SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Tissue Adhesive
Device Trade Name:	DERMABOND (a formulation of 2-octyl cyanoacrylate)
Applicant's Name and Address:	CLOSURE Medical Corporation (CLOSURE) 5265 Capital Boulevard Raleigh, NC 27616
Premarket Approval Application (PMA) Number:	P960052
Date of Panel Recommendation:	January 30, 1998
Date of GMP Inspection:	November 3, 1997
Date of Notice of Approval to the Applicant:	August 26, 1998
Expedited Review:	Expedited review was granted on December 12, 1996 based on the potential public health benefit from reducing patient pain and anxiety related to the closure of low tension lacerations.

II. INDICATIONS FOR USE

DERMABOND Topical Skin Adhesive is intended for topical application to hold closed easily approximated skin edges from surgical incisions, including punctures from minimally invasive surgery, and simple, thoroughly cleansed, trauma-induced lacerations. DERMABOND may be used in conjunction with, but not in place of, subcuticular sutures.

III. DEVICE DESCRIPTION

DERMABOND is a sterile, liquid tissue adhesive containing a monomeric (2-octyl cyanoacrylate) formulation and the colorant D & C Violet #2. It is provided in a single-use applicator packaged in a blister pouch. The applicator is comprised of a crushable glass ampule contained within a plastic vial with attached applicator tip. As manufactured, a chemical initiator is incorporated into the tip applicator. As applied to the skin, the liquid adhesive is slightly more viscous than water and polymerizes within minutes.

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Within approximately one minute of removal of the applicator tip from normally dry skin, DERMABOND polymerizes and develops enough strength to hold the wound edges together without manual approximation. Full mechanical strength of the adhesive film is achieved in approximately 2.5 minutes following application. Once formed as an adhesive film, DERMABOND is flexible and provides continuous approximation of the wound edges for 5-10 days. DERMABOND is not absorbed by the skin or underlying tissue. DERMABOND sloughs from the wound as re-epithelialization of the skin occurs (typically 5-10 days).

IV. CONTRAINDICATIONS

DERMABOND adhesive is contraindicated for use on any wounds with evidence of active infection, gangrene, or wounds of decubitus etiology.

DERMABOND adhesive is contraindicated for use on mucosal surfaces or across mucocutaneous junctions (e.g., oral cavity, lips), or on skin which may be regularly exposed to body fluids or with dense natural hair (e.g., scalp).

DERMABOND adhesive is contraindicated for use on patients with a known hypersensitivity to cyanoacrylate or formaldehyde.

Precautions and Warnings can be found in the labeling.

V. ALTERNATIVE PRACTICES AND PROCEDURES

There are a limited number of medical devices to surgically close skin wounds from surgical incisions or traumatic lacerations. Nonabsorbable monofilament sutures have traditionally been used to suture together and hold in apposition the edges of the skin. The sutures are to remain in place until there is sufficient epithelialization to prevent wound dehiscence. The sutures must then be removed and the wound continues to heal. In recent decades, removable skin staples and strip-type adhesive wound closures (narrow strips of fabric or polymeric material with adhesive backing) have come into clinical practice.

VI. POTENTIAL ADVERSE EFFECTS

Adverse reactions encountered during the clinical study:

Clinical Study Outcomes	***No Subcuticular Sutures***		***With Subcuticular Sutures***	
	DERMABOND	Control	DERMABOND	Control
	N (%)	N (%)	N (%)	N (%)
Accounting				
N, patients enrolled	240	243	167	168
N, patients treated	239	242	167	166
Patients completed	228 (95%)	215 (88%)	164 (98%)	162 (97%)
Adverse Reactions:				

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*Suspected Infection**	8 (3.6%)	2 (0.9%)	6 (3.6%)	2 (1.2%)
Wound type				
# Lacerations	8	2	1	0
# Incisions	0	0	5	2
Dehiscence with Need for Retreatment	6 (2.5%)	5(2.1 %)	3(1.8%)	0
Acute Inflammation				
Erythema	26 (11.5%)	74 (33.0%)	52 (31.3%)	75 (45.1%)
Edema	22 (9.7%)	28 (12.5) %	62 (37.3%)	71 (42.8%)
Pain	14 (6.1%)	13 (5.8%)	56 (33.7%)	57 (34.3%)
Warmth	3 (1.3%)	6 (2.6%)	3 (1.8%)	4 (2.4%)

*In the clinical study, presence of infection was to be identified by observation of redness more than 3-5 mm from the repaired wound, swelling, purulent discharge, pain, increased skin temperature, fever, or other systemic signs of infection. Confirmatory culture was not routinely obtained (See Clinical Study). Example: a 7 year old boy struck in the head with a bat sustained an eyebrow laceration which was closed with DERMABOND without wound irrigation or other cleansing, and developed cellulitis the next day which progressed to peri-orbital abscess requiring emergent surgical incision and drainage. Cultures grew B - hemolytic streptococcus. Among cases of suspected infection for DERMABOND, 7/14 (50%) were in patients less than 12 years old with traumatic lacerations; overall, 8 of the 14 (approximately 60%) of DERMABOND wounds with suspected infections were associated with sub-optimal cosmetic outcome.

