SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1. *GENERAL INFORMATION*

Device Generic Name: ..... Vascular Access Graft

Device Trade Name: ..... The ProCol® Vascular Bioprosthesis

Applicant's Name and Address: ..... Hancock Jaffe Laboratories, Inc.
2807 McGaw Avenue
Irvine, CA 92614

PMA Application Number: P020049

Date of Panel Recommendation: ..... None

Date of Notice of Approval to the Applicant: July 29, 2003

2. *INDICATIONS AND USAGE*

The ProCol® Vascular Bioprosthesis is intended for the creation of a bridge graft for vascular access subsequent to at least one previously failed prosthetic access graft.

3. *CONTRAINDICATIONS*

There are no contraindications related to the use of the ProCol® Vascular Bioprosthesis.

4. *WARNINGS AND PRECAUTIONS*

The Warnings and Precautions can be found in the Instructions for Use for this product.

5. *DEVICE DESCRIPTION*

The ProCol® Vascular Bioprosthesis is derived from a continuous segment of bovine mesenteric vein processed with glutaraldehyde. Branches are ligated with surgical suture. The bioprosthesis has a nominal diameter of 6 mm and is manufactured with a minimum length ranging from 10 cm to 40 cm. Flow direction is indicated by a loop of green surgical suture attached to the outflow end of the device. The inflow end of the device is beveled both to identify the inflow end of the vessel and to assist in inserting the irrigation needle during the pre-implantation rinse procedure. Each device is identified by a unique serial number imprinted on a PETG identification tag sutured to the bioprosthesis.

The finished bioprosthesis is supplied on a glass mandril, immersed in buffered physiological saline. Devices are packaged in a borosilicate glass packaging tube with screw type closure and terminally sterilized by exposure to gamma radiation.

Each unit is supplied inside an individual corrugated carton with polyethylene foam liner and sealed with PVC shrink wrap. The device has a shelf life of 54 months.

6. *ALTERNATE PRACTICES AND PROCEDURES*

For a patient population consisting of at least one already failed synthetic access graft, alternative practices to achieve dialysis would include placement of another synthetic graft to create another site for needle dialysis, or resorting to peritoneal or catheter based dialysis. Creation of an access site using the patient's native vein is another alternative.

7. *MARKETING HISTORY*

The ProCol® Vascular Bioprosthesis has had a CE mark approval since June 1998. Approximately 4,000 devices have been shipped to ten European countries since October 1992 in diameters ranging from 3 to 6 mm. In countries outside of the U.S., the device is used to establish vascular access, accomplish peripheral vascular reconstruction, or to reconstruct one or more coronary arteries. Distribution has been to the following countries: The United Kingdom, Switzerland, Italy, France, Germany, The Netherlands, Austria, Spain, Turkey, and Greece. The ProCol® Vascular Bioprosthesis has not been withdrawn from marketing for any reason relating to safety or effectiveness of the device.

8. *POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH*

The following adverse events may be associated with use of a vascular access graft: needle stick damage resulting in bleeding and/or pseudoaneurysms, hemorrhage, anastomotic aneurysms, steal, patient sensitivity to device materials, graft dilatation, thrombosis/occlusion of graft, infection, pain, swelling of affected limb, embolic events, stenosis, slow wound healing, failure to achieve access, events associated with an invasive surgical procedure and possibly death.

9. *SUMMARY OF PRE-CLINICAL STUDIES*

The ProCol® Vascular Bioprosthesis for vascular access was subjected to a comprehensive pre-clinical testing program. Testing methods were in accordance with the FDA draft "Guidance for the Preparation of Research and Marketing Applications for Vascular Graft Prostheses".

