SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Tissue Adhesive

Device Trade Name: Histoacryl and Histoacryl Blue

Applicant: Tissue Seal LLC
5643 Plymouth Rd.
Ann Arbor MI. 48105

Premarket Approval (PMA) Application Number: P050013

Date of Panel Recommendation: None

Date of Notice of Approval to the Applicant: February 16, 2007

II. INDICATIONS FOR USE

Histoacryl and Histoacryl Blue topical skin adhesives are intended for topical application to hold closed easily approximated skin edges of minimum-tension wounds from clean surgical incisions and simple, thoroughly cleansed, trauma-induced lacerations. Histoacryl and Histoacryl Blue may be used in conjunction with, but not in place of, deep dermal sutures.

III. CONTRAINDICATIONS

- Histoacryl and Histoacryl Blue topical skin adhesives are not to be applied to subdermal layers of tissue. The polymerized adhesive is not absorbed by tissues and may elicit a foreign body reaction.

- The topical skin adhesive is not to be applied to any internal organs, blood vessels, nerve tissue, mucosal surfaces or mucocutaneous junctions, areas with dense natural hair, or within the conjunctival sac of the eye.

- The topical skin adhesive is not to be applied to the surface of the eye. If the eye is accidentally bonded closed, release eyelashes with warm water by covering with a wet pad. The adhesive will bond to eye protein and will cause periods of weeping which will help to debond the adhesive. Keep the eye covered until debonding is complete – usually within 1 to 3 days. Do not force the eye open.

- The topical skin adhesive is not to be applied to wounds subject to high skin tension, or on areas of increased skin tension such as the elbows, knees, or knuckles. The topical skin adhesive is not to be used in areas of skin excision.

- The topical skin adhesive is not to be applied to wounds that show evidence of infection, gangrene or wounds of decubitus etiology.

- The topical skin adhesive is not to be used on patients with known preoperative systemic infections, uncontrolled diabetes, or diseases or conditions that are known to interfere with the wound healing process.

- The topical skin adhesive is not to be used on patients with a known hypersensitivity to cyanoacrylate, formaldehyde, or the dye D&C Violet #2.

IV. WARNINGS AND PRECAUTIONS

Warnings and precautions can be found in the Histoacryl physician's labeling.

V. DEVICE DESCRIPTION

Histoacryl and Histoacryl Blue are sterile liquid topical skin adhesives composed of n-butyl-2-cyanoacrylate monomer. The two products are different in only one respect: Histoacryl is provided as a colorless liquid, and Histoacryl Blue is colored with the dye D&C Violet #2 in order to make it easier to see how thick a layer has been applied. Histoacryl and Histoacryl Blue topical skin adhesives are supplied in 0.5 ml single patient use plastic ampoules. Each ampoule is sealed within a plastic vial so the exterior of the ampoule can remain sterile. Both tissue adhesives remain liquid until exposed to water or water-containing substances/tissue, after which it cures (polymerizes) and forms a film that bonds to the underlying surface. All references to Histoacryl below refer to both Histoacryl (without dye) and Histoacryl Blue (with dye) unless stated otherwise.

VI. ALTERNATE PRACTICES AND PROCEDURES

Skin wounds can be closed utilizing various medical devices in order to maintain tissue apposition during the critical phase of wound healing. The most commonly utilized device is the non-absorbable monofilament suture. The sutures remain in place for approximately 7-10 days, at which time the patient returns to have the sutures removed. Similarly, metal skin staples are utilized in the same fashion as sutures, requiring a return visit for staple removal. Adhesive tapes have also been used to hold skin wound edges together. In addition, another commercially available tissue adhesive may be use to maintain approximation of skin wound edges caused by surgical incisions or traumatic lacerations.

VII. MARKETING HISTORY

Histoacryl has been marketed by B. Braun outside the U.S. since 1979.

VIII. POTENTIAL ADVERSE EFFECTS ON HEALTH

In studies[1-4] with 1338 patients and 1492 wounds, the following adverse reactions were reported:

Table 1 Adverse Reactions[1-4]

	Amiel et al[1]	Barnett et al[2]		Quinn et al[3]		Bruns et al[4]	
	Histoacryl	Histoacryl	Sutures	Histoacryl	Sutures	Histoacryl	Sutures
N, patients treated	1033	83	80	41	40	30	31
N, wounds treated	1150	100	100	41	40	30	31
*Dehiscence***							
Dehiscence-At Any Time	11 (1.1%)	0/62	0/40	3(8.1%)	2 (5.3%)	1 (3.0%)	1 (3.0%)
Wound Edge Separation Requiring Re-Treatment	1	0	0	2	1	0	0
Infection***							
Suspected Infection	*	0/62	2/49	1/37 (2.7%)	1/38 (2.6%)	1/30 (3.0%)	*
Acute Inflammation							
Erythema	57 (5.5%)	*	*	1 (2.7%)	4 (11.5%)	*	*
Edema	5 (0.5%)	*	*	*	*	*	*
Drainage	20 (1.9%)	*	*	*	*	*	*

* No reported data

** Dehiscence is any disruption in which the edge of the skin wound separates sufficiently to expose subcutaneous tissues.

