



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration \*  
9200 Corporate Boulevard  
Rockville MD 20850

Ellen Redding, M.S.N.  
Director  
Regulatory Affairs  
Advance Tissue Sciences  
10933 North Torrey Pines Road  
La Jolla, California 92037-1005

**MAR 18 1997**

Re: P960007  
Dermagraft Temporary Covering, Dermagraft-TC™  
Filed: March 29, 1996  
Amended: May 28 and 31, August 6, 14, 16, and 19,  
September 9, October 15, 22, and 23, and December 3, 5,  
and 16, 1996 and February 26, and March 17, 1997.

Dear Ms. Redding:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Dermagraft-TC™. This device is indicated for use as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109.

In addition to the postapproval requirements in the enclosure, the postapproval reports must include the following information:

1. The results of a postapproval study should be performed as outlined in your February 27, 1997 FAX. This study will assess the incidence of burn wound

infections which occur in the setting of Dermagraft-TC™ use compared to an historical control group. A complete description of the postapproval study protocol must be submitted within 30 days of the date of this approval order in the form of a PMA Supplement and approved before the study begins. This study will be a multi-center, nonrandomized, unmasked study enrolling 200 patients to obtain at least 100 patients who have received Dermagraft-TC™ at 5-10 investigational centers. The results of the data must be reflected in the labeling (via a supplement) when the postapproval study is completed.

2. While 21 CFR 820.180 requires Batch Records to be maintained for two years we recommend that the following information be maintained for at least 5 years: 1) any deviations in your Standard Operating Practices for Dermagraft-TC manufacture and 2) data which permit correlation of donor and production lot number.
3. Please be advised that FDA considers the manufacture of Dermagraft-TC™ with a new cell line as a change that affects the safety and effectiveness of your device. Consequently, and as per 21 CFR 814.39, you will be required to submit in advance of commercial distribution of Dermagraft-TC™ manufactured with a new cell line, a PMA supplement which describes the test results for the Donor Cells, the Master Cell Bank, the Manufacturer's Working Cell Bank, and end-of-production cells for each new fibroblast cell line as well as both the in-process and final test results for the Dermagraft-TC™ product manufactured with this new cell line.

Expiration dating for this device has been established and approved at 6 months at -70°C.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this

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decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

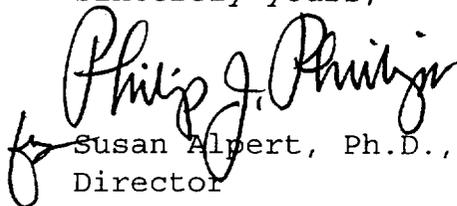
You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)  
Center for Devices and Radiological Health  
Food and Drug Administration  
9200 Corporate Blvd.  
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Gail Gantt, R.N. at (301) 594-3090.

Sincerely yours,



Susan Alpert, Ph.D., M.D.  
Director

Office of Device Evaluation  
Center for Devices and  
Radiological Health

Enclosure

## **SUMMARY OF SAFETY AND EFFECTIVENESS**

### **I. General Information**

Device Generic Name: Interactive wound and burn dressing

Device Trade Name: Dermagraft-TC™

Applicant's Name and Address: Advanced Tissue Sciences  
10933 North Torrey Pines Road  
La Jolla, California 92037-1005

Date of Panel Recommendation: November 19, 1996

Premarket Approval Application (PMA) Number: P960007

Date of Good Manufacturing Practice Inspection: November 22, 1996

Date of Notice of Approval to Applicant: March 18, 1997

Expedited Review: Dermagraft-TC™ was granted expedited review status on June 1, 1995 because Dermagraft-TC™ has the "potential to provide a viable alternative in the treatment of patients requiring a temporary covering for burn injuries."

### **II. Indications for Use**

Dermagraft-TC™ is indicated for use as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement.

### **III. Device Description**

Dermagraft-TC™ is a composite product consisting of a biosynthetic bilaminate membrane onto which human neonatal fibroblasts have been cultured. The biosynthetic bilaminate membrane is a commercially available temporary wound covering, consisting of an ultrathin, semipermeable silicone membrane mechanically bonded to a flexible, knitted nylon mesh coated with porcine dermal collagen. The nylon mesh side of the bilaminate membrane serves as the scaffolding onto which the fibroblasts are grown. As the fibroblasts proliferate, they secrete dermal collagen, extracellular matrix proteins and growth factors. Following freezing, no fibroblastic metabolic activity remains; however, the tissue matrix and bound growth factors are left intact. The silicone layer is semipermeable to water vapor and gases, and helps act as a barrier.

The fibroblasts proliferate within the interstices of the nylon scaffold and secrete a matrix of collagen, other extracellular proteins and growth factors. A bioreactor contains two pieces of Dermagraft-TC™, each measuring 5 x 7.5 inches. Following the growth

process, each bioreactor is removed from the manufacturing system, individually packaged, and frozen to and stored at -70 °C. The product retains no fibroblast metabolic activity following the freezing process, while the tissue matrix and matrix-bound growth factors are left intact.

#### **IV. Contraindications**

Dermagraft-TC™ may contain trace amounts of animal proteins due to exposure in the manufacturing process and the pre-coating of the nylon mesh with porcine dermal collagen. Dermagraft-TC™ is contraindicated in those patients with known hypersensitivity to porcine dermal collagen or bovine serum albumin.

The warnings and precautions can be found in the Dermagraft-TC™ labeling.

#### **V. Alternative Practices and Procedures**

In the treatment of large full-thickness burns, surgeons typically excise the damaged tissue and cover the wound as soon as possible. This usually involves the use of temporary coverings to limit infection, reduce pain and prevent loss of body fluids, followed by grafting of the patient's own skin (autograft) as it becomes available. Autografts are surgically harvested from areas of the body where the skin is still intact. Typically, the skin at such a donor site is surgically split so that the removed graft consists of the entire epidermis and the upper portion of the dermis (known as a split-thickness graft), leaving the bottom portion of the dermis with the remnants of its epidermal appendages in the donor site to allow healing and possible repeat harvesting. The autograft is then meshed or interspersed with holes to allow the skin to be expanded to cover a larger area.

In some cases, it may not be possible to access adequate autograft initially to cover a patient's wounds. This may be due to the limited availability of unburned skin or the inability of the patient to tolerate the additional trauma of a prolonged surgical procedure. When sufficient autograft is not available, human cadaver skin (allograft), porcine skin (xenograft) and synthetic dressings are often used as a temporary dressing for excised wounds until adequate autograft can be obtained.

#### **VI. Marketing History**

As of this submission, the device had not been commercialized in the U.S. or in other countries.

#### **VII. Potential Adverse Effects of the Device on Health**

##### **A. Observed Adverse Effects of the Device**

There was 1 study wound infection considered possibly related to the Dermagraft-TC™ product. The infection was diagnosed by culture at the time of temporary covering

removal with no clinical evidence of infection.

#### **B. Potential Adverse Effects of the Device on Health**

The possibility exists that long duration application of Dermagraft-TC™ may result in immunological rejection by the patient because the extent of HLA antigen expression by the human fibroblasts remains undetermined. Consequently, physicians should remain alert to this possibility as burn patients regain immune competency.

Other potential adverse effects for Dermagraft-TC™ may include adverse events observed with the other legally marketed interactive wound dressings including contact dermatitis reactions characterized by erythema and papulovesicular and bullous lesions of the skin in the area surrounding the device, sensitivity to the porcine collagen component and infection.

### **VIII. Summary of PreClinical Studies**

#### **A. Nonclinical Laboratory Studies**

##### Infectious Agent Testing

Extensive screening is performed in regard to infectious agents to qualify the safe use of human fibroblast cell strains in the manufacture of Dermagraft-TC™. A number of screening tests are performed on the fibroblast cell strains at various stages of harvesting and manufacturing. This includes screening and testing of sera from the mothers of donors and testing of individual cell strains, which is consistent with the CBER document "Points to Consider in Human Somatic Cell Therapy and Gene Therapy" (August 1991). This extensive testing ensures that all cell strains used in the production of Dermagraft-TC™ have been shown to be free from detectable adventitious agents.

Furthermore, additional studies are performed to qualify the use of particular cell strains, as well as testing completed at the end of production to demonstrate the lack of contamination of the cells in the final product. The creation and testing of the cell banks and testing of the cells at the end of production are consistent with the CBER "Points to Consider in the Characterization of Cell Strains Used to Produce Biologicals" (May 1993). The multi-tiered testing regime was used to qualify cell strains used to produce clinical product and will be used for all future cell strains required for commercial production. The results of this testing demonstrated that the cell strains used for the manufacture of Dermagraft-TC™ are safe for their intended use in regard to identification, characterization, and freedom from infectious agents.