9.1 *BIOCOMPATIBILITY, IMMUNOLOGY, AND TOXICOLOGY STUDIES*

Selected toxicity and biocompatibility studies were conducted for the bioprosthesis. Testing was conducted on finished irradiated product of the same dimensions and using the same manufacturing processes as the current model but with a fabric cover. The

current model would not be more toxic or mutagenic than the tested device which includes the presence of the additional component (polyester). The testing was conducted in accordance with Good Laboratory Practices per 21CFR 58 and ISO 10993. The ProCol® bioprosthesis is classified by ISO 10993 as an implantable device, blood contact, C - long-term.

Results of the testing performed are summarized in Table 1. As there is a long history of use of glutaraldehyde fixed bovine tissue, and there was a history of use with the ProCol® device outside of the U.S., the sponsor did not conduct many of the recommended biocompatibility tests, such as sensitization, irritation, systemic toxicity, thrombogenicity, chronic toxicity or carcinogenicity. The results of the testing performed and other animal studies (described in the next section) suggested a biocompatible device.

TABLE 1: BIOCOMPATIBILITY STUDIES

TEST	TEST METHOD/EXTRACT	RESULT
Cytotoxicity – MEM Elution Method	60 sq cm test article placed in 20 mls MEM supplemented with 5% bovine serum, extracted at 37° C for 24 hours. MEM aliquot as negative control. Latex as positive control.	Intermediate toxicity after 72 hours was comparable to a control product.
Genotoxicity - Ames Test for Mutagenicity	Ames et. al (1975), modified to permit utilization of test article extracts (saline extract, incubated at 37° C for minimum 48 hours).	Test article was non-mutagenic.
Hemolysis – Direct Contact Method	1 gram test article placed in 5 ml 0.9% Sodium Chloride USP. 5 ml water and 0.1 ml blood as positive control. 5 ml 0.9 % Sodium Chloride USP and 0.1 ml blood as a negative control.	Test article was non-hemolytic.
Sensitization, Irritation, Systemic toxicity, Sub-chronic toxicity, Implantation, Coagulation	See animal and clinical study results.	No positive indications.

9.2 ANIMAL STUDIES

Objective: To verify functionality and healing characteristics of the ProCol® bioprosthesis in a canine model.

Methods: Thirteen animals received 6 mm bioprostheses as either descending aorta to vena cava shunts (Group 1, n=8), or descending aorta to iliac artery shunts (Group 2,

n=5). Four Group 1 animals were implanted with an earlier device model featuring a cloth covered graft. Angiography was performed at several postoperative intervals. Grafts were examined by physical examination and blood flow via cannulation at explant. Following explant, in situ examination, gross anatomical evaluation, and histological evaluation of the explanted graft was performed.

Results: The results are summarized in Table 2.

TABLE 2: ANIMAL STUDIES

ID #	Location	Date Implanted	Date of Sacrifice	Reason for sacrifice	Graft condition at sacrifice	Result
F45	Descending aorta to vena cava	11/8/83	5/29/84	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft
F85	Descending aorta to vena cava	11/16/83	11/20/83	Animal experienced non-graft related complications of surgery.	N/A - considered lost from study	N/A – Less than 6 months
F118	Descending aorta to vena cava	1/25/84	1/27/84	Animal expired	N/A – considered lost from study	N/A – Less than 6 months
F124	Descending aorta to vena cava	1/30/84	10/19/84	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft
F202	Descending aorta to vena cava	11/28/83	6/21/84	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft
F227	Descending aorta to vena cava	4/4/84	3/14/85	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft
F244	Descending aorta to vena cava	12/6/83	6/21/84	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft
F254	Descending aorta to vena cava	2/21/84	10/19/84	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft
D240	Descending aorta to iliac artery	4/23/84	6/12/84	Graft occluded	Occluded – technique related to postoperative leg position causing kinking	N/A – Less than 6 months
D248	Descending aorta to iliac artery	4/23/84	6/12/84	Graft occluded	Occluded – technique related to postoperative leg position causing kinking	N/A – Less than 6 months
D269	Descending aorta to iliac artery	7/23/84	3/14/85	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft
D274	Descending aorta to iliac artery	7/13/84	10/10/85	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft
D185	Descending aorta to iliac artery	7/31/85	11/13/86	≥6 months post implant	Patent	No significant inflammatory or foreign body response to graft

9.3 MECHANICAL TESTING

A summary of the mechanical testing conducted on the ProCol® Bioprosthesis is presented in Table 3. Testing was in substantive compliance with AAMI/ISO 7 198 (1998). The data demonstrates the mechanical properties of the ProCol® Bioprosthesis are suitable for its intended use for vascular access.