- Reactions may occur in patients who are hypersensitive to cyanoacrylate or formaldehyde. See CONTRAINDICATIONS.
- The polymerization of DERMABOND adhesive on the skin releases small amounts of heat which may cause a sensation of heat or discomfort in some patients.
- Adverse reactions may be experienced following DERMABOND contact with the eye.

VII. MARKETING HISTORY

DERMABOND was granted the CE mark for commercial distribution throughout the European Community (EC) on August 20, 1997. DERMABOND Sales have commenced in Germany, France, Italy, and the United Kingdom. DERMABOND has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. SUMMARY OF PRECLINICAL STUDIES

The following preclinical data, information and reports related to the safety and effectiveness of this device are described in this PMA:

- biocompatibility testing (including cytotoxicity, sensitization, irritation/intracutaneous reactivity, eye irritation, acute systemic, subchronic systemic, genotoxicity, implantation, hemocompatability, and pyrogenicity studies)
- laboratory animal testing (adhesion and tensile strength

Batteries of *in vitro* and *in vivo* biocompatibility tests were performed on DERMABOND and another formulation of 2-OCA. The other formulation of 2-OCA is a product for CLOSURE Medical Corporation that has been cleared by FDA for oral application in dentistry which received FDA clearance for marketing through the premarket notification process. This alternate formulation of 2-OCA in is very similar to that of DERMABOND and FDA believes that the preclinical data on the alternate formulation is relevant to the assessment of the safety and effectiveness of DERMABOND. A wide range and number of animals were used in these studies: 15-40 guinea pigs, 2-30 rabbits, 10-30 mice, 3 pigs, and 32-50 rats. Collectively, the biocompatibility studies for these two formulations of 2-OCA constitute the relevant information base for evaluating the biocompatibility of DERMABOND, tabulated below.

Type of Test	Alternate Formulation of 2-OCA	DERMABOND
Cytotoxicity	X	X
Sensitization	X	X
Irritation/Intracut. Reactivity	X	X
Eye Irritation	X	X
Acute Systemic	X	X
Subchronic Systemic	X	
Genotoxicity	X	
Implantation	X	X
Hemocompatibility	X	
Pyrogenicity	X	

CYTOTOXICITY

Cytotoxicity testing of DERMABOND included an Agar Overlay Assay to determine the biocompatibility with mammalian cells (mouse L-929) and an MEM Elution Assay to determine the cytotoxicity of an extract prepared from the polymerization of DERMABOND in Minimum Essential Medium (MEM), where films of polymerized DERMABOND were extracted in medium at 37°C for 24 hours. The conclusion for these tests is that DERMABOND is not cytotoxic when evaluated in mouse fibroblast L-929 cells in the MEM Elution Assay nor in the Agar Overlay Assay.

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SENSITIZATION

Sensitization testing included the following three tests:

1) Dermal Sensitization Study of DERMABOND in Guinea Pigs - Maximization Test, where a saline extract of the DERMABOND formulation (extracted according to ISO guidelines) was evaluated for its sensitization potential in the Kligman-Magnusson procedure.

2) Dermal Sensitization Study of 2-Octyl Cyanoacrylate Formulation in Guinea Pigs - Maximization Test, where a saline extract prepared from the polymerization of the alternate formulation of 2-OCA was evaluated for its sensitization potential in the Kligman-Magnusson procedure.

3) Evaluation of the Sensitization Potential of 2-Octyl Cyanoacrylate Formulation, where 2-OCA monomer in the liquid formulation of the alternate formulation of 2-OCA was evaluated for its sensitization potential in hairless guinea pigs. The conclusions of these tests were that neither the extract of DERMABOND nor the extract of the alternate 2-OCA formulation is considered to be a skin sensitizer in guinea pigs when evaluated in the Kligman-Magnusson procedure. However, the alternate formulation of 2-OCA exhibited a weak sensitizing response when evaluated in the hairless guinea pig model. A clear sensitization response was not produced.

IRRITATION / INTRACUTANEOUS REACTIVITY

The Irritation/Intracutaneous reactivity tests include the following three tests:

1) Acute Intracutaneous Test in Rabbits of DERMABOND, where rabbits received an intracutaneous injection of a saline extract prepared from the polymerization of DERMABOND.
2) Acute Intracutaneous Test in Rabbits of Formulated 2-OCA, where the local tissue reaction following intracutaneous injection in rabbits of a saline extract prepared from the polymerization of the alternate formulation of 2-OCA was evaluated.

3) Acute Intracutaneous Test in Rabbits of Formulated 2-OCA, where the local tissue reaction following intracutaneous injection in rabbits of a cottonseed oil extract prepared from the polymerization of the alternate formulation of 2-OCA was evaluated. The conclusions of these tests were that neither DERMABOND nor the alternate 2-OCA formulation are irritating when saline extracts are injected intracutaneously into rabbits. Cottonseed oil extract of polymerized 2-OCA formulation produced no greater irritation than that observed with the oil blank.