## Biocompatibility Studies

To establish the biocompatibility of Dermagraft-TC™, a series of studies were conducted. The results of these studies provide evidence that the components and materials used in the manufacture of the device are biocompatible and nonimmunogenic. Assessments were made regarding the biocompatibility of Dermagraft-TC™ manufacturing materials, the bilaminate scaffolding, and the fibroblasts and extracellular matrix, and the finished device. This testing is summarized in the table below:

**Biocompatibility Assessments in Support of Dermagraft-TC™**

<b>Manufacturing Materials (including scaffolding)</b>	<b>Bilaminate Scaffolding<sup>1</sup></b>	<b>Fibroblasts and Extracellular Matrix</b>	<b>Dermagraft-TC™ Finished Product</b>
USP <i>In Vitro</i> Cytotoxicity	USP <i>In Vitro</i> Cytotoxicity	GLP Long-Evans Rat full-thickness skin grafting	SPF Farm Pigs Full-thickness Burn Wound
USP <i>In Vivo</i> Systemic Toxicity	USP Sensitization (Guinea Pig Maximization)	GLP Dermal replacement in mini-pigs	GLP Genotoxicity - Mouse Lymphoma Assay ( <i>In Vitro</i> )
USP Intracutaneous Toxicity	USP Intracutaneous Toxicity	GLP <i>In Vitro</i> Tumorigenicity (colony formation in soft agar)	GLP Genotoxicity - Ames Assay (bacterial reverse mutation assay)
-----	USP <i>In Vivo</i> Systemic Toxicity	GLP Karyology and Isoenzyme Species Verification Analysis	Clinical Persistence <i>in situ</i> (biopsy and male-specific DNA detection in female patients)
----	USP Subchronic Toxicity (Guinea Pig Sensitization and rabbit skin irritation)		----

<sup>1</sup> commercially available product

### Manufacturing Materials

USP Class VI testing of the manufacturing materials for Dermagraft-TC™ was performed. These test results show that the component materials used in Dermagraft-TC™ do not directly, or through their material constituents, produce adverse local or systemic toxic effects *in vivo*. A series of tests was completed on manufacturing components to determine the biological response of animals to the plastics and other polymeric components that have direct or indirect product contact.

The components were assembled and sterilized in the configuration and manner that will be used in commercial manufacturing. Following sterilization, the final assemblies were subject to three Class VI protocols: 1) *in vitro* L929 mouse fibroblast cytotoxicity; 2) *in vivo* systemic toxicity in the mouse model; and 3) intracutaneous irritation in the rabbit. All tests were performed to determine whether leachables extracted from the test materials would cause *in vitro* toxicity, acute toxicity in mice, or local dermal irritation in rabbits. The results of this USP testing established that the materials used in the manufacture of Dermagraft-TC™ do not generate a toxic response in test animals.

### Bilaminate Scaffolding Biocompatibility

In addition to the biocompatibility testing presented for the manufacturing materials, test data have also been generated for the bilaminate scaffolding, which is the scaffold material for production of Dermagraft-TC™. The USP testing described previously (see **Biocompatibility Assessments in Support of Dermagraft-TC™ table**) included testing of the bilaminate scaffolding as part of the polycarbonate cassette which provides the mesh framework for cell growth. To supplement this testing, the sponsor refers to a series of biocompatibility studies that was conducted as part of the premarket approval of the bilaminate scaffolding. This additional testing showed no indications of systemic toxicity, sensitization, or reactivity when tested in several animal species.

### Genotoxicity

Two genotoxicity studies have been performed on Dermagraft-TC. One test is a bacterial reverse mutation assay designed to evaluate the mutagenic potential of the final device in several strains of *Salmonella typhimurium* and in *Escherichia coli*. The second study is an *in vitro* mammalian cell gene mutation test evaluated in L5178Y mouse lymphoma cells. The test results indicated that Dermagraft-TC was nonmutagenic under the conditions of these test methodologies.

### Animal Studies Supporting Biocompatibility

To support the biocompatibility of Dermagraft-TC™, implant studies utilizing Long-Evans rat and mini-pig animal models were performed. The first was a rat study that tested the potential of placing cultured skin equivalent into a full-thickness wound. In this

study, the scaffolding was inoculated with previously isolated and cultured rat dermal fibroblasts and then grown to confluence. The resultant product was placed on full thickness wounds. Histologically, well organized skin tissue grew around the grafts, with a normal-appearing dermal-epidermal junction. The dermal grafts supported epithelialization and appeared similar to the dermal-epidermal grafts on histologic examination. This study provided evidence of the safety and biocompatibility of placing dermal fibroblasts and associated extracellular matrix material into full-thickness wounds in pigs.

In the second study, a similar device (using Dexon mesh as the scaffolding) was evaluated as a dermal replacement in mini-pigs with implants over six months. This study was designed to determine if the device cultured with human fibroblasts would incorporate safely into full-thickness wounds. This device appeared to incorporate well into full- and split-thickness wounds. No significant adverse effects were noted, up to nine months post-graft. Early inflammatory reactions to the mesh fibers were seen, as expected. However, the device did not appear to be acutely rejected or to lead to graft failure. Wounds treated with the device appeared normal long-term in regard to dermal-epidermal junctions on histology. This study provided evidence of the safety and biocompatibility of placing dermal fibroblasts and associated extracellular matrix material into full-thickness wounds of pigs.

### Immunology

Preclinical evaluation of Dermagraft-TC™ pertinent to the issue of immunology was conducted using specific pathogen-free (SPF) farm pigs. These studies were conducted to evaluate the functionality of Dermagraft-TC™ as well as the histological characteristics associated with the coverage of a burn wound.

Using the SPF pig model, full thickness burns were established, and the wounds were then monitored for the ability to accept Dermagraft-TC™, to form granulation tissue, and to support autografting after removal of the test material. Results of the pig studies showed no evidence of rejection of the test material up to 32 days after placement in the wound bed. Interestingly, included within the study was a comparison of tissue histology from animals that were immunosuppressed (using Cyclosporine and Prednisone) versus an animal that was not immunosuppressed. A comparison of the granulation tissues from the immunosuppressed and non-immunosuppressed pigs showed similar levels of lymphocyte infiltration in reaction to the test material. This suggests that the materials used in this model were well tolerated from an immunologic standpoint.

The fibroblasts used in the manufacture of Dermagraft-TC™ are grown in medium containing bovine calf serum (BCS). The presence of this serum may result in residual concentrations of bovine serum albumin (BSA). Testing in the final product was completed to quantify the amount of BSA in Dermagraft-TC™ to which patients may be exposed. The results indicated that there were approximately 2 µg of BSA per square inch

of Dermagraft-TC™ tissue. The clinical relevance of the BSA content has not been established.

The information provided in this section establishes that the constituent parts of Dermagraft-TC™, namely the dermal fibroblasts, collagen and extracellular proteins, the bilaminate scaffolding, and residual bovine serum albumin from the cell growth medium have demonstrated no immunological activation in these animal studies.

### Tumorigenicity and Persistence

As a corollary to the biocompatibility and immunological issues previously discussed, the safety of fibroblasts as it relates to tumorigenicity is important when considering the practice of placing human fibroblast cells in a wound bed. In addition, an understanding of persistence or the potential for fibroblasts to remain in the wound bed after removal of the device is important in evaluating the relative safety of the device.

While independent studies have shown that fibroblasts are nontumorigenic, testing of cell strains used in Dermagraft-TC™ manufacturing was completed. The assay assessed the capacity of cells to form colonies in soft agar, an indication of anchorage independent growth. These cell lines did not demonstrate anchorage independent growth which is a property of transformed cells. The results of this testing demonstrate that the cell line used in the manufacture of Dermagraft-TC™ is that of normal human fibroblasts and are not transformed.

Fibroblast persistence in the wound bed was evaluated in a series of experiments. Two approaches have been taken to determine the persistence of Dermagraft-TC™ fibroblasts in the burn wound. The first used highly polymorphic microsatellite markers that could be used with all patients, but had limited sensitivity. The first of these was applied to patients treated with the original Dermagraft, viable fibroblasts seeded on a vicryl mesh, product developed for deep partial and full thickness burns. Using this approach, no Dermagraft cells were detected later than two weeks after application in this burn population.