*** **Infection is defined as a purulent discharge from the wound, a positive culture or microbial count for pathogen that can be documented.**

- *Potential Adverse Effects*

Clinical experience with Histoacryl used outside the United States suggests that the following adverse events, (not reported in the above cited studies) may occur: bonding to unintended tissues, thermal discomfort during polymerization, allergic reaction, foreign body reaction, tattooing, and chronic non-healing of a wound.

IX. NONCLINICAL STUDIES

Preclinical testing for Histoacryl examined whether it was biocompatible (Table 2), possessed adequate performance characteristics and sufficiently stable to claim a 2 year expiration date (Tables 3 and 4).

Biocompatibility studies

Histoacryl was tested in accordance with ISO 10993-1 for a surface-contacting device with a prolonged contact duration of between 24 hours and 30 days. The results of the Histoacryl biocompatibility testing are presented in Table 2.

Table 2: Summary of Biocompatibility Tests

Test	Results / Conclusions
Cytotoxicity	Serum-free media extracts of Histoacryl did not cause cell lysis or toxicity
Mouse Lymphoma Forward Mutation Assay	Neither polymerized Histoacryl nor serum-free media extracts of the device were mutagenic in the presence or absence of metabolic activation

Systemic Toxicity	Saline, alcohol, PEG, and sesame oil extracts of Histoacryl did not cause systemic toxicity
ISO Maximization Sensitization	Saline extracts of Histoacryl did not cause sensitization in guinea pigs
Hemolysis	Saline extracts of Histoacryl did not cause hemolysis of human erythrocytes
Intramuscular Implantation	Implantation of polymerized Histoacryl did not cause tissue reactions or toxic effects in rabbits followed for 3 days
Intracutaneous Irritation	Saline, alcohol, PEG, and sesame oil extracts of Histoacryl did not cause a skin reaction or adverse effects in rabbits

Table 3: Summary of Performance Tests

Test	**Results / Conclusions**
Setting Time	Polymerization times of 1, 3-10 and 5-30 seconds were observed when drops of Histoacryl were placed in aqueous solutions of 0.01%, 0.1% and 1% g/l histidine, respectively.
Hydrolytic Degradation	A 15 day incubation of samples from two lots of polymerized Histoacryl in a 50°C saline solution resulted in 1-butanol concentrations of 232 µg and 89 µg per gram of Histoacryl. The amount of formaldehyde (another decomposition product) was below the limit of detection (i.e., 5 ppm) for both lots
Bond Strength	The bond strength of Histoacryl tested in accordance with ASTM F 2458-0 (with freshly harvested porcine skin) was 21.73 Newtons (after cure times of 30 and 60 seconds) compared to 11.47 Newtons for another legally marketed tissue adhesive device. Histoacryl bond strengths of 8.24 and 9.32 Newtons were observed when shorter cure times (i.e., 35-45 and 60-67 seconds, respectively) were used
Bond Strength Testing of Aged Material	The average bond strengths of Histoacryl samples tested in accordance with ASTM F 2458-0 and stored for 6, 12, and 24 months were 19.9, 15.5 and 14.6 Newtons, respectively
Dye extraction	The amount of D&C Violet #2 dye extracted from polymerized Histoacryl Blue was below the level of detection (i.e., less than 5.6 µg of dye / gram of adhesive)
Tensile strength	As per the ASTM C633-01, forces of 655 ± 78 lbs (Histoacryl) and 551 ± 93 lbs (another legally marketed tissue adhesive) were required to separate two ½" diameter steel rods after a 2 hour cure time
Adhesive Force Test	The force required to separate two pieces of lyophilized bovine pericardium glued together with Histoacryl (and cured for 75 minutes) was 105.70 ± 24.38 N