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EYE IRRITATION

Primary Eye irritation studies included evaluating: the eye irritancy potential of a saline extract of DERMABOND polymer when instilled into the eyes of rabbits, the eye irritancy potential of DERMABOND when placed directly on the eyes of rabbits followed by washing of the eye, and the eye irritancy potential of DERMABOND when placed directly on the eyes of rabbits without washing of the eye. A study was also conducted to evaluate the eye irritancy potential of a saline extract prepared from the polymerization of the alternate formulation of 2-OCA when instilled into the eyes of rabbits. The conclusions from these tests were that neither the saline extract of the alternate formulation of 2-OCA nor the saline extract of DERMABOND polymer is an eye irritant. DERMABOND application to the eye, and DERMABOND application followed by a one minute rinse, resulted in no damage to the eye, but produced mild irritation to the conjunctiva by indirect contact.

ACUTE SYSTEMIC TOXICITY

The following Acute Systemic Injections Tests were conducted:

1) Systemic Injection Test in Mice of DERMABOND, where a saline extract prepared from the polymerization of DERMABOND was administered intravenously and intraperitoneally to mice to determine if the material is toxic.

2) The same tests were applied using a saline extract prepared from the polymerization of the alternate formulation of 2-OCA.

3) An intravenous injection of both DERMABOND and the alternate formulation of 2-OCA was given to determine toxicity as well.

4) Systemic Injection Test in Mice of Formulated 2-OCA, where a cottonseed oil extract prepared from the polymerization of the alternate formulation of 2-OCA was administered intraperitoneally to mice. The conclusions from these tests were that DERMABOND does not exhibit acute system toxicity when saline extracts are administered intravenously or intraperioneally to mice, and neither the saline extract of the DERMABOND or the Formulated 2-OCA polymers were toxic following intravenous injection in mice. The alternate 2-OCA formulation, does not exhibit acute systemic toxicity when saline extracts are administered intravenously or intraperitonally to mice nor does it exhibit acute systemic toxicity when cottonseed oil extracts are administered intraperitoneally to mice.

SUBCHRONIC SYSTEMIC TOXICITY

The Subchronic Systemic Toxicity Tests consisted of:

1) 2-Week Oral Gavage Range-Finding Study with 2-Octyl Cyanoacrylate formulation in Rats, where five groups of 5 male and 5 female rats, approximately seven weeks old at start of treatment, received 0, 250, 500, 1000, and 2000 mg/kg/day

of powder prepared from the polymerization of the alternate formulation of 2-OCA, suspended in corn oil, by daily oral gavage for two weeks.

2) 4-Week Oral Gavage Toxicity Study with 2-Octyl Cyanoacrylate Formulation in Rats, where four groups of 10 male and 10 female rats, approximately 40 days old at start of treatment, received 0, 125, 250, and 500 mg/kg/day of powder prepared from polymerization of the alternate formulation of 2-OCA, suspended in corn oil, by daily oral gavage for four weeks. The conclusions were that the dose of 500 mg/kg/day in the 2-week study of powder prepared from polymerization of 2-OCA formulation, The alternate formulation of 2-OCA, was a clear no effect level. The dose of 500 mg/kg/day in the 4-weeek study was a clear no toxic effect level. Therefore, even the repeated oral ingestion of powder prepared from polymerization of the alternate 2-OCA formulation at doses far in excess of those conceivably encountered by humans, is not likely to result in leachables or degradation products that represent a toxic hazard to patients.

GENOTOXICITY

The genotoxicity studies consisted of:

1) Salmonella/Mammalian-Microsome Mutagenesis Assay (Ames Test) with 2-Octyl Cyanoacrylate Formulation in Rats, where an acetone solution of dissolved powder prepared from polymerization of the alternate formulation of 2-OCA was evaluated for its ability, in the presence and absence of mammalian microsomal enzymes, to induce reverse mutations at the histidine locus in the genome of several strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537, and TA1538).

2) Mutagenicity Test with 2-Octyl Cyanoacrylate Formulation in a Cytogenicity Study: Chinese Hamster Ovary (CHO) Cells In Vitro, where an acetone solution of dissolved powder prepared from polymerized 2-OCA was evaluated for its ability to induce chromosomal aberrations in Chinese hamster ovary cells with and without metabolic activation.

3) Test for Chemical Induction of Mutation in Mammalian Cells in Culture with 2-Octyl Cyanoacrylate Formulation: The L5178Y TK+/- Mouse Lymphoma Assay, where an acetone solution of dissolved powders from polymerization of 2-OCA to induce mutations at the thymidine kinase (TK) locus in the mouse lymphoma L5178Y cell line.

4) Mutagenicity Test on Saline Extract of 2-Octyl Cyanoacrylate Formulation Measuring Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells, where a saline extract prepared from polymerization of 2-OCA was evaluated for its ability to induce chromosomal aberrations in Chinese hamster ovary cells with and without metabolic activation. The conclusions were that the acetone solution of powder prepared from polymerization of the alternate 2-OCA formulation was negative in the Ames Salmonella bacterial assay when conducted both with and without metabolic

activation and the induction of chromosomal aberrations in the CHO cells. The acetone solution of powder prepared from polymerization of the alternate 2-OCA formulation was negative for the induction of mutations at the TK locus in L5178Y mouse lymphoma cells either in the presence or absence of metabolic activation. The saline extract of 2-OCA formulation was negative for the induction of chromosomal aberrations in the CHO cells.