In the second study, persistence of fibroblasts was evaluated by detection of male-specific DNA in biopsies of Dermagraft-TC™-treated wound sites in female patients. In these patients, Dermagraft-TC™ was applied to the burn wound for up to 16 days prior to removal and autografting. Biopsies were “taken immediately after removal of Dermagraft-TC™. No male-specific DNA was detected in the biopsies and was concluded that no viable fibroblast cells remained in the wound site following treatment with Dermagraft-TC™.

### C. Functional Testing

Functional testing has been completed which provides supporting evidence of the structural integrity of Dermagraft-TC™. Included are results of testing on bilaminate

scaffolding, which provides the underlying nylon mesh of the device, and results of animal studies which demonstrate that Dermagraft-TC™ provides the necessary coverage and adherence appropriate for a temporary covering of burn wounds.

#### Elongation and Burst Testing

The principal source of the physical integrity of Dermagraft-TC™ stems from the underlying bilaminate scaffolding on which the fibroblasts are grown. In this study, the elongation and burst force of bilaminate scaffolding was evaluated. In one direction, the percent elongation at breakage was  $350 \pm 58$  percent with a burst force of  $10.3 \pm 2$  pounds per square inch. In the perpendicular direction, the percent elongation at breakage was  $482 \pm 39$  percent with a burst force of  $6.1 \pm 0.6$  pounds per square inch. This testing provided evidence that the bilaminate scaffolding material is relatively elastic and has resistance to bursting. Therefore, as the underlying structural component of Dermagraft-TC™, it provides a source of physical integrity of the product.

#### Animal Studies

Two animal studies provide pertinent information regarding the functional performance of Dermagraft-TC™. From these animal studies, it can be shown that the structure of the device is appropriate for use as a temporary covering of burns to maintain the wound site until autograft is available. The discussion provides data from studies conducted on athymic nude mice and specific pathogen free (SPF) pigs.

#### Mouse Adherence Testing

In the first experiment, the ability of Dermagraft-TC™ to remain adherent in a surgically created wound bed was evaluated. A total of 118 mice were used in the study for the mechanical adherence testing. The biosynthetic bilaminate membrane, Dermagraft-TC™ in 2 forms, one cryopreserved to maintain the viability of the fibroblasts after thawing and the other cryopreserved to have nonviable fibroblasts after thawing, were compared to cadaveric allograft for implants from 1 to 20 days. The results from this study indicated that Dermagraft-TC™ in both forms was adherent to the wound bed.

#### Full-Thickness Burn Wound Grafting in Pigs

The second group of experiments utilized SPF farm pigs to compare the following test materials; Dermagraft-TC™ in 2 forms with viable fibroblasts and without viable fibroblasts, and cryopreserved human cadaveric skin (HCS) for adherence, durability, and support of an autograft on full-thickness burn wounds. The porcine model was used because of the similarities between human and porcine skin. A pilot study of four animals and a larger study of 12 animals were conducted.

In the 4 animal pilot study utilizing 3 immunosuppressed and 1 non-immunosuppressed SPF farm pigs, the test materials all performed similarly in regard to adherence, durability, prevention of infection and acceptance of an autograft. No significant differences were seen between test materials with regard to rejection. In particular, there was no significant difference between the immunosuppressed and non-immunosuppressed animals. No adverse reactions to the test materials were seen in this evaluation.

In the larger study of 12 animals, the test materials were observed and biopsied as per protocol until Day 18 when they were autografted and then observed and biopsied until Day 39. The test materials all performed similarly in regard to adherence, durability, prevention of infection, condition of the granulation bed at the time of autograft, and the acceptance of an autograft. All clinical wound observations and histopathology observations were roughly the same for all test materials except for HCS, which displayed higher exudate values on Days 14 and 18 and increased inflammation on Day 24. There were no adverse device events or evidence of test material rejection within the animal study population.

#### D. Stability, Shipping, and Thawing Studies

Results of testing are presented that support the safe storage, shipping and handling of Dermagraft-TC™ prior to application on the burn wound. Specifically, the testing demonstrated that the product and package integrity were maintained during freezing, storage, shipping and thawing.

##### Stability Study

This section describes the product shelf life or stability testing that was performed. This testing demonstrated that the product was stable for up to 6 months. Various assays were used to evaluate the product following real-time aging to show that there is no significant material degradation over time. Information gathered from the packaging and stability studies demonstrates that Dermagraft-TC™ can be stored frozen for up to 6 months at -70 °C and can be shipped to health care facilities without compromising product integrity.

##### Thawing Study

Also presented are the results of testing which establishes the conditions for the safe thawing of the 2-piece, 5 x 7.5 inch product. The results of this testing support the thawing of single or multiple bioreactors in a 37 °C water bath. Confirmation of the adequacy and safety of the thawing procedure was based on results of product assays that show the product attributes continue to fall within their specifications following this procedure.

## Shipping Studies

The shipping studies included 3 separate tests. The first test determined the maximum time the insulated shipping container would maintain the internal temperature at minimum of -50<sup>0</sup>C for 72 hours when exposed to external temperatures up to 45<sup>0</sup>C. The second test evaluated the durability of the packaging when exposed to extreme vibration and dropping to ensure the product could be shipped safely. The final test evaluated the suitability of the container under actual air freight shipment conditions to maintain package integrity and product sterility. The results of these tests support the safe shipment of Dermagraft-TC<sup>TM</sup> within a single insulated dry ice shipping container by air freight.

### E. Comparability Testing

The clinical trials were done on a modified version of the device. To demonstrate the comparability of structure and function of both the 5 x 7.5 inch marketed device and the original 4 x 6 inch modified version, the following tests were performed by analyzing 3 consecutive lots of each product: 1. MTT reduction assay for cell viability, 2. DNA assay for the total number of cells present, 3. Sirius Red for the amount of collagen, 4 . Aniline Blue to measure ECM proteins and 5. Mouse adhesion force assay.

## **IX. Summary of Clinical Studies**

### **Dermagraft-TC<sup>TM</sup> Clinical Investigations**

Advanced Tissue Sciences had initiated 4 trials in the investigation of Dermagraft-TC<sup>TM</sup> as a temporary skin substitute in the management of deep partial- and full-thickness thermal burn wounds. There have been a total of 89 patients treated with 198 pieces of Dermagraft-TC<sup>TM</sup>.

### **CLINICAL RESULTS**

The following clinical studies have been performed with Dermagraft-TC<sup>TM</sup> using a modified version of the marketed device:

1. 10 subject, randomized, controlled, within-patient, unmasked pilot study.
2. 66 subject, randomized, controlled, paired within-patient, unmasked study to assess the safety and effectiveness of a single piece of Dermagraft-TC<sup>TM</sup>. (Controlled Single-Piece Study)
3. 11 subject, open-label, unmasked study to evaluate the effects of multiple pieces of Dermagraft-TC<sup>TM</sup> (4-20 pieces).
4. 31 patients who were originally enrolled in the Dermagraft-TC<sup>TM</sup> pilot or 66 patient pivotal study, were followed from the original application of Dermagraft-TC<sup>TM</sup>, from 99 to 672 days.
5. 2 patients treated in an emergency use.

**Summary of Single-Piece and Multiple-Piece Studies**

<b>Variable</b>	<b>Controlled Single-Piece Study</b>	<b>Multi-Piece Study</b>
Number of Patients Enrolled	66	11
Age (mean)	36.3 yrs age (range 2-89)	28.2 yrs age (range 6-67)
Gender		
Male	45 (68.2%)	7 (63.6%)
Female	21 (31.8%)	4 (36.4%)
Race		
Caucasian	40 (60.6%)	4 (36.4%)
Black	14 (21.2%)	2 (18.2%)
Hispanic	12 (18.2%)	3 (27.3%)
American Indian	0	1 (9.1%)
Asian	0	1 (9.1%)
Length of Follow-up	28 days post autograft	28 days post autograft
Number of Patients completing 28 day post auto-graft follow-up	48	8 <sup>1</sup>
% BSA <sup>2</sup> Total Burn (mean)	44.3% (range 4-95%)	51.5% (range 12-95%)
% BSA <sup>2</sup> Full Thickness (mean)	27.8% (range 0-95%)	44.6% (range 11-95%)
% BSA <sup>2</sup> Deep Partial Thickness (mean)	16.5% (range 0-50%)	6.9% (range 0-35%)
Number of DGTC Devices Applied	74	102
Length of time <sup>3</sup> DGTC applied (mean)	13.8 days (range 6-42 days)	34.4 days (range 7-74 days)

		13.2 days (median)
% Autograft “take” <sup>4</sup> on post autograft day 14	n=46 patients DGTC 94.7% mean Control 93.1% mean	n=6 patients DGTC (by Patient) 77.7% mean 93% median 81.5% mean (by piece) 96% median

<sup>1</sup>one patient evaluated at Day 14 had Dermagraft-TC™ coverage for 74 days prior to autograft.