TABLE 3: MECHANICAL TESTING

DESCRIPTION OF TEST	SPECIMEN DESCRIPTION	RESULT
Visual Inspection	Finished device (Crosslinked vein with dissection and ligation processes completed). Inspection conducted prior to packaging and irradiation.	Product is 100% inspected. Device must conform to acceptance criteria documented in inspection procedures.
Leakage	Finished, irradiated device – identical to current models	Mean leakage per cm graft length per minute: 0.6 ml/cm graft length/min. (SD: 0.4 ml)
Pressurized Burst Strength	Finished, irradiated device –identical to current models	Mean burst: 381 mmHg (50.8 kPa) Standard Deviation: 59 mmHg (7.9 kPa)
Determination of Usable Length	The length of each presterile product is measured at a load of zero as a condition of release.	Product is 100% inspected. The measured length must be at least as long as the specified length.
Pressurized Internal Diameter	Finished product - irradiated device – fabric removed prior to testing making specimen identical to current model.	Mean internal diameter: 6.0 mm (Standard Deviation: 0.29 mm).
Wall Thickness	Finished product - irradiated device – fabric removed prior to testing making specimen identical to current model	Mean wall thickness: 0.48 mm (Standard deviation: 0.09 mm)
Suture Retention	Finished product - irradiated device – fabric removed prior to testing making specimen identical to current model.	Mean suture pullout: 1.61 lbs. (730g) Standard deviation. 0.33 lbs (150g).
Kink Radius	Finished product - irradiated device – identical to current model	Kink Radius: 16 mm Standard Deviation: 6.0 mm
Compliance	Finished product – irradiated – with fabric cover. At physiological pressure the device is not restricted by the fabric cover which has a larger diameter (8.5 mm). Therefore, results of this study are applicable to the device with or without the fabric cover.	Plot prepared to display compliance showed superior compliance to control devices.

9.4 ADDITIONAL STUDIES

This device contains no software or electrical components.

10. SUMMARY OF CLINICAL STUDIES

10.1 OBJECTIVES

This clinical study compared primary and secondary patency rates at one year and the overall incidence of postoperative complications for patients receiving the ProCol® Vascular Bioprosthesis as a vascular access graft to patients receiving standard synthetic vascular access grafts. All patients had at least one prior failed synthetic vascular access graft.

10.2 STUDY DESIGN

This multi-center (seven U.S. hospitals), non-randomized clinical study compared the access patency of the ProCol® Vascular Bioprosthesis (n=183) to the results of a concomitant control cohort subsequent to the loss of a previously placed synthetic vascular graft. The concomitant control cohort (n=93) were those subjects in whom vascular access was established with a synthetic access graft during the same implanting period as the treatment arm, by surgeons in the same center but not participating in the trial at the time of implant. Additionally, when the implant and abandonment dates were available for the ProCol® patient's prior failed graft (n=128), the secondary patency of the prior graft (internal control cohort) was compared to the secondary patency of the ProCol® cohort.

Efficacy was determined by primary and secondary patency of the ProCol® Vascular Bioprosthesis as compared to the concomitant control cohort and the internal control cohort (for secondary patency only). Primary patency was defined as any event that caused a loss of graft patency or required an intervention to the lumen of the graft. Secondary patency was the cumulative graft survival time from graft placement until the graft was considered no longer salvageable and deemed abandoned. Safety was measured by comparing the frequency of anticipated and unanticipated events of the ProCol® Vascular Bioprosthesis to the concomitant control cohort.