Overlap shear strength	The lap shear strength of Histoacryl (i.e., 34.6 lbs) tested in accordance with ASTM D882-02 was similar to that observed with another legally marketed tissue adhesive device (i.e., 36.91 lbs)
Peel adhesion strength	The peel strength of Histoacryl cured for 2 hours and tested in accordance with ASTM D 3330 was 3.5 lbs
Ease of Expression	A force of 1 pound was required to express Histoacryl from its packaging
Differential Scanning Calorimetry (DSC)	DSC analyses of Histoacryl from two lots displayed normalized cure peaks of approximately 260 J/g and 310 J/g
Heat of Polymerization	33 – 76 C (57C mean) increases in temperature were observed when 20 ul of a 0.1 g/l histidine solution was added to 50 ul of NBCA in the presence of a thermocouple
Antibacterial Activity	Carriers coated with polymerized Histoacryl were inoculated with approximately 10^9 cfu/ml suspensions of *P. aeruginosa, E. coli, S. aureus, M. ferrae, B. atrophaeus, C. albicans and A. niger*. Test organisms were not detected on carriers after incubating for 30 seconds, 10 minutes and 1 hour
Shelf-life	The 24 month stability of 3 lots of Histoacryl was assessed for liquid appearance, chemical composition, adhesive strength, absence of packaging leaks and sterility

Table 4: Animal Studies

Test	Results / Conclusions
Wound Healing in Guinea Pigs	The tensile strength associated with Histoacryl closure alone (188 ± 101 g) was significantly lower than percutaneous suture closure alone (420 ± 253 g) in a model where incisions to deep fascia were made on the backside of albino guinea pigs
Wound Healing in Guinea Pigs- 2	The breaking strength of a wound closed by sutures was greater than by Histoacryl-closure on the day of treatment (day 0). After healing for 7 days the breaking strength for suture and Histoacryl-closed wounds were not significantly different

X. CLINICAL STUDIES

While the original PMA submission included eleven publications on the clinical applications of Histoacryl, the sponsor and FDA agreed that the results from four major studies were the best reflection of product performance. The issues critical in selecting these publications included, (when possible), 1) prospectively-designed and controlled studies, 2) adverse event data collected by active monitoring of patient outcomes rather than voluntary reporting, and 3) a description of baseline demographics (e.g., age, race, wound-type), so that patients at a greater risk for the incidence, type or severity of any

adverse event beyond that reported for the overall patient population could be identified. The four clinical studies best meeting these criteria are described below:

[1]G.E. Amiel, I. Sukhotnik, B. Kawar, and L. Siplovich, "Use of N-butyl-2-cyanoacrylate in elective surgical incisions—long-term outcomes," *J. Am. Coll. Surg.* **Jul; 189(1)**: 21-5 (1999)

A. Study Design

The study was an open-label retrospective trial designed to evaluate the safety and effectiveness of Histoacryl Blue in approximating surgical incisions at three Israeli centers.

The study population included pediatric patients undergoing elective surgical incisions (i.e., orchidopexy, inguinal hernia, umbilical hernia or hydrocele repair). All incisions were 2 and 5 cm in length and closure was achieved with standard surgical techniques by attending physicians. Final cutaneous closure was performed with Histoacryl.

Patients were discharged after 4-6 hours of observation. Follow-up visits were 7 days and 4 to 8 weeks (if needed) after surgery. A 12-item questionnaire was completed during a telephone interview with a family member within 6 months after treatment.

B. Study Results

Patient Accounting and Demographics

A summary of patient accounting and demographics as well as wound characteristics are presented in Table 5.

Table 5: Summary of Patient Accounting, Demographics and Wound Characteristics Reported by Amiel et. al

Accounting	**No. of pts (%)**
Patient records reviewed	1098
Patients treated with Histoacryl	1033 (100%)
Wounds treated with Histoacryl	1150
Patients completing 7 day follow-up	905 (87.6%)
Patients attending 4 week follow-up	401 (38.8%)
Surgical Procedure	**N (%)**
Right inguinal hernia repair	407 (37%)
Left inguinal hernia repair	199 (18%)
Bilateral inguinal hernia repair	119 (11%)
Umbilical hernia repair	43 (4%)
Hydrocele repair	167 (15%)
Orchidopexy	163 (15%)
Patient Age	1 mo – 16 yrs
Number of Incisions	1150

Wound Depth	
No. wounds < 5mm deep	0
No. wounds >/= 5mm deep	1150
Local Anesthetic use	
Patients using local anesthetic	1033 (100%)

Study Outcomes

The adverse reactions observed in patients are described in Table 1. 1022/1033 (98.9%) of the patients treated with Histoacryl achieved wound closure without dehiscence or wound edge separation requiring re-treatment.