<sup>2</sup>Body Surface Area

<sup>3</sup>only temporary coverings that remained on the wound for at least 5 days were included in the effectiveness analysis.

<sup>4</sup>“take” was defined as the amount of the autograft that was present, adherent and vascularized.

### Pilot Study

This study evaluated two forms of Dermagraft-TC™. The study was performed at 3 centers with 10 patients enrolled examining autograft “take” at 14 days post autograft over deep partial- and full-thickness thermal burns, which had temporary coverings. For the 7 patients evaluated for autograft “take”, mean autograft “take” was 97.9% for the form of Dermagraft-TC™ that was subsequently evaluated in the Single piece study, compared to 96.4% for Control (cryopreserved cadaver allograft).

### Controlled Single-Piece Study

There were 66 patients enrolled in 12 centers over an 11 month period. The 12 centers were West Penn Hospital, Shriners Burn Institute (Galveston, TX), University of Tennessee Medical Group, Virginia Health Science Center, University of Iowa Burn Treatment Center, University of California at Davis Medical Center, Texas Southwestern Medical Center, Maricopia Medical Center, Augusta Regional Medical Center, University of California at San Diego Medical Center, Ramsey Medical Center, and Hennepin County Medical Center.

The primary study objective was to demonstrate the equivalence of Dermagraft-TC™ to Control, cryopreserved cadaver allograft, by measuring the percentage of autograft “take” at 14 days after graft placement on the study wounds which had temporary coverings. In this study the treatment wounds were deep partial- and full-thickness thermal burns that had been excised to the level of fat, fascia or dermis.

**Autograft-“take”**

The primary study objective was to demonstrate the equivalence of Dermagraft-TC™ to Control, cryopreserved cadaver allograft, by measuring the percentage of autograft “take” at 14 days after graft placement on the study wounds which had temporary coverings. Dermagraft-TC™ was considered to be equivalent to or better than the Control if the difference (Control-Dermagraft-TC™) in percent “take” of the autograft at post autograft day 14 was no more than 9%. The evaluations of graft “take” were done by the unmasked principal investigator.

The results of autograft “take” at 14 days post autograft, the primary effectiveness endpoint, were obtained on 46 evaluable patients. Twenty patients were excluded for the following reasons: 8 died before post autograft day 14; 2 received treatment other than autograft; 7 had temporary covering application deviations; and 3 had removal of temporary coverings or autograft prior to the endpoint because of medical circumstances.

Analysis of the primary effectiveness endpoint (based on the principal investigator's evaluation) demonstrated that at post autograft Day 14, the mean autograft “take” of wounds treated with Dermagraft-TC™ was statistically equivalent to that of wounds treated with allograft (94.7% for Dermagraft-TC™ vs. 93.1% for frozen cadaver allograft, p=0.0001).

**Percent “take” of Autograft for Post Autograft Days 5, 9, 14, 21, and 28**

<b>Days Post Autograft Number of Patients</b>	<b>Mean % Autograft “take” on Dermagraft-TC™ Wounds</b>	<b>Mean % Autograft “take” on Control Wounds</b>
Day 5 n=47	64.7%	62.4%
Day 9 n=42	80.6%	81.1%
Day 14 n=46	92.4%	91.4%
Day 21 n=40	95.7%	94.7%
Day 28 n=41	97.0%	97.6%

An independent evaluation through photographs of autograft “take” at day 14 post autograft by 3 masked observers supported the results obtained with the subjective evaluation done by the unmasked principal investigator. Photographs were available on 40 of the 46 patients that completed the primary endpoint.

Observer	Autograft “take”			Mean
	1	2	3	
Dermagraft-TC™	96.9%	87.3%	89.3%	91.6%
Control	96.7%	88.6%	91.1%	92.4%

Secondary endpoints were evaluated through unmasked assessments by the Principal investigator. These assessments were done only if the temporary covering remained on the study wound for at least 5 days.

#### Secondary endpoints

1. adherence of the temporary coverings to the underlying wound bed at specified protocol intervals;
2. amount of fluid accumulation under the temporary coverings;
3. incidence of infection of the study wounds;
4. relative ease and method of covering removal prior to autograft placement;
5. vascularity of the study wound beds as determined by the amount of wound bleeding at the time of covering removal; and
6. closure of the wounds following autografting.

#### Adherence

Adherence of the temporary coverings to the wound bed was subjectively assessed by visual inspection to the nearest even numbered percentage by the unmasked investigator. On the temporary covering removal day, there was no statistically significant difference with respect to percent adherence of the temporary coverings between Dermagraft-TC™ (mean 76.6%, range 0-100%) and Control (mean 77.3%, range 0-100%) wounds (p=0.898, n=48).

#### Fluid Accumulation

The amount of fluid accumulation under the temporary coverings was assessed according to a 6 point scale (0=none to 5=heavy) by the unmasked investigator at various timepoints. There was a statistically significant difference: on temporary covering day 5 between Dermagraft-TC™ (mean 1.2) and Control (mean 0.8) (p=0.0038, n=60); on temporary covering day 9 between Dermagraft-TC™ (mean 1.4) and Control (mean 0.8) (p=0.0061, n=50); on temporary covering day 14 between Dermagraft-TC™ (mean 1.6) and Control (mean 0.7) (p=0.0020, n=27); and on day of removal of temporary covering between Dermagraft-TC™ (mean 1.2) and Control (mean 0.7) (p=0.0211, n=48).

#### Ease of Removal

The effort required to remove the temporary coverings assessed by the unmasked investigators according to a 5 point scale (1=it came off too easily, 3=it was optimal, 5=it was excessive). For Dermagraft-TC™ the effort was rated as: 1 for 6 coverings, 2 for 14 coverings, 3 for 27 coverings, 4 for 5 coverings, and 5 for 1 covering. For Control the effort was rated as: 1 for 6 coverings, 2 for 9 coverings, 3 for 27 coverings, 4 for 10 coverings, and 5 for 6 coverings.

#### Excision

The percentage of temporary covering that required surgical excision on the day of temporary covering removal was estimated to the nearest 5% by the unmasked investigator. There was a statistically significant difference for the percentage of

temporary covering requiring excision between Dermagraft-TC™ (mean 0.6%, range 0-30%) and Control (mean 13.8%, range 0-100%) (p=0.002, n=48).

#### Bleeding

Bleeding of the wound on the day of removal of the temporary coverings was rated on a 6 point scale by the unmasked investigator (0=none to 5=heavy). There was a statistically significant difference in bleeding between the Dermagraft-TC™ (mean 2.8) and Control wounds (mean 3.2) (p=0.015, n=49).

#### Wound Closure

There was no statistically significant difference in percent wound closure, as estimated to the nearest 5% by the unmasked investigator, for the meshed autograft placed on the Dermagraft-TC™ and Control wounds for day 5 Dermagraft-TC™ (mean 64.7%) and Control (mean 62.4%)(p=0.204, n=47), day 9 Dermagraft-TC™ (mean 80.6%) and Control (mean 81.1%)(p=0.722, n=42), day 14 Dermagraft-TC™ (mean 92.4%) and Control (mean 91.4%)(p=0.474, n=46), day 21 Dermagraft-TC™ (mean 95.7%) and Control (mean 94.7%)(p=0.557, n=40) and day 28 Dermagraft-TC™ (mean 97%) and Control (mean 97.6%)(p=0.643, n=41) post autografting.

#### Multipiece Study

This study was done to confirm that multiple pieces of Dermagraft-TC when applied to deep partial-thickness and full-thickness excised thermal burn wounds performs adequately regarding temporary coverage and autograft-”take” at Day 14 after graft placement. A total of 11 patients were enrolled in this study. Effective performance of Dermagraft-TC™ was defined as adherence to the wound bed that does not require removal or replacement of greater than or equal to 80% of the covering prior to the time determined by the investigator to be most appropriate for autografting.

Dermagraft-TC™ remained on patients from 7 to 74 days. One patient had 11 pieces of Dermagraft-TC™ on for 63 days, 8 pieces for 73 days and 1 piece for 74 days. Autograft “take” was reported by patient and by piece. There were 6 patients for which autograft “take” at day 14 post autograft could be assessed. Autograft “take” for these 6 patients was 77.7% mean, 93% median. There were 43 pieces of autograft for which autograft “take” at day 14 could be assessed, 81.5% mean, 96% median.

