SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

DEVICE GENERIC NAME:	Graftskin
DEVICE TRADE NAME:	Apligraf® (Graftskin)
APPLICANT:	Organogenesis Inc. 150 Dan Road Canton, MA 02021
PREMARKET APPROVAL APPLICATION (PMA):	P950032
SUPPLEMENT NUMBER:	S016
DATE OF PANEL RECOMMENDATION:	May 8, 2000
DATE OF NOTICE OF APPROVAL OF APPLICATION:	June 20, 2000
EXPEDITED REVIEW:	Expedited processing was authorized on August 7, 1995, based on the potential of Apligraf® to provide a clinically important advance over existing alternatives in the treatment of neuropathic diabetic foot ulcers.

II. INDICATIONS FOR USE

Apligraf® is indicated for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. A Summary of the Safety and Effectiveness Data for this indication can be found at *http://www.fda.gov/cdrh/pdf/p950032.pdf.*

Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure.

III. DEVICE DESCRIPTION

Apligraf is supplied as a living, bi-layered, skin substitute, which contains Type I bovine collagen, extracted and purified from bovine tendons and viable allogeneic human fibroblast and keratinocyte cells isolated from human infant foreskin. Apligraf consists of two primary layers. The upper "epidermal-like" layer, formed of living human keratinocytes, has a well differentiated stratum corneum which has been shown in *in vitro* experiments to provide a natural barrier to topical infection and wound desiccation. In the supporting "dermis-like" layer of Apligraf, the major cell type is the fibroblast. Apligraf fibroblasts produce many of the matrix proteins found in human dermis, such as collagen type IV, tenascin, decorin, hyaluronate, and fibronectin. In addition, collagen type IV, laminin, laminin 5, heparin sulfate, proteoglycan, and β_4 integrin are present at the dermal-epidermal junction. Apligraf also expresses many of the cytokines found in human skin including PDGF-A, PDGF-B, TGFα, TGFβ_1, TGFβ_3, ECGF, FGF-1, FGF-2, FGF-7, IGF-1, IGF-2, CSF, IL-lα, IL-6, IL-8 and IL-11. Other cells found in human skin, Langerhans cells, melanocytes, macrophages and lymphocytes as well as secondary structures such as blood vessels and hair follicles are not present in Apligraf. In a 10 patient venous leg ulcer study to determine the longevity of Apligraf cells, 2 of 8 patients evaluated at 4 weeks demonstrated Apligraf DNA. Neither of these patients showed Apligraf DNA at 8 weeks.

Apligraf is supplied ready to use, in a plastic container/carrier and is intended for single use only. This container protects and supports the product and provides a supply of agarose gel nutrient medium to maintain cell viability until use. The carrier is sealed in a heavy gauge polyethylene bag containing a 10% CO_2/air atmosphere. Apligraf is kept in the sealed bag at 20-31°C until use. Apligraf is supplied as a circular disk 75 mm in diameter. The thickness of the product is 0.75 mm. The agarose shipping medium contains agarose, L-glutamine, hydrocortisone/bovine serum albumin, bovine insulin, human transferrin, triiodothyronine, ethanolamine, O-phosphorylethanolamine, adenine, selenious acid, DMEM powder, HAM's F-12 powder, sodium bicarbonate, calcium chloride and water for injection.

To maintain cell viability, the product is aseptically manufactured, but not terminally sterilized. Apligraf is shipped following a preliminary sterility test with a 48 hour incubation to determine the absence of microbial growth. Final (14 day incubation) sterility tests results are not available at the time of application.

Information concerning the following sections of this Summary of Safety and Effectiveness Data is included in the product labeling at the end of this document.

IV. CONTRAINDICATIONS

- Apligraf is contraindicated for use on clinically infected wounds.
- Apligraf is contraindicated in patients with known allergies to bovine collagen.
- Apligraf is contraindicated in patients with a known hypersensitivity to the components of the Apligraf agarose shipping medium.

The warnings and precautions can be found in the Apligraf labeling, which is available on the FDA web site at *http://www.fda.gov/cdrh/pdf/p950032.pdf.*

V. ALTERNATIVE PRACTICES AND PROCEDURES

Extensive debridement of non-viable tissue, saline moistened dressings and off loading to decrease pressure on the study extremity are the standard of treatment for neuropathic diabetic foot ulcers. Surgical alternatives for neuropathic diabetic foot ulcers include arterial bypass grafting to re-establish blood supply and skin grafting.

VI. POTENTIAL ADVERSE EFFECTS

Information about the adverse events observed in the treatment of Venous Leg Ulcers (VLU) may be found in the product labeling.

Regarding the Treatment of Diabetic Foot Ulcers (DFU)

A total of 208 patients (112 Apligraf, 96 Control) were evaluated for safety in a clinical trial for the treatment of neuropathic diabetic foot ulcers. Adverse events were recorded as mild, moderate, severe or life-threatening.