[2]P. Barnett, F.C. Jarman, J. Goodge, G. Silk, and R. Aickin. "Randomized trial of Histoacryl blue tissue adhesive glue versus suturing in the repair of pediatric lacerations," *J. Paediatr. Child Health* **34**, 548-550 (1998)

A. Study Design

The study was a prospective, randomized trial designed to compare the safety and effectiveness of Histoacryl Blue and sutures in closing simple pediatric lacerations in an emergency room setting at three facilities in Australia and New Zealand.

Patients between the ages of 4 -12 years were enrolled if they had a clean laceration on any part of the body that was less than 5 cm in length. Patients were excluded if: the wound occurred on the eyelid, mucous membrane or a joint margins (i.e. under any added tension) or if the wound required debridement or plastic surgery.

Patients were assessed after wound closure and at 1 week, 3 and 12 months after treatment.

B. Study Results

Patient Accounting and Demographics

A summary of patient accounting and demographics as well as wound characteristics are presented in Table 6.

Table 6: Patient Accounting, Baseline Demographics and Wound Characteristics Reported in Barnett et al

	Histoacryl Blue	**Control Sutures**
Patient Accounting		
N, patients enrolled	83	80
N, patients treated	83	80
Patients completed: 1 week	62 (74.6%) 46 (55.0%)	49 (61.2%) 44 (55.0%)

90 days 12 months	36 (43.0%)	34 (43.0%)
Patient Demographics		
Mean Age in months (standard deviation) Males	69.5 (29) 48 (57.8%)	68.4 (30) 68 (85%)
Wound Characteristics		
Mean Length (standard deviation) Mean Width (standard deviation) Wound Class: Clean *Incisions* Lacerations *Body Part* Face Scalp Other	15.4 mm (9.5mm) 3.4 mm (5.5) 100% 100% 49 39 16	16.8 mm (8.4 mm) 2.8 mm (1.6 mm) 100% 100% 64 29 7
Use of Anaesthesia		
General Local only None	0 0 83 (100%)	0 80 (100%) 0

Study Outcomes

The adverse reactions observed patients are described in Table 1. Closure of all 163 (100%) wounds was achieved in both treatment groups without dehiscence.

[3]J.V. Quinn, A. Drzewiecki, M.M. Li, I.G. Stiell, T. Sutcliffe, T.J. Elmslie, and W.E. Wood, "A randomized, controlled trial comparing a tissue adhesive with suturing in the repair of pediatric facial lacerations," *Ann. Emerg. Med.* **Jul;22(7)**:1130-5 (1993)

A. Study Design

This study was a prospective, randomized controlled trial comparing closure of pediatric facial lacerations with Histoacryl Blue and sutures in a single Canadian Emergency room facility.

Patients, under the age of 18, with clean facial lacerations less than 4 cm in length and 0.5 cm in width were eligible for enrollment. Patients with wounds requiring deep layer closure, caused by animal bites, lacerations on hair-bearing surface, crossing mucocutaneous junctions or heavily soiled and requiring debridement were excluded from enrollment.

Patients were evaluated immediately after treatment as well as 5 days and 3 months after wound approximation.

B. Study Results

Patient Accounting and Demographics

A summary of patient accounting and demographics as well as wound characteristics are presented in Table 7.

Table 7: Summary of Patient Accounting, Baseline Demographics and Wound Characteristics Reported by Quinn et al.

	Histoacryl Blue	**Control Sutures**
Patient Accounting		
N, patients enrolled	41	40
N, patients treated	37	38
Patients completed: 90 days	33 (89.1%)	36 (94.7%)
Patient Demographics		
Age (years)	0.7-16	0.5-15
Mean (years)	4.7	4.5
Sex (Male)	58%	42%
Wound Characteristics		
Length in cm, mean	1.53	1.52
Length Range in cm	0.5-3.5	0.5-3.5
Class: Clean	100%	100%
Incisions		
Lacerations-facial	100%	100%
Use of Anaesthesia		
General	0	0
Local only		38 (100%)
None	37(100%)	

Study Outcomes

The adverse reactions observed in patients are described in Table 1. Wound closure without dehiscence was achieved in 34/37 (91.9%) of the Histoacryl and 36/38 (94.7%) of the suture-treated patients.

[4]T.B. Bruns, H.K. Simon, D.J. McLario, K.M. Sullivan, R.J. Wood, and K.J.S. Anand, "Laceration Repair Using a Tissue Adhesive in a Children's Emergency Department," *Pediatrics*, **98**: 673-675 (1996)

A. Study Design

This study was a prospective, randomized trial comparing closure of pediatric lacerations with Histoacryl Blue and sutures at three Emergency rooms within the U.S.

