167)	97.1% (67/69)

(a) Device Success = number of patients in whom hemostasis was achieved using the Duett sealing device alone with freedom from major complications vs. the number attempted.
(b) Procedure Success = number of patients in whom hemostasis was achieved with freedom from major complications vs. the number attempted.
† The number of patients is less than the total patients studied due to missing data for some patients.

C. U.S. Phase I and Two European Clinical Investigations

1. Methods

These investigations were performed to evaluate the performance of the DUETT in achieving hemostasis of the femoral arterial puncture site in patients who have undergone a percutaneous diagnostic or intervention procedures, to evaluate the resulting time to hemostasis and time to ambulation, and to monitor for device-related complications. The safety endpoints were incidence and severity of device-related complications. The effectiveness endpoints were: device hemostasis success rate, mean time to hemostasis, mean time to ambulation and device performance. Only safety data was collected during the European Registry Study.

2. Results

Table 7 summarizes the mean time-to-hemostasis and the mean time-to-ambulation results from the U.S. Phase I clinical investigation, European Feasibility Study and European Multi-center Clinical Investigation. A summary of the adverse events (complications and device malfunctions) reported during these clinical investigations is reported in Table 3 (see section IX).

Table 7: Summary of Mean Times to Hemostasis and Ambulation

Study		U.S. Phase I	European Feasibility	European Multi-Center
Number of deployments D: diagnostic, I: interventional		D = 29, I = 13,	D = 19, I = 5	D = 33, I = 15
Mean time-to-hemostasis	Diagnostic	4.0 ± 1.5 min.	2.5 ± 0.9 min.	3.9 ± 1.4 min.
	Interventional	6.9 ± 4.2 min.	6.0 ± 2.2 min.	6.7 ± 4.6 min.
Mean time-to-ambulation	Diagnostic	2.1 ± 0.6 hrs	2.6 ± 0.5 hrs	6.5 ± 12.7 hrs
	Interventional	5.5 ± 2.1 hrs	16.3 ± 4.9 hrs	4.9 ± 5.7 hrs

XII. Conclusions Drawn from Studies

Results of *in vitro* testing, animal studies, and clinical investigations provide valid scientific evidence and reasonable assurance that the DUETT sealing device is safe and effective when used in accordance with its labeling. The safety of the device has been demonstrated by the fact that the incidence of major complications in the randomized clinical investigation was equivalent for both treatment arms (DUETT sealing device procedure compared to Standard Compression therapy). The effectiveness of the DUETT sealing device was demonstrated by a significant reduction in time to hemostasis and time to ambulation in patients assigned to DUETT sealing device treatment compared to those assigned to Standard Compression.

XIII. 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 Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by the panel.

IX. FDA Decision

FDA issued a PMA approval letter to Vascular Solutions, Inc. on JUN 22 2000. FDA also performed an inspection of the manufacturing facilities and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820).

X. Approval Specifications

Instructions for Use: See the labeling

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

Postapproval Requirements and Restrictions: See approval order.