10.3 EVALUATION OF GENDER BIAS

Study inclusion and exclusion criteria were designed and the study was conducted in a manner to avoid gender bias in the subject population. A primary selection criterion in the study was identification of subjects with a prior failed synthetic access graft.

Table 4 displays the percentage of females to males enrolled in the study. Overall, more females were enrolled than males. This finding reflects the higher percentage of women than men having a prosthetic graft in the general population. However, the gender makeup was comparable between ProCol® and the concomitant control cohort.

10.4 DEMOGRAPHIC DATA

TABLE 4: PATIENT CHARACTERISTICS

Characteristic	ProCol®	Concomitant Control[1]	p-value[2]
Female	59.6%	59.1%	1
Hypertension	85.8%	90.2%	0.342
Diabetes	44.8%	54.3%	0.160
Hypercoagulation	20.2%	8.7%	**0.015**
African American	71.3%	75.0%	0.221
Number prior grafts	2.08 + 1.13	1.63 + 0.94	**<0.001**

[1] Concomitant control = commercially available synthetic graft: ePTFE (n=90), silicone (n=1), polyetherurethaneurea (n=2).

[2] Bold indicates statistical significance.

10.5 DATA ANALYSIS AND RESULTS

The total implant time represented in this study was 188.16 years (ProCol® bioprosthesis) and 91.68 years (concomitant control).

Patency Rates: The primary patency was not statistically different between the two cohorts. The secondary patency for the ProCol® Vascular Bioprosthesis was significantly higher per log rank (p=0.0361) than both the concomitant control and internal control cohorts. The Kaplan-Meier patency rates for primary and secondary patency are presented in Table 5.

TABLE 5: KAPLAN-MEIER GRAFT SURVIVAL RATES FOR HEMODIALYSIS ACCESS

Study Cohort		Total (n)	Primary Patency			Secondary Patency		
			6 mo.	12 mo.	24 mo.	6 mo.	12 mo.	24 mo.
Concomitant control	Synthetic redo graft	93	44%	28%	16%	70%	56%	45%
Internal control	Study patient's prior synthetic graft	128	-----	------		48%	34%	18%
ProCol® Cohort [1]	Redo grafts	183	45%	36%	22%	75%	66%	60%
DOQI-goal[2] Both first time and redo arteriovenous access grafts		-----	-----	-------			**70%**	

[1] Secondary patency significant at Log-rank p<0.0361, for all grafts in intention to treat analysis.

[2] DOQI-goal stated in National Kidney Foundation-Dialysis Outcomes Quality Initiative Guideline 36.

Complication Rates: Complications observed in the study are described in Table 6. The linearized rate of moderate events was lower in the ProCol® cohort with a rate of 1.2 events/graft year compared to a rate of 2.0 events/graft year in the concomitant control group. The rates of infection and thrombosis were significantly lower with the ProCol® Vascular Bioprosthesis than with the concomitant control, as was the rate for seroma. The rate for technical complication was significantly higher in the ProCol® cohort. Interventions to restore or maintain patency were performed at a rate of 1.3743/year (concomitant control) compared to 0.9726/year for the ProCol cohort (p=0.0031).