#### Follow-up Study

This study summarized the experience of 31 patients at 10 centers who were originally enrolled in either the Dermagraft-TC™ pilot or single piece study. Of the 31 enrolled, 3 were from the pilot study (at only 1 site) and 28 from the single piece study. Patients had to have received Dermagraft-TC™ at least 3 months prior to this evaluation. The range of follow-up from the original application of Dermagraft-TC™ was 99 to 672 days with a mean of 252.3 days. All study wounds remained 100% closed with no new study wound

site-specific infections and no surgical revisions of the study wounds at the time of the evaluation. There were no adverse device effects reported.

### Emergency Use

The first patient was a 15 y.o. male with 60% TBSA on 10/13/94. The wound bed on the anterior torso was debrided to fascia. The patient received 5 pieces of Dermagraft-TC™ on 10/14/94 that remained on the wound for 33 days. The lower anterior torso debrided to fascia received 3 pieces of Dermagraft-TC™ on 11/2/94 that remained on the wound for 14 days. It was reported that skin integrity over the Dermagraft-TC™ sites remained good when the patient was last seen on 11/02/95. The second patient was a 55 y.o. male with 50% TBSA burn on 12/18/94. The back was debrided to fat and fascia and covered with 5 pieces of Dermagraft-TC™ on 12/19/94 and remained on for 9 days. The patient expired on 12/28/94 from complications of the burn injury determined unrelated to the Dermagraft-TC™ use.

## **X. Safety Profile**

### Adverse Events (AEs)

There were 130 adverse events in the 87 patients treated in the 3 clinical trials. The most frequently occurring adverse events were expected in this population of critically-ill burn patients. None of the less frequently occurring adverse events were reported to have a relationship to the study device.

In the 10 patient pilot trial all 10 patients experienced AEs. The most frequently occurring were fever in 6 patients and cellulitis of the nonstudy wound in 5 patients. One patient was discontinued from the study due to an AE that resulted in loss of temporary coverings.

In the 66 patient pivotal trial AEs were experienced by 63 of the patients. The most frequently occurring was sepsis, 30 patients. There were 12 patients that discontinued from the study prematurely due to AEs. There were 10 patients that died as a result of their AEs. Two patients discontinued due to AEs that resulted in loss of temporary covering.

In the 11 patient multipiece study 10 patients experienced AEs. The most frequently occurring were infection (non-wound infections), 8 patients, and infection of nonstudy wounds, 8 patients. There were 2 patients that died as a result of their AEs.

### Study Wound Site-Specific Infections

There was one effect that was considered possibly related to Dermagraft-TC™: 1 study wound infection that occurred in the 66 patient single piece trial. The infection was diagnosed by culture at the time of temporary covering removal with no clinical evidence

of infection and no adverse effect on the patient.

In the Single Piece study, there were 6 Dermagraft-TC™ wound and 4 Control wound infections prior to application of the temporary covering, during the temporary covering there were 18 Dermagraft-TC™ and 13 Control wound infections, and after autografting there were 2 wound infections on both Dermagraft-TC™ and Control treated sites. Study wound site-specific infections were diagnosed either on the basis of clinical assessment alone, quantitative wound culture alone, or using both clinical and microbiologic criteria.

There was no correlation between infection and patient age, sex, total body surface area of burn, tissue composition of the wound, the length of time the temporary covering was on, and fluid accumulation. Autograft “take” evaluated at Day 14 for those who were evaluable was not adversely affected when a study wound infection was diagnosed during temporary covering. Dermagraft-TC™ is transparent and allows direct visual monitoring of the wound bed which may permit earlier detection of clinical signs of infection.

In the 11 patient Multiple-Piece study, 5 patients were diagnosed with study wound site-specific infections during temporary covering with Dermagraft-TC™. One patient had a study wound infection after autografting. There was only one Dermagraft-TC™ study wound infection reported in the Pilot Study.

# Dermagraft-TC™

HUMAN FIBROBLAST-DERIVED TEMPORARY SKIN SUBSTITUTE

Aseptically processed -- conforming to  
USP sterility requirements, nonpyrogenic

Model No. ZT-8000

Sheet Size:

5x7.5 in. (13x19 cm.)

Cassette contains two sheets

Caution: U.S. federal law restricts this device to sale,  
distribution and use by or on the order of a physician.

#### Warnings:

- ◆ Carefully read instruction sheet provided prior to use
- ◆ Product must not be used if there is evidence of container breakage or thawing
- ◆ Do not reuse, refreeze or sterilize the product or its container
- ◆ Once thawed, use within 2 hours

Storage: Keep frozen at -70°C.

US PAT Nos. 4,963,489; 5,266,480; 5,460,939  
EP No. 0309456

 ADVANCED TISSUE  
SCIENCES™

10933 North Torrey Pines Road  
La Jolla, CA 92037-1005  
Phone: (619) 450-5730  
Fax: (619) 450-5703

Note: Advanced Tissue  
Sciences, Inc. has no  
liability for use of  
Dermagraft-TC™ outside  
this application.

Dermagraft-TC™  
ZT-8000

 ADVANCED TISSUE  
SCIENCES™

← Peel-Off Label -- Before thawing remove  
label and place on patient chart. This label bears  
a unique lot number and will facilitate the collection  
of product monitoring information.

FR0157/001

## DIRECTIONS FOR USE

### **DERMAGRAFT-TC™**

#### **HUMAN FIBROBLAST-DERIVED TEMPORARY SKIN SUBSTITUTE**

#### **DESCRIPTION**

Dermagraft-TC is a human fibroblast-derived temporary skin substitute consisting of a polymer membrane and neonatal human fibroblast cells cultured under aseptic conditions *in vitro* on a nylon mesh. Prior to cell growth, this nylon mesh is coated with porcine dermal collagen and bonded to a polymer membrane (silicone). This membrane provides a transparent synthetic epidermis when applied.

As fibroblasts proliferate within the nylon mesh, they secrete human dermal collagen, matrix proteins and growth factors. Following freezing, no metabolic activity remains; however, the tissue matrix and bound growth factors are left intact. The human fibroblast derived temporary skin substitute provides a protective barrier which is removed prior to autograft. Dermagraft-TC is transparent and allows direct visual monitoring of the wound bed.

#### **BIOLOGICAL COMPONENT TESTING**

Dermagraft-TC is aseptically produced. Extensive testing is performed on Maternal Sera, Donor cells, Master Cell Bank (MCB), Manufacturer's Working Cell Bank (MWCB), and "End-of-Production" Cells (EPC) to exclude the presence of known human pathogenic agents, such as bacteria, fungi, mycoplasma, and viruses. The final product is tested for bacteria, fungi, mycoplasma and pyrogens.

#### **INDICATIONS FOR USE**

Dermagraft-TC is indicated for use as a temporary wound covering for surgically excised full-thickness and deep partial-thickness thermal burn wounds in patients who require such a covering prior to autograft placement.

#### **CONTRAINDICATIONS**

Dermagraft-TC is contraindicated in those patients with known hypersensitivity to porcine dermal collagen or bovine serum albumin. Dermagraft-TC may contain trace amounts of animal proteins due to exposure in the manufacturing process and the pre-coating of the nylon mesh with porcine dermal collagen. In Dermagraft-TC, the nylon mesh is covered by naturally secreted dermal proteins which may reduce exposure of the animal proteins to the patient.

## **WARNINGS**

Allergic reactions have been reported to the polymer membrane and nylon mesh coated with porcine collagen, a major component of Dermagraft-TC. If a patient shows evidence of immunologic reactions, use of the product should be discontinued. No allergic reactions to Dermagraft-TC have been reported to date.

## **PRECAUTIONS**

Do not reuse, refreeze or sterilize the product or its container.

Do not use the product if there is evidence of container damage or premature thawing.

The product must remain frozen at -70°C continuously until thawed no more than two hours before use.

The possibility exists that long duration application of Dermagraft-TC may result in immunological rejection by the patient because the extent of HLA antigen expression by the human fibroblasts remains undetermined. Consequently, physicians should remain alert to this possibility as burn patients regain immune competency.

## **SPECIAL PATIENT POPULATION**

Safety and effectiveness of Dermagraft-TC has not been established in:

1. pregnant women;
2. children under the age of 2 years;
3. wounds on the head, hands, feet or buttocks; and
4. wounds caused by electrical or chemical sources.

## **ADVERSE EVENTS (AE's)**

There were 136 adverse events experienced by 87 patients in the Dermagraft-TC clinical trials. The types of adverse events experienced are common in populations of critically-ill burn patients. None of the adverse events reported in the table below were reported to have a relationship to the study device. Since the studies involved within-patient controls, accounting for a true device relationship for systemic toxicity is unclear.