IMPLANTATION

The implantation tests consisted of the following:

1) Implantation Test of DERMABOND in Rabbits, where local tissue reaction to formed DERMABOND implanted directly into the muscle of rabbits for seven days was evaluated. Necropsy observations were unremarkable and the implanted samples were not encapsulated. Histological observations consisted of an acute inflammatory reaction accompanied by myofiber degeneration, hyperplasia of myofiber nuclei, lymphoplasmacytic and macrophage infiltration and mineralization. These changes were comparable between the DERMABOND and USP standard samples. The formed DERMABOND, following implantation into the muscle of rabbits, resulted in a mild degree of inflammatory reaction that was comparable to that which resulted from the implantation of the USP reference standard. Therefore, no significant adverse effects were attributed to the polymer.

2) Fourteen Day Pilot Implant Study to Evaluate the Irritation Potential of a 2-Octyl Cyanoacrylate Formulation, where tissue reaction to the polymerization and presence of the alternate formulation of 2-OCA® placed directly into the muscle of rabbits for fourteen days was evaluated. The 2-OCA formulation following implantation into the muscle of rabbits for 14 days, resulted in a mild degree of inflammatory reaction that was somewhat greater than that which resulted from the implantation of the USP reference negative control plastic. However, even with the slightly increased reaction, no degenerative changes were noted. Therefore, no significant adverse effects were attributed to the 2-OCA formulation.

3) Ninety Day Implant Study to Evaluate the Irritation Potential of a 2-Octyl Cyanoacrylate Formulation, where tissue reaction to the polymerization and presence of the alternate formulation of 2-OCA® placed directly into the muscle of rabbits for ninety days was evaluated. The 2-OCA formulation, following implantation into the muscle of rabbits for 90 days, resulted in a mild degree of inflammatory reaction (typical for foreign body responses) that was somewhat greater than that which resulted from the implantation of the USP reference negative control plastic. However, even with the slightly increased reaction, no degenerative changes were noted. Therefore, no significant adverse effects were attributed to the 2-OCA formulation.

HEMOCOMPATIBILITY AND PYROGENICITY

Hemocompatibility and pyrogenicity testing consisted of:

1) In Vitro Hemolysis Study with 2-Octyl Cyanoacrylate Formulation in Rabbit Whole Blood, where saline extracts prepared from the polymerization of the alternate formulation of 2-OCA were evaluated to determine if they contain hemolysins.

2) Pyrogen Study in Rabbits of Formulated 2-OCA, where the potential for a saline extract prepared from the polymerization of the alternate formulation of 2-OCA polymer was evaluated for its ability to produce a pyrogenic response when administered intravenously to rabbits. The conclusions were that the saline extract of 2-OCA formulation was not pyrogenic and was negative for hemolytic activity.

CONCLUSIONS REGARDING BIOCOMPATIBILITY

Under the conditions of its intended use, these biocompatibility studies of DERMABOND and the alternate formulation of 2-OCA suggest that DERMABOND does not raise any significant biocompatibility concerns.

LABORATORY ANIMAL TESTING

Three nonclinical studies were conducted to characterize and evaluate the wound closure attributes and associated tensile strength of the DERMABOND . The studies were conducted in juvenile pig and rat model systems. The juvenile pig model was chosen due to the juvenile pig's skin being similar to human skin with regard to skin closure techniques. The rat model lent itself to biomechanical quantification.

1) A Comparative Study of the Efficacy of DERMABOND and 5-0 Nylon Suture in Closing Skin Incisions in the Pig, where rates of wound dehiscence for DERMABOND and 5-0 nylon sutures in the closing of skin incisions in the pig were compared. Three female pigs were used. In each animal, six vertical skin incisions, 2.5 cm in length and 5 mm in depth, were made two inches apart on each side of the back. The incisions were then closed either by suturing or by applying one of the two adhesives. Animals were observed for ten days after surgery. The animals were then sacrificed and the incision sites preserved for possible future examination. The study conclusion was that the animals appeared normal throughout the observation period, and wound dehiscence was not observed among sites closed with DERMABOND or sutures.

2) The Role of DERMABOND Topical Surgical Skin Adhesive in Linear Incision Wound Healing: A Biomechanical and Histopathological Evaluation, where the biomechanical strength of wounds closed with DERMABOND and currently marketed skin closure devices were evaluated. Male Sprague-Dawley rats were anesthetized and divided into three groups. In each animal, two longitudinal skin full thickness incisions, 2.5 cm in length, were made on each dorsolateral flank. The incisions were then closed either by suturing (three 5-0 nylon interrupted sutures),

by applying three strip-type adhesive wound closures (or "Steri-Strips"), or by applying DERMABOND. One group of animals was observed for seven days after surgery, and a second group for fourteen days. Ten (10) animals per group were then prepared for biomechanical analysis. The incision sites of animals (6 per group) that did not undergo biomechanical tests were subjected to histopathological examination. The same evaluations were carried out for both the seven day and the fourteen day groups. The study conclusions were that incision wounds closed with DERMABOND had wound strengths comparable to those seen with sutures and "Steri-Strips" at both seven and fourteen days. The histopathological characteristics of wound healing were comparable between the three methods of wound closure. Additionally, wounds closed with DERMABOND showed wound strength characteristics of healing that were comparable to those seen with sutures or adhesive (strip) wound closures at both the seven and fourteen day intervals.