Patients between the ages of 1 – 18 years old with lacerations less than 5 cm were enrolled. Wounds requiring the use of subcutaneous sutures were enrolled in this

study. Patients with lacerations in areas of high skin mobility or tension (e.g., joints, hands, feet, eyelids, ears, nose, mouth or perineum) were excluded from the study as were lacerations caused by dog bites or extending to the muscle or bone.

Patients were evaluated after wound closure and at 1 week and 2 months after treatment.

B. Study Results

Patient Accounting and Demographics

A summary of patient accounting and demographics as well as wound characteristics are presented in Table 8.

Table 8: Summary of Patient Accounting, Baseline Demographics and Wound Characteristics Reported by Bruns et al

Patient Accounting		
	Histoacryl	**Sutures**
N, patients treated	30	31
N, wounds treated	30	31
Attending 2 month visit	30	25
Baseline Demographics		
Median Age	4 years	3 years
Gender (G: male)	24 (80)	25 (80)
Race		
White	14 (47)	19 (61)
Black	16 (53)	12 (39)
Wound Characteristics		
Mean Length, (mm)	15	15
Depth, (mm)		
<5mm	22	22
>5mm	8	9
Width (mm)		
Range	<.5	<.5
Lacerations		
Smooth	30	31
Body Locations		
Face	22	31
Other (scalp)	7	0
Unknown	1	0
Wound Depth		
No. wounds < 5mm deep	22	22
No. wounds >/= 5mm deep	8 (27)	9 (29)
Local Anesthetic used		
Patients treated with	13/30 (43%)	31/31

Patient Accounting		
	Histoacryl	**Sutures**
anesthetic		(100%)

Study Outcomes

The adverse reactions observed in patients after surgery are described in Table 1. Wound closure without dehiscence was achieved in 29/30 (96.7%) of the Histoacryl and 30/31 (96.8%) of the suture-treated patients.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The chemical structures and anticipated clinical performance of Histoacryl and Histoacryl Blue are sufficiently similar, so that the preclinical and clinical data collected with Histoacryl Blue may be used in support of approval of Histoacryl without D&C Violet Dye #2.

Preclinical testing of Histoacryl demonstrated that the device is biocompatible, displays adequate performance characteristics, and sufficiently stable to claim a 2 year expiration date.

The 11 publications submitted in this PMA document the safe and effective use of Histoacryl in approximating the skin edges associated with minimum-tension wounds from clean surgical incisions and simple, thoroughly cleansed, trauma-induced lacerations in 6452 patients.

Based upon the criteria of: 1) prospectively-designed and controlled studies (when possible), 2) adverse event data collected by active monitoring of patient outcomes rather than voluntary reporting, and 3) a description of baseline demographics (e.g., age, race, wound-type), FDA and the sponsor selected four publications that describe the treatment of 1183 patients over a 5 year period, for preparing the product label. In these studies skin edge approximation was achieved in almost every simple, thoroughly cleansed, minimum-tension surgical incision and lacerations wound, (as long as Histoacryl was used in conjunction with, but not in place of, dermal sutures). Similarly, the incidence of wound dehiscence (i.e., a range of 0-8.1%), infection (i.e., a range 0-3.0%), redness/tenderness, (i.e., range 0-5.5%), swelling (0-0.5%) and fever (0-0.1%) were consistently low in each study and similar in incidence to wounds closed with sutures.

While the publications submitted in this PMA described the impact of Histoacryl use on scar appearance, time to wound closure, and level of pain associated with wound closure, FDA does not believe that these data meet the definition of valid scientific evidence presented in 21 CFR 860.7. This determination was based on the subjective nature of each claim and the inability of FDA to review individual patient outcomes. Because wound healing is a complex process, several different issues can alter the final outcome (e.g., underlying disease, wound bed preparation methods and patient

compliance with post-treatment care), evaluating individual patient conditions is important when attempting to correlate wound outcome with Histoacryl use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515c(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. FDA DECISION

FDA issued an approval order on XXXXXX

The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

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

Postapproval Requirement and Restrictions: See the approval order.

XV. REFERENCES

1. G.E. Amiel, I. Sukhotnik, B. Kawar, and L. Siplovich, "Use of N-butyl-2-cyanoacrylate in elective surgical incisions—long-term outcomes," *J. Am. Coll. Surg.* **Jul;189(1)**: 21-5 (1999)

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