In the 66 patient Controlled Single-Piece study, there were 6 Dermagraft-TC wound and 4 control wound infections prior to application of the temporary covering, during the temporary covering there were 18 Dermagraft-TC and 13 Control wound infections, and after autografting there were 2 wound infections on both Dermagraft-TC and Control treated sites. In the 11 patient Multiple-Piece study, 5 patients were diagnosed with study wound site-specific infections during temporary covering with Dermagraft-TC. One patient had a study wound infection after autografting. There was one Dermagraft-TC study wound infection reported in the Pilot Study.

There was one effect that was considered possibly related to Dermagraft-TC, a study wound site-specific infection. The infection was diagnosed by culture at the time of temporary covering removal with no clinical evidence of infection.

There was no correlation between infection and patient age, sex, total body surface area of burn, tissue composition of the wound, the length of time the temporary covering was on and fluid accumulation beneath the temporary covering. Autograft take evaluated at Day 14 for those who were evaluable for this endpoint was not adversely affected when a study wound infection was diagnosed during temporary covering.

**Other Adverse Events<sup>1</sup>** (None of these events were reported to have a relationship to the study device)

Event	Pilot Study n=10	Controlled Single-Piece Study n=66	Multiple-Piece Study n=11
Sepsis	2(20%)	30 (45.5%)	6 (54.5%)
Pneumonia	1(10%)	19 (28.8%)	6 (54.5%)
Respiratory disorder	2(20%)	14 (21.2%)	3 (27.3%)
Infection, nonstudy wound	1(10%)	13 (19.7%)	8 (72.7%)
Urinary tract infection	1(10%)	12 (18.2%)	1 (9.1%)
Infection	0	12 (18.2%)	8 (72.7%)
Death	0	10(15.2%)	2(18.2%)
Pneumothorax	1(10%)	9 (13.6%)	1 (9.1%)
Dyspnea	0	8 (12.1%)	0
Kidney Failure	0	7 (10.6%)	2 (18.2%)
Hyperglycemia	4(40%)	7(10.6%)	3(27.3%)
Hypotension	1(10%)	6 (9.1%)	4 (36.4%)
Anemia	0	6(9.1%)	0
Pulmonary Edema	1(10%)	6(9.1%)	1(9.1%)
Fever	6(60%)	5(7.6%)	0
Hypertension	0	5(7.6%)	1(9.1%)
Supraventricular tachycardia	0	5(7.6%)	0
Diarrhea	0	5(7.6%)	0
Agitation	0	5(7.6%)	1(9.1%)
Lab Test Abnormality	5(50%)	4(6.1%)	0
Coagulation Disorder	0	4(6.1%)	2(18.2%)
Apnea	0	4(6.1%)	0
Acute Kidney Failure	0	4(6.1%)	0
Cellulitis - Nonstudy wound	5(50%)	3(4.5%)	1(9.1%)
Deep Thrombophlebitis	1 (10%)	3(4.5%)	0
Cardiac Arrest	1(10%)	3(4.5%)	0
Heart Failure	0	3(4.5%)	1(9.1%)
Sinus Bradycardia	0	3(4.5%)	0
Hypervolemia	3(30%)	3(4.5%)	1(9.1%)
Bone Necrosis	0	3(4.5%)	0
Depression	1 (10%)	3(4.5%)	1(9.1%)
Sinusitis	0	3(4.5%)	0
Skin Ulcer	0	3(4.5%)	1 (9.1%)
Anxiety	4(40%)	1(1.5%)	0
Infection - fungal	0	1 (1.5%) moniliasis	4 (36.4%)
Insomnia	4(40%)	0	1(9.1%)

<sup>1</sup> Reported are those events that occurred in three or more patients of all patients treated in these three trials.

## **CLINICAL STUDIES**

The following clinical studies have been performed with Dermagraft-TC using a modified version of the marketed device:

1. 10 subject, randomized, controlled, within-patient, unmasked pilot study.
2. 66 subject, randomized, controlled, paired within-patient, unmasked study to assess the safety and effectiveness of Dermagraft-TC (Controlled Single-Piece).
3. 11 subject, open-label, unmasked study to evaluate the effects of multiple pieces of Dermagraft-TC (4-20 pieces).
4. 31 patients who were originally enrolled in the Dermagraft-TC Pilot or 66 patient Controlled Single-Piece study, were followed from the original application of Dermagraft-TC, from 99 to 672 days.
5. there were 2 patients treated in an emergency use.

**Summary of Controlled Single-Piece and Multiple-Piece Studies**

Variable	Controlled Single-Piece Study	Multiple-Piece Study
Number of Patients Enrolled	66	11
Age (mean)	36.3 yrs (range 2-89)	28.2 yrs (range 6-67)
Gender		
Male	45 (68.2%)	7 (63.6%)
Female	21 (31.8%)	4 (36.4%)
Race		
Caucasian	40 (60.6%)	4 (36.4%)
Black	14 (21.2%)	2 (18.2%)
Hispanic	12 (18.2%)	3 (27.3%)
American Indian	0	1 (9.1%)
Asian	0	1 (9.1%)
Length of Follow-up	28 days post autograft	28 days post autograft
Number of Patients completing 28 day post autograft follow-up	48	8 <sup>1</sup>
% BSA <sup>2</sup> Total Burn (mean)	44.3% (range 4-95%)	51.5% (range 12-95%)
% BSA <sup>2</sup> Full-Thickness Burn (mean)	27.8% (range 0-95%)	44.6% (range 11-95%)
% BSA <sup>2</sup> Deep Partial - Thickness Burn (mean)	16.5% (range 0-50%)	6.9% (range 0-35%)
Number of Dermagraft-TC Devices Applied	74	103
Length of time <sup>3</sup> Dermagraft-TC applied	13.8 days mean (range 5-42 days)	34.4 days 13.2 days median (range 7-74 days)
% Autograft Take <sup>4</sup> on post autograft Day 14	n=46 patients Dermagraft-TC 94.7% mean Control 93.1% mean	n=6 patients Dermagraft-TC (by patient) 77.7% mean, 93% median 81.5% mean (by piece), 96% median (by piece)

<sup>1</sup> one patient was evaluated at Day 14 and had Dermagraft-TC coverage for 74 days prior to autograft was not included in the Number of Patients Completing 28 day post autograft follow-up.

<sup>2</sup> Body Surface Area

<sup>3</sup> only temporary coverings that remained on the wound for at least 5 days were included in the effectiveness analysis.

<sup>4</sup> take was defined as the amount of the autograft that was present, adherent, and vascularized.

### **Pilot Study**

A pilot study at 3 centers with 10 patients evaluated two forms of Dermagraft-TC. The study examined autograft take at 14 days over deep partial- and full-thickness thermal burns, which had temporary coverings. For the 7 patients evaluated mean autograft take was 97.9% for the form of Dermagraft-TC that was subsequently evaluated.

### **Controlled Single-Piece Study**

There were 66 patients enrolled in 12 centers over an 11 month period. The primary study objective was to demonstrate the equivalence of Dermagraft-TC to Control cryopreserved cadaver allograft, by measuring the percentage of autograft take at 14 days after graft placement on the study wounds which had temporary coverings. In this study the treatment wounds were deep partial and full-thickness thermal burns that had been excised to the level of fat, fascia or dermis.

### **Autograft Take**

Based on the principal investigator's unmasked evaluation at post autograft Day 14, the mean autograft take of wounds treated with Dermagraft-TC was statistically equivalent to that of wounds treated with allograft (94.7% for Dermagraft-TC vs. 93.1% for frozen cadaver allograft,  $p=0.0001$ ,  $n=46$ ; due to the statistical technique used  $p \leq 0.05$  would imply equivalence).

A number of secondary endpoints were assessed by the Principal Investigator. These assessments were done only if the temporary covering remained on the wound for at least 5 days.

### **Adherence**

Adherence of the temporary coverings to the wound bed was subjectively assessed by visual inspection to the nearest even numbered percentage by the unmasked investigator. On the temporary covering removal day, there was no statistically significant difference with respect to percent adherence of the temporary coverings between Dermagraft-TC (mean 76.6%, range 0 - 100%) and Control (mean 77.3%, range 0 - 100%) wounds ( $p=0.898$ ,  $n=48$ ).

### **Fluid Accumulation**

The amount of fluid accumulation under the temporary coverings was assessed according to a 6 point scale (0=none to 5=heavy) by the unmasked investigator at various timepoints. There was a statistically significant difference on day of removal of temporary covering between Dermagraft-TC (mean 1.2) and Control (mean 0.7) ( $p=0.0211$ ,  $n=48$ ).