3) A Evaluation of the Acute Incisional Strength with DERMABOND Surgical Tissue Adhesive Wound Closure, where the biomechanical strength of wounds within one hour of closure with DERMABOND, under various application techniques, or currently marketed skin closure devices were evaluated. Male Sprague-Dawley rats were divided into groups of 10 animals each: Group A animals were to receive one stroke of DERMABOND; Group B animals were to receive 5-0 sutures; Group C animals were to receive 6-0 sutures; Group D animals were to receive multiple strokes of DERMABOND; Group E animals were to receive minimal surface exposure with DERMABOND. In each animal, two longitudinal skin incisions were made on each dorsolateral flank. The incisions were then closed either by suturing or by applying DERMABOND. The animals were then prepared for biomechanical analysis at time intervals up to one hour after surgery.

The conclusions were that the biomechanical analysis demonstrated that wounds closed with DERMABOND reached maximum strength after 2.5 minutes and remained constant for up to the one hour time point. DERMABOND wound strengths at one hour were somewhat lower than for sutures, but DERMABOND showed wound strength that was at an optimum when multiple strokes of the adhesive were applied.

CONCLUSIONS REGARDING EFFECTIVENESS IN ANIMAL TEST MODELS

These studies contributed to the development of test methodology for wound closure devices and demonstrated DERMABOND performance with respect to: biomechanical strength as a topical tissue adhesive for closure of skin wound, setting time under application conditions, and application technique. Furthermore, these studies demonstrated that DERMABOND in the animal models performs comparably with sutures and strip-type adhesive wound closures.

IX. SUMMARY OF CLINICAL INVESTIGATIONS

Description: A prospective, randomized, controlled, unmasked study was conducted to evaluate the safety and effectiveness of closing the approximated skin edges of surgical incisions, including punctures from minimally invasive surgery, trauma-induced lacerations using

DERMABOND in comparisons to USP size 5-0 or smaller suture, adhesive strips or staples, with or without dermal closure (subcuticular suture) as per investigator judgment.

Summary of Effectiveness Results Comparing DERMABOND to Sutures (U.S.P. size 5-0 and smaller diameter), Staples, and Adhesive Strips

Clinical Study Outcomes	*NSS*		*WSS*	
	DermaBond	Control	DermaBond	Control
	N (%)	N (%)	N (%)	N (%)
N, patients enrolled	240	243	167	168
N, patients treated	239	242	167	166
Patients completed	228 (95%)	215 (88%)	164 (98%)	162 (96%)
N, control: suture/strips/staples/ Missing		194/46/1/1		116/45/5/0
Wound Closure Assessment				
Immediate: Additional Devices	18 (7.5)	13 (5.4)	2 (1.2)	11 (6.6)
@ 5-10 days: 100% epidermal apposition	169 (75.1%)	199 (88.8%)	140 (84.3%)	160 (96.4%)
>50% epidermal apposition	205 (91.1%)	214 (95.5%)	163 (98.2%)	(165 (99.4%)
@ 3 months: Cosmesis Score*= 0 (optimal)	188 (82.5%)	180 (83.7%)	128 (78.0%)	128 (79.0%)
Median Time for Treatment (Minutes)	1.5	6.0	1.3	2.9

*** Cosmesis: modified Hollander Cosmesis Scale**

1. Step off borders: edges not in same plane? yes / no
2. Edge inversion: edges sink or curl? yes / no
3. Contour irregularities: wrinkle or pucker near wound? yes / no
4. Excessive *inflammation*: redness, swelling, discharge? yes / no
5. Wound margin separation: gap between edges? yes / no
6. Overall Appearance: poor / good?

The study population included patients at least one year of age, in good general health, who signed informed consent and agreed to follow-up visits. Patients were excluded if presenting with: significant multiple trauma, peripheral vascular disease, insulin dependent diabetes mellitus, blood clotting disorder, keloid formation or hypertrophy history (patient or family), cyanoacrylate or formaldehyde allergy, burst or stellate lacerations due to crush or hard blow, animal or human bite, and decubitus ulcer. Follow-up was at 5-10 days and at 3 months. All wounds were assessed by visual inspection at 5-10 days after wound closure: 100% apposition, 50% to 99% epidermal apposition, <50% epidermal apposition, <50% dehiscence, and >50% dehiscence. See Adverse Reactions section for definition of infection.

If the primary method of closure was insufficient for closure, an additional securing device was placed. The time to perform treatment included the time required later to remove the closure device when applicable.

The following tables summarize pertinent aspects of the study:

TABLE 1 PATIENT DEMOGRAPHICS

Patient Demographics	NSS				WSS			
	Treatment	Control			Treatment	Control		
	DermaBond	Sutures	Strips	Staples	DermaBond	Sutures	Strips	Staples
# patients	239	194	46	1	167	116	45	5
Age (A; years old)								
Mean	25.1	19.8	32.3	24.0	41.4	40.0	52.2	27.8
SD	19.82	19.15	9.69	-	18.97	17.94	17.73	15.66
# of < 19 year old patients	105 (43.9%)	116 (59.8%)	2 (4.4%)	0 (0.0%)	18 (10.8%)	14 (12.1%)	0 (0.0%)	1 (20.0%)
Gender (G: male)	118 (49.4%)	115 (59.3%)	6 (13.0%)	1 (100.0%)	98 (58.7%)	42 (36.2%)	43 (95.6%)	5 (100.0%)
Race (R)								
White	164 (68.6%)	156 (80.4%)	18 (39.1%)	0 (0.0%)	123 (73.7%)	96 (82.8%)	27 (60.0%)	1 (20.0%)
Black	51 (21.3%)	16 (8.3%)	27 (58.7%)	0 (0.0%)	15 (9.0%)	10 (8.6%)	3 (6.7%)	3 (60.0%)
Other	24 (10.0%)	22 (11.4%)	1 (2.2%)	1 (100.0%)	29 (17.4%)	10 (8.6%)	15 (33.3%)	1 (20.0%)

Note: This table shows patient characteristics for each treatment method.

TABLE 2 WOUND DIMENSIONS

Wound Dimensions (WD)	NSS				WSS			
	Treatment	Control			Treatment	Control		
	DermaBond	Sutures	Strips	Staples	DermaBond	Sutures	Strips	Staples
# patients	239	194	46	1	167	116	45	5
mean length, range, cm	1.5 (n=239)	1.4 (n=194)	1.9 (n=46)	2.0 (n=1)	3.2 (n=167)	1.8 (n=116)	6.0 (n=45)	10.5 (n=5)
mean depth, mm	5.7 (n=230)	2.4 (n=184)	19.8 (n=46)	4.0 (n=1)	3.5 (n=167)	4.4 (n=115)	2.1 (n=44)	15.0 (n=5)
mean width, mm	2.5 (n=230)	2.8 (n=184)	1.2 (n=46)	2.0 (n=1)	5.3 (n=166)	6.4 (n=115)	1.1 (n=45)	17.6 (n=5)

Note: This table shows wound dimensions for each treatment method.

TABLE 3 PROCEDURES CONDUCTED PER WOUND

Procedure/Wound (P/W)	NSS				WSS			
	Treatment	Control			Treatment	Control		
	DermaBond	Sutures	Strips	Staples	DermaBond	Sutures	Strips	Staples
# patients	239	194	46	1	167	116	45	5
*Lacerations***								
Jagged	36 (21.4%)	27 (16.9%)	2 (22.2%)	0 (0.0%)	6 (31.6%)	5 (29.4%)	0 (0.0%)	0 (0.0%)
Smooth	132 (78.6%)	133 (83.1%)	7 (77.8%)	1 (100%)	13 (68.4%)	12 (70.6%)	0 (0.0%)	1 (100%)
*Incisions****								
Excisions	33 (46.5%)	33 (97.1%)	0 (0.0%)	0 (0.0%)	70 (47.3%)	74 (74.8%)	0 (0.0%)	0 (0.0%)
MIS	38 (53.5%)	0 (0.0%)	37 (100%)	0 (0.0%)	20 (13.5%)	19 (19.2%)	2 (4.4%)	3 (75.0%)
Other	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	58 (39.2%)	6 (6.1%)	43 (95.6%)	1 (25.0%)

**Percentages based on lacerations only.
***Percentages based on incisions only.

Note: This table shows types of wounds treated for each treatment method.

TABLE 4 BODY LOCATION

Body Location (BL)	NSS				WSS			
	Treatment	Control			Treatment	Control		
	DermaBond	Sutures	Strips	Staples	DermaBond	Sutures	Strips	Staples
# patients	239	194	46	1	167	116	45	5
Face	92 (38.5%)	84 (43.3%)	1 (2.2%)	0 (0.0%)	45 (27.0%)	40 (34.5%)	0 (0.0%)	0 (0.0%)
Torso	44 (18.4%)	5 (2.6%)	37 (80.4%)	0 (0.0%)	73 (43.7%)	29 (25.0%)	44 (97.8%)	2 (40.0%)
Hands	50 (20.9%)	33 (17.0%)	6 (13.0%)	0 (0.0%)	9 (5.4%)	12 (10.3%)	1 (2.2%)	0 (0.0%)
Neck	15 (6.3%)	20 (10.3%)	0 (0%)	0 (0.0%)	8 (4.8%)	12 (10.3%)	0 (0.0%)	0 (0.0%)
Eyes	15 (6.3%)	31 (16.0%)	0 (0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ears	2 (0.9%)	3 (1.6%)	0 (0%)	0 (0.0%)	11 (6.6%)	7 (6.0%)	0 (0.0%)	0 (0.0%)
Other	21 (8.8%)	18 (9.3%)	2 (4.4%)	1 (100.0%)	20 (12.0%)	16 (13.8%)	0 (0.0%)	3 (60.0%)

Note: This table shows body locations treated for each treatment method.

TABLE 5 WOUND DEPTH

Wound Depth	NSS				WSS			
	Treatment	Control			Treatment	Control		
	DermaBond	Sutures	Strips	Staples	DermaBond	Sutures	Strips	Staples
# patients	239	194	46	1	167	116	45	5
# wounds < 2 mm deep	68 (29.6%)	62 (33.7%)	3 (6.5%)	0 (0.0%)	60 (35.9%)	15 (13.0%)	43 (97.7%)	0 (0.0%)
# wounds ≥ 2 mm deep	162 (70.4%)	122 (66.3%)	43 (93.5%)	1 (100 %)	107 (64.1%)	100 (87.0%)	1 (2.3%)	5 (100.)%

Note: This table shows distribution of wound depth for each treatment method.