TABLE 6: COMPLICATIONS REQUIRING AN INTERVENTION OR LOSS OF GRAFT PATENCY

Complication	ProCol® (n=183 grafts)			Control (n=93 grafts)			Cox[2] P-value
	# Event	# Grafts with Event	Event Rate[1] (#/graft year)	# Event	# Grafts with Event	Event Rate[1] (#/graft year)	
Subject Related							
Bleeding	3	3	0.0159	4	2	0.0436	0.1767
Steal	3	3	0.0159	2	2	0.0218	0.6963
Swelling	20	12	0.1063	9	4	0.0982	0.8609
Wound Healing	7	7	0.0372	0	0	0.0000	0.0327
Total Subject Related	3		0.02	6		0.07	
Technique Related							
Invasive Radiology	4	4	0.0213	3	3	0.0327	0.5504
Dialysis Cannulation Trauma	19	18	0.1010	8	6	0.0873	0.7456
Technical Complication[3]	10	10	0.0531	0	0	0.00	**0.0086**
Total Technique	21		0.14	4		0.05	
Graft Involved							
High Venous Pressure	13	10	0.09	6	6	0.07	0.686
Low Flow	4	4	0.03	0	0	0.00	0.100
Dilatation	6	6	0.0319	0	0	0.00	0.0515
Infection	10	8	0.0531	18	15	0.1963	**0.006**
Kinking	3	3	0.0159	1	1	0.0109	0.7958
Pseudoaneurysm	3	3	0.0159	5	3	0.0545	0.0814
Seroma	0	0	0.0000	6	4	0.0654	**0.0004**
Thrombosis	133	93	0.7068	124	59	1.3525	**<.0001**
Total Graft Involved	161	---	1.06	148	---	1.71	
Total Moderate Events	221	128	1.1745	180	74	1.9633	<0.0001
Repeat Thrombosis[4]	36	25	0.9726	65	31	1.3743	**0.0031**

[1] Event Rate = Events / Graft Year. Total time: ProCol® = 152.53 years; Control = 86.76 years.

[2] Cox F-Test: compares total number of events. Bold indicates statistical significance.

[3] Technical events: Anastomosed to known diseased vessel (3); graft physically compressed (3); sizing (1); implant technique (1); and radiology infiltrated graft (1).

[4] Repeat Thrombosis: Total Time- ProCol=33.55 years; Control=25.76 years. Events in thrombosis tally.

TABLE 7: RELATIVE RISK OF EVENTS INVOLVING AN INTERVENTION OR LOSS OF PATENCY IN A HIGH-RISK POPULATION

Event	ProCol® Event Rate #/graft year (Confidence interval[2])	Control Event Rate #/graft year (Confidence interval)	Relative Risk[1] (ProCol® = 1)
Infection	0.053 (0.087)	0.196 (0.285)	3.70
Thrombosis	0.707 (0.813)	1.353 (1.564)	1.91
Total Complications	1.175 (1.310)	1.963 (2.216)	1.67
Total Interventions	0.973 (1.097)	1.374 (1.588)	1.41
Abandonment: Infection	0.027 (0.052)	0.120 (0.192)	4.51
Abandonment: Thrombosis	0.128 (0.176)	0.295 (0.400)	2.31
Graft Abandonment (all)	0.324 (0.398)	0.502 (0.635)	1.55

[1] Relative risk: the occurrence of events observed in the concomitant control divided by the rate observed in the ProCol® cohort and suggests the higher frequency the event will occur.

[2] 95% Upper confidence limit for linearized rate.

11. CONCLUSIONS DRAWN FROM STUDIES

The data established that the ProCol® Vascular Bioprosthesis is suitable for its intended use for vascular access subsequent to one or more previously failed prosthetic access graft(s). The ProCol® Vascular Bioprosthesis was successfully used for vascular access in a high-risk population. Secondary patency results achieved with ProCol® Vascular Bioprosthesis approached the National Kidney Foundation-Dialysis Outcomes Quality Initiative goal of 70% at 12 months with lower complication and intervention rates than a concurrent concomitant control cohort implanted with synthetic vascular grafts.

12. PANEL RECOMMENDATION

In accordance with the provisions of section 515©(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 this panel and the FDA.

13. CDRH DECISION

The results from the preclinical and clinical data provide reasonable assurance the ProCol® device is safe and effective for patients who already have at least on failed prosthetic access graft. The preclinical data demonstrate that the device is biocompatible, and possesses the mechanical and physical strength necessary for an access indication. The applicant's manufacturing facility was inspected and found to be in compliance with the Quality System Regulation (21 CFR 820). CDRH issued an approval order on July 29, 2003.

14. APPROVAL SPECIFICATIONS

Directions for use: See the labeling

Postapproval Requirements and Restrictions: See approval order

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