### Ease of Removal

The effort required to remove the temporary coverings was scored by the unmasked investigator according to a 5 point scale ("1"= it came off too easily, "3"= it was optimal, "5"= it was excessive). There were 28 Dermagraft-TC plus 22 control temporary coverings rated "3" = it was optimal.

### Excision

The percentage of temporary covering that required surgical excision on the day of temporary covering removal were estimated to the nearest 5% by the unmasked investigator. There was a statistically significant difference for the percentage of temporary covering requiring excision between Dermagraft-TC (mean 0.6 %, range 0 - 30%) and Control (mean 13.8%, range 0 - 100%) (p=0.002, n=48).

### Bleeding

Bleeding of the wound on the day of removal of the temporary coverings was rated on a 6 point scale by the unmasked investigator (0= none to 5= heavy). There was a statistically significant difference in bleeding between the Dermagraft-TC (mean 2.8) and Control wounds (mean 3.2) (p=0.015, n=49).

### Multiple-Piece Study

This study was done to confirm that multiple pieces of Dermagraft-TC when applied to deep partial-and full-thickness excised thermal burn wounds perform adequately regarding temporary coverage and autograft-take at 14 days. A total of 11 patients were enrolled in this study at 3 centers. If the Dermagraft-TC remained on the wound for at least 5 days, it was included in the effectiveness analysis.

Dermagraft-TC remained on patients from 7 to 74 days. The following lists the ranges for the length of time the original pieces of Dermagraft-TC remained on the 11 patients: 7-10 days for 38 pieces; 12-23 days for 22 pieces; and 63-74 days for 20 pieces. Autograft take was reported by patient and by piece. There were 6 patients for which autograft take at Day 14 post autograft could be assessed. Autograft take for these patients was a mean of 77.7% and median of 93%. There were 43 pieces of autograft for which autograft take at Day 14 could be assessed, 81.5% mean, 96% median.

### Follow-up Study

Data on 31 patients at 10 centers, 3 patients were from the Pilot study (at only 1 site) and 28 were from the Controlled Single-Piece study were reported. Patients had to have received Dermagraft-TC and subsequent autograft application at least 3 months prior to this evaluation. The range of follow-up from the original application of Dermagraft-TC was 99 to 672 days with a mean of 252.3 days. All study wounds remained 100% closed with no new study wound site-specific infections and no surgical revisions of the study wounds at the time of the evaluation. There were no adverse device effects reported.

## **SURGICAL GUIDELINES**

Necrotic tissue must be fully excised to provide a wound bed suitable for grafting.

Small slits may be cut into Dermagraft-TC to facilitate drainage and adherence. **Dermagraft-TC should NOT be meshed, stretched, or expanded prior to application.**

## **DIRECTIONS FOR USE**

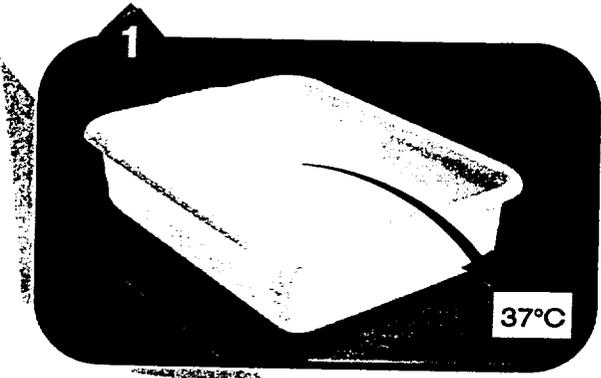
Materials Required for Preparation and Application:

- Water bath (37°C)
- Sterile scissors
- Nonsterile scissors
- Protective insulated thermal gloves
- Surgical gloves
- Clock or timer
- Sterile blunt-end forceps (optional)
- Weights for thawing

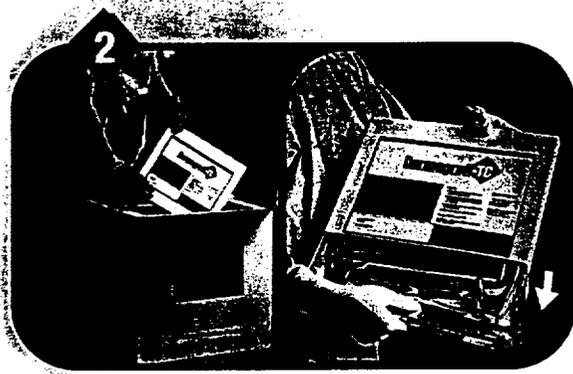
### **Peel-off Label**

Before thawing, remove the peel-off label from the lower left of the Dermagraft-TC box label and place it on the patient's chart. This label bears a unique lot number and will facilitate the collection of product monitoring information.

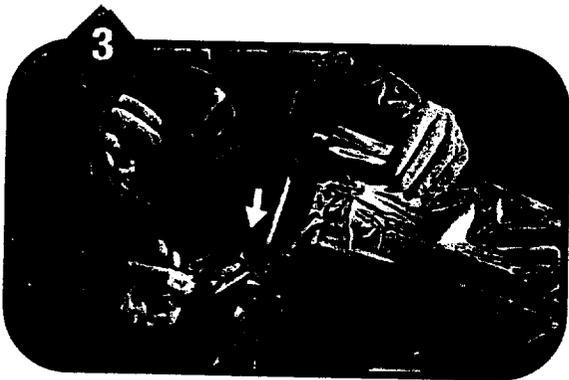
## PREPARATION



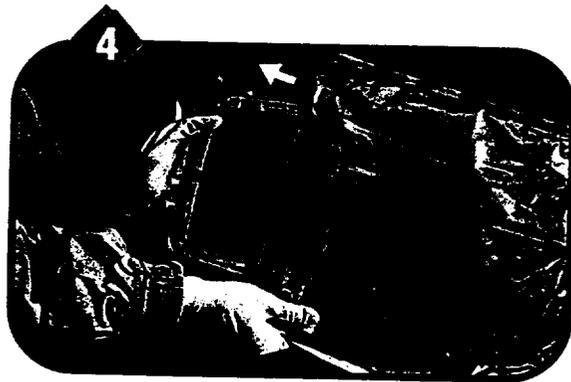
Thaw in water bath only. Preheat circulating water bath or fill a tub or sink with water to 37°C (98.6°F). **Water temperature must not exceed 37°C. Do not microwave.**



Using protective gloves, remove Dermagraft-TC from either the freezer or shipping box. **Product must remain frozen at -70°C until thawing process begins.**

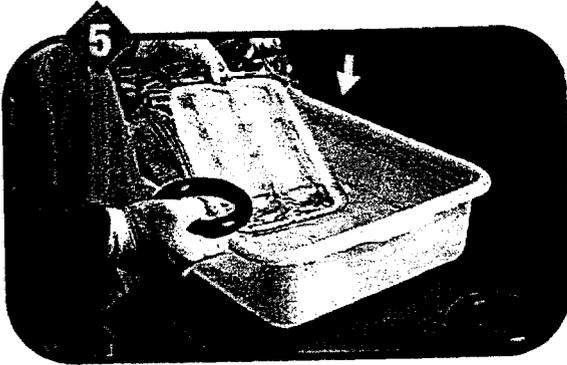


Immediately tear open the outer foil bag at the tear notch.

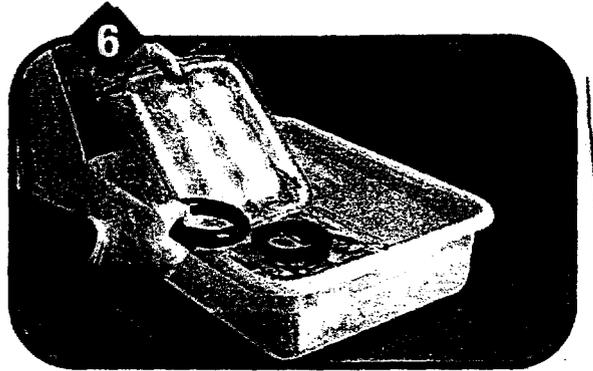


Remove the clear bag containing both a plastic tray and cassette from the foil pouch. Do not open the bag.