TABLE 6 WOUND LOCAL ANESTHETIC USE

Wound Local Anesthetic (LA) use	NSS				WSS			
	Treatment	Control			Treatment	Control		
	DermaBond	Sutures	Strips	Staples	DermaBond	Sutures	Strips	Staples
# patients	239	194	46	1	167	116	45	5
% patients with LA use	99 (41.4%)	192 (99.0%)	39 (84.8%)	0 (0.0%)	134 (80.2%)	106 (91.4%)	29 (64.4%)	1 (20.0%)

Note: This table shows the percent of patients who received local anesthetic for each treatment method.

TABLE 7 OUTCOME BY GENDER (MALE)

Gender = male	NSS				WSS			
	Treatment	Control			Treatment	Control		
	DermaBond	Sutures	Strips	Staples	DermaBond	Sutures	Strips	Staples
# patients	118	115	6	1	98	42	43	5
Complete Apposition @ 5-10d (Cat 1 vs Other)	75 (63.6%)	90 (78.3%)	4 (66.7%)	1 (100.0%)	81 (82.7%)	40 (95.2%)	43 (100.0%)	5 (100.0%)
Complete Apposition @ 5-10d (Cat 1,2 vs Other)	95 (80.5%)	101 (87.8%)	5 (83.3%)	1 (100.0%)	96 (99.0%)	42 (100.0%)	43 (100.0%)	5 (100.0%)
Additional Securing Device	12 (10.2%)	7 (6.1%)	0 (0.0%)	0 (0.0%)	2 (2.0%)	2 (4.8%)	1 (2.3%)	0 (0.0%)
MHCS @ 3 mos=0	87 (73.7%)	82 (71.3%)	3 (50.0%)	1 (100.0%)	74 (75.5%)	28 (66.7%)	40 (93.0%)	2 (40.0%)

Note: This table shows study outcome for male patients for each treatment method.

TABLE 8 OUTCOME FOR YOUTHS

Age < 19 year old	NSS				WSS			
	Treatment	Control			Treatment	Control		
	DermaBond	Sutures	Strips	Staples	DermaBond	Sutures	Strips	Staples
# patients	105	116	2	0	18	14	0	1
Complete Apposition @ 5-10d (Cat 1 vs Other)	76 (72.4%)	97 (83.6%)	2 (100%)	-	12 (66.7%)	12 (85.7%)	-	1 (100.0%)
Complete Apposition @ 5-10d (Cat 1,2 vs Other)	94 (89.5%)	105 (90.5%)	2 (100%)	-	15 (83.3%)	14 (100.0%)	-	1 (100.0%)
Additional Securing Device	5 (4.8%)	4 (3.5%)	0 (0.0%)	-	0 (0.0%)	1 (7.1%)	-	0 (0.0%)
MHCS @ 3 mos=0	71 (67.6%)	79 (68.1%)	1 (100.0%)	-	9 (50.0%)	7 (50.0%)	-	0 (0.0%)

Note: This table shows outcome for patients less than 19 years old.

Gender Bias: 75/118 (63.6%) of males achieved Category 1 wound closure at 5-10 days in the DermaBond NSS group, and 94/120 (77.7%) of females achieved Category 1 wound closure at 5-10 days in the DermaBond NSS group. 95/118 (80.5%) of males achieved Category 1 and 2 wound closure at 5-10 days in the DermaBond NSS group, and 110/120 (90.9%) of females in the DermaBond NSS group achieved Category 1 and 2 wound closure at 5-10 days. 12/118 (10.2%) of males required additional securing devices in the DermaBond NSS group, and 6/120 (5%) of females required additional securing devices in the DermaBond NSS group. 87/118

80

(73.7%) of males achieved a MHCS of 0 at 3 months, and 101/120 (83.5%) of females achieved a MHCS of 0 at 3 months.

95/122 (77.9%) of males achieved Category 1 wound closure at 5-10 days in the Control NSS group, and 104/119 (87.4%) of females achieved Category 1 wound closure at 5-10 days in the Control NSS group. 107/122 (87.7%) of males achieved Category 1 and 2 wound closure at 5-10 days in the Control NSS group, and 107/119 (89.9%) of females in the Control NSS group achieved Category 1 and 2 wound closure at 5-10 days. 7/122 (5.7%) of males required additional securing devices in the Control NSS group, and 6/119 (5%) of females required additional securing devices in the Control NSS group. 86/122 (70.5%) of males achieved a MHCS of 0 at 3 months in the Control NSS group, and 94/119 (79%) of females achieved a MHCS of 0 at 3 months in the Control NSS group.

81/98 (82.7%) of males achieved Category 1 wound closure at 5-10 days in the DermaBond WSS group, and 59/69 (85.5%) of females achieved Category 1 wound closure at 5-10 days in the DermaBond WSS group. 96/98 (97.9%) of males achieved Category 1 and 2 wound closure at 5-10 days in the DermaBond WSS group, and 67/69 (97.1%) of females in the DermaBond WSS group achieved Category 1 and 2 wound closure at 5-10 days. 2/98 (2%) of males required additional securing devices in the DermaBond WSS group, and 0/69 (0%) of females required additional securing devices in the DermaBond WSS group. 74/98 (75.5%) of males achieved a MHCS of 0 at 3 months in the DermaBond WSS group, and 54/69 (78.3%) of females achieved a MHCS of 0 at 3 months in the DermaBond WSS group..

88/90 (97.7%) of males achieved Category 1 wound closure at 5-10 days in the Control WSS group, and 72/76 (94.7%) of females achieved Category 1 wound closure at 5-10 days in the Control WSS group. 90/90 (100%) of males achieved Category 1 and 2 wound closure at 5-10 days in the Control WSS group, and 75/76 (98.7%) of females in the Control WSS group achieved Category 1 and 2 wound closure at 5-10 days. 3/90 (3.3%) of males required additional securing devices in the Control WSS group, and 8/76 (10.5%) of females required additional securing devices in the Control WSS group. 70/90 (77.7%) of males achieved a MHCS of 0 at 3 months in the Control WSS group, and 58/76 (76.3%) of females achieved a MHCS of 0 at 3 months in the Control WSS group.

There were more males enrolled in the study than females. This is most likely indicative of the fact that more males receive lacerations in the general population than females. When looking at Categories 1 and 2 for wound closure, cosmesis at 3 months, and need for additional securing devices, females performed slightly better than males in all categories. However, there do not appear to be any large differences in outcome in any category.

76/105 (72.4%) youths achieved Category 1 wound closure at 5-10 days in the DermaBond NSS group, and 99/118 (83.9%) youths achieved Category 1 wound closure at 5-10 days in the Control NSS group. 94/105 (89.5%) youths achieved Category 1 and 2 wound closure at 5-10 days in the DermaBond NSS group, and 107/118 (90.7%) youths achieved Category 1 and 2 wound closure at 5-10 days in the Control NSS group. 5/105 (4.8%) required additional securing devices in the DermaBond NSS group, and 4/118 (3.4%) youths required additional securing

devices in the Control NSS group. 71/105 (67.6%) youths achieved a MHCS of 0 at 3 months in the DermaBond NSS group, and 80/118 (67.8%) youths achieved a MHCS of 0 at 3 months. Regarding young patients in the WSS group, only 33 patients were treated. Although the table shows a poorer outcome for youths than is found in either of the gender groups, the numbers are too small to draw conclusions.

X. OVERALL CONCLUSIONS

The sponsor conducted a study to compare the safety and effectiveness of DERMABOND to commercially-available wound closure devices (i.e., sutures, adhesive strips, and staples). The original primary endpoint to be compared between the two groups was 100% apposition at 5-10 days post-treatment. Therefore, the study hypothesis was that the proportion of patients who achieve 100% apposition with DERMABOND is greater than or equal to the proportion of patients who achieve 100% apposition with commercially-available wound closure devices at 5-10 days post-treatment. Analysis of the results showed that the null hypothesis was not rejected. However, after the sponsor modified the success criteria to include both 100% apposition and 50 to 99% epidermal apposition (categories 1 and 2 on the wound closure scale), the sponsor was able to reject the null hypothesis. The sponsor then conducted a linear and logistic regression analysis to determine if other covariates (i.e., age, gender, smoking, etc.) may have contributed to the result. The results of the regression analysis were inconclusive. FDA had concerns about changing the primary endpoint after study completion to proportion of patients with less than 50% epidermal separation and asked the General and Plastic Surgery Devices Panel to provide their recommendation.

XI. ADMINISTRATIVE REVIEW OF DATA AND INFORMATION

PANEL RECOMMENDATION

This device was presented for review by the General and Plastic Surgery Devices Panel on January 30, 1998. The discussion focused on three main areas: the primary endpoint, the infection rate, and issues raised by the FDA.

There was also discussion about the higher infection rate in the DERMABOND™ groups as compared to the control groups. Overall, the infection rates in both groups were small, but the infection rate in the treatment groups were at least three times higher than in the control groups (see POTENTIAL ADVERSE REACTIONS section). The panel felt that one factor that may have contributed to the higher rate was lack of adequate wound cleansing and debridement and that this should be addressed in the labeling via precautions or statements. The revised labeling should inform the user that the product should not be used on contaminated wounds, that adequate wound cleansing was still necessary prior to application of the adhesive, and that use of the product does not constitute antimicrobial usage.

The panel felt that although effectiveness at 5-10 days was not demonstrated in the study on the basis of looking at complete apposition, the most important parameters to look at in evaluating the results of the study were cosmesis at 3 months, wound dehiscence, and infection rate.

The panel recommended 8-0 in favor of approval of the premarket approval application (PMA) with the condition that the labeling include a more specific indications for use statement that addresses the need for adequate wound cleansing and clarifies the fact that DERMABOND™ is not intended to replace subcuticular sutures.

CDRH DECISION

Based on the data in the premarket approval application (PMA), and the results of the panel meeting, FDA decided to approve the application after the labeling was modified appropriately.

A GMP inspection was conducted of Closure Medical Corporation facilities on May 12, 1998, and they were found to be in compliance with the device Good Manufacturing Practice regulations.

FDA issued an approval order on August 26, 1998.

APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.