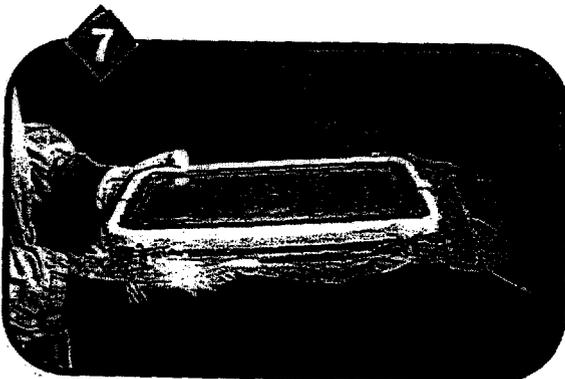
**PREPARATION (cont.)**



Using a weight, completely submerge the clear bag horizontally in the 37°C water bath. Water temperature does not need to be monitored from this point. Allow 15 to 25 minutes for thawing. The process is complete when there is no ice remaining in the cassette(s). **DO NOT overheat or refreeze Dermagraft-TC.**

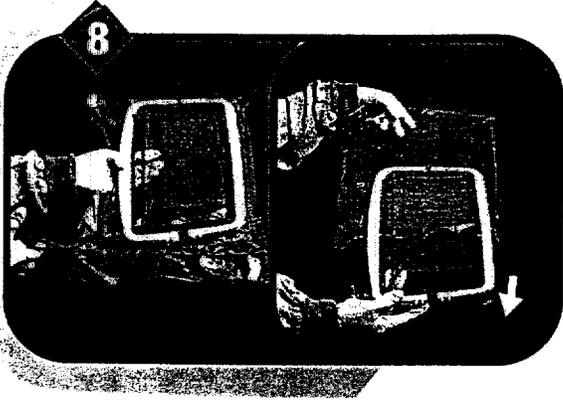


Multiple cassettes may be thawed simultaneously. A weight must be placed between each cassette to allow adequate circulation.

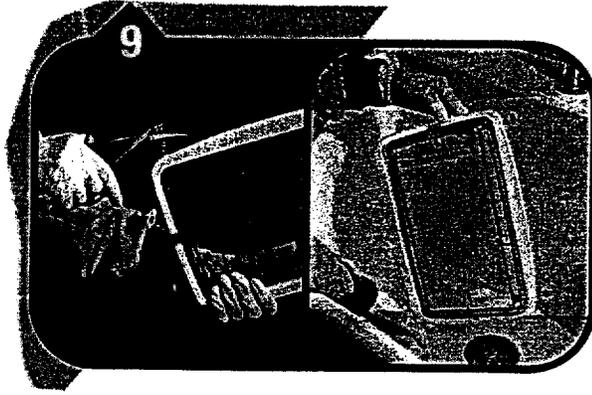


After thawing, remove the cassette from the water bath and place horizontally until ready for application. **Dermagraft-TC must be applied within two hours of thawing.**

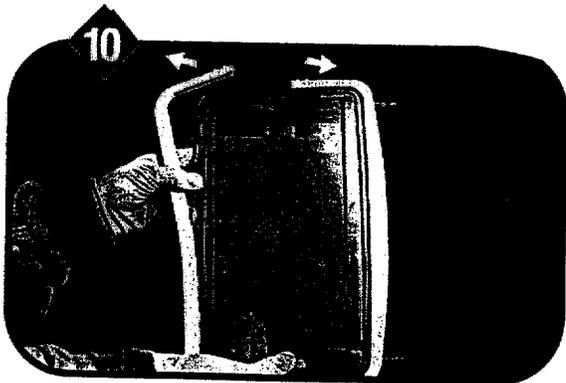
**PREPARATION (cont.)**



When ready to apply, use nonsterile scissors to cut the clear bag surrounding the cassette. Remove the cassette from the clear plastic bag and tray.



Holding the cassette with the drain tubes upward, use sterile scissors to cut both tubes. Completely drain the cassette over a basin or sink.



Remove the retaining band by lifting up the ends and peeling the band from the edges of the cassette.

**PREPARATION (cont.)**



Use the center clasp to gently open the cassette. A thin layer of human cells (tissue overgrowth) may attach to the product removal tab during manufacturing. If necessary, it may be easily removed prior to application using sterile forceps.

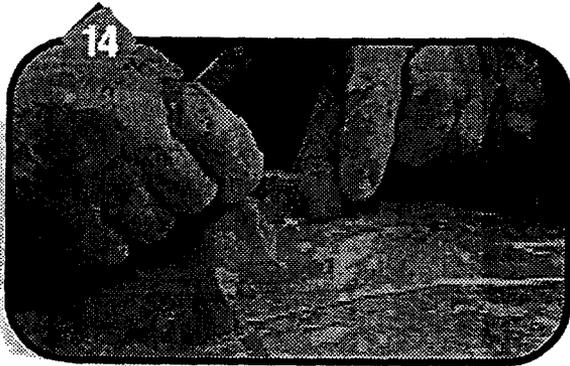


Present the cassette.

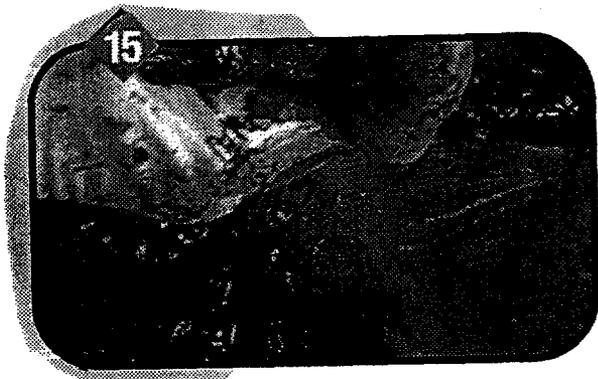


Remove Dermagraft-TC from the cassette by pressing down on the center of the product removal tab and grasping its top edge. Gently pull Dermagraft-TC away from the cassette.

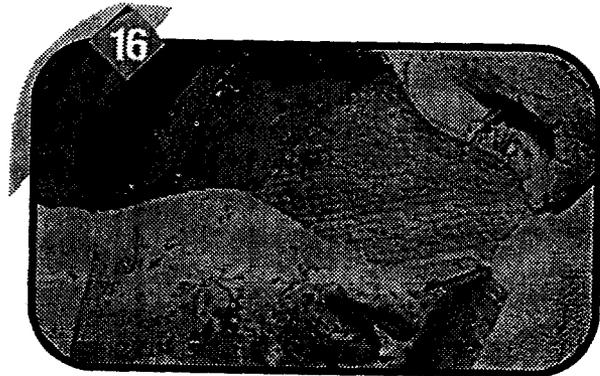
## APPLICATION



Place Dermagraft-TC on the fully excised wound bed following instructions on the product removal tab.



Remove the product removal tab once Dermagraft-TC is correctly placed on the wound. If necessary, trim with surgical scissors (in a similar fashion to cutting cadaveric tissue) to prepare Dermagraft-TC to the correct size and shape. Gently smooth the product into place using a gloved finger or blunt forceps.



Attach securely to the wound bed according to customary surgical practice using staples or sutures. Multiple pieces are applied in a similar fashion to single pieces. Edges should meet edge-to-edge so that both pieces can be attached together and to the patient with one surgical attachment. After attachment, Dermagraft-TC should be taut; however, it should not be stretched or meshed.

## **APPLICATION NOTES**

Once Dermagraft-TC has been applied, dress the wound according to your institution's customary practice. Post-operative care of the patient should follow standard protocols and practices.

If desired, staples or sutures may be removed 5 days after application.

Dispose of all portions of Dermagraft-TC, its cassette, and any other components in accordance with institutional or governmental environmental regulations.

## **REMOVAL OF DERMAGRAFT-TC FROM WOUND BED**

After removing staples or sutures, remove Dermagraft-TC by peeling. If peeling is not possible, the covering should be surgically excised.

### **How Supplied**

Dermagraft-TC™ is supplied in a cassette containing two aseptically processed (conforming to USP sterility requirements) sheets, each approximately 5 inches by 7.5 inches (12.5 x 19 cm).

Dermagraft-TC is an aseptically processed product and grown in the cassette under aseptic conditions; only those components and surfaces having contact with the product conform to USP sterility requirements and are non-pyrogenic.

### **STORAGE**

Dermagraft-TC must be stored at -70°C.

Results from shelf-life studies performed on product that was stored for six months at this temperature indicated that the product still conformed to USP sterility requirements and was non-pyrogenic. Degradation of cellular matrix components did not occur.

**CUSTOMER ASSISTANCE**

For product orders, technical support, product questions, reimbursement information or to report any adverse reactions or complications, call Advanced Tissue Sciences, Inc. -- Customer Service Department 24 hours a day toll-free at (888) 287-7546.

**ADVANCED TISSUE SCIENCES, INC.**

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US PAT Nos. 4, 963, 489; 5, 266, 480; 5, 460, 939  
EPC No. 0309456

**CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE,  
DISTRIBUTION, AND USE BY OR ON THE ORDER OF A PHYSICIAN.**

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Date: 03/97