There were no life-threatening adverse events and 10 severe infections reported in the Apligraf group, and there were 2 reports of life threatening adverse events and 18 reports of severe infections in the Control arm. The severe infections in Apligraf patients include 1 report of wound infection, 7 reports of cellulitis, and 2 reports of osteomyelitis. In the Control arm, the severe infections were: 4 reports of wound infections, 4 reports of cellulitis, and 10 reports of osteomyelitis. The 2 life threatening events experienced by

patients in the Control arm (death, dyspnea) were not related to Control treatment. When all infections regardless of severity are considered (wound infection, cellulitis, and osteomyelitis), 6 Apligraf and 5 Control events were assessed as related to the ulcer treatment.

All reported adverse events that occurred in Apligraf patients in the DFU pivotal clinical study at the incidence of 1% or greater are listed in Table 1 in descending order according to frequency. For Apligraf treated patients, there was no relationship between the number of applications of Apligraf and the number or severity of adverse events.

Table 1

Adverse Events Reported in Greater than 1.0% of Apligraf Patients in the Diabetic Foot Ulcer Study

	Apligraf (n = 112)	Control (n = 96)
	Total	Total
Neuropathic ulcer (non-study site[2])	19 (17.0%)	9 (9.4%)
Suspected wound infection[1] (non-study site)	15 (13.4%)	7 (7.3%)
Non-neuropathic skin alteration (non-study site)	13 (11.6%)	11 (11.5%)
Suspected wound infection[1] (study site)	12 (10.7%)	13 (13.5%)
Cellulitis[3] (non-study site)	11 (9.8%)	4 (4.2%)
Cellulitis[3] (study site)	10 (8.9%)	8 (8.3%)
Osteomyelitis (non-study site)	10 (8.9%)	3 (3.1%)
Vesicular bullous rash (non-study site)	9 (8.0%)	5 (5.2%)
Pain (overall body)	8 (7.1%)	4 (4.2%)
Fungal infection (non-study site)	7 (6.3%)	9 (9.4%)
Hypoglycemia	7 (6.3%)	3 (3.1%)
Infection (overall body)	6 (5.4%)	4 (4.2%)
Hematoma (non-study site)	6 (5.4%)	2 (2.1%)
Deteriorating ulceration (study site)	5 (4.5%)	6 (6.3%)
Rash (non-study site)	5 (4.5%)	4 (4.2%)
Non-neuropathic skin alteration (study site)	5 (4.5%)	2 (2.1%)
Pain (non-study site)	5 (4.5%)	1 (1.0%)
Bone Dislocation (non-study site)	5 (4.5%)	1 (1.0%)

Table 1 (continued)
Adverse Events Reported in Greater than 1.0% of
Apligraf Patients in the Diabetic Foot Ulcer Study

	Apligraf (n = 112)	Control (n = 96)
	Total	Total
Peripheral edema	4 (3.6%)	11 (11.5%)
Accidental injury (overall body)	4 (3.6%)	8 (8.3%)
Injury accident (non-study site)	4 (3.6%)	5 (5.2%)
Fever (overall body)	4 (3.6%)	5 (5.2%)
Hyperglycemia	4 (3.6%)	4 (4.2%)
Dry skin (non-study site)	4 (3.6%)	2 (2.1%)
Chest pain	4 (3.6%)	1 (1.0%)
Bronchitis	4 (3.6%)	0 (0.0%)
Osteomyelitis (study site)	3 (2.7%)	10 (10.4%)
Nausea	3 (2.7%)	6 (6.3%)
Pharyngitis	3 (2.7%)	6 (6.3%)
Anemia	3 (2.7%)	5 (5.2%)
Right heart failure	3 (2.7%)	3 (3.1%)
Abscess (study site)	3 (2.7%)	3 (3.1%)
Urinary tract infection	3 (2.7%)	2 (2.1%)
Deteriorating ulceration (non-study site)	3 (2.7%)	2 (2.1%)
Gastroenteritis	3 (2.7%)	2 (2.1%)
Cataract	3 (2.7%)	2 (2.1%)
Abscess (overall body)	3 (2.7%)	0 (0.0%)
Gastritis	3 (2.7%)	0 (0.0%)
Spontaneous bone fracture	3 (2.7%)	0 (0.0%)
Diarrhea	2 (1.8%)	8 (8.3%)
Positive wound culture[4] (study site)	2 (1.8%)	3 (3.1%)
Arthrosis (non-study site)	2 (1.8%)	3 (3.1%)
Malaise	2 (1.8%)	2 (2.1%)
Rash (study site)	2 (1.8%)	2 (2.1%)
Hematoma (study site)	2 (1.8%)	2 (2.1%)
Gangrene (non-study site)	2 (1.8%)	2 (2.1%)
Dyspepsia	2 (1.8%)	1 (1.0%)
Injury accident (study site)	2 (1.8%)	1 (1.0%)
Infection (non-study site)	2 (1.8%)	0 (0.0%)
Gangrene (study site)	2 (1.8%)	0 (0.0%)
Spontaneous bone fracture (non-study site)	2 (1.8%)	0 (0.0%)
Viral infection	2 (1.8%)	0 (0.0%)
Back pain	2 (1.8%)	0 (0.0%)
Angina pectoris	2 (1.8%)	0 (0.0%)
Arteriosclerosis	2 (1.8%)	0 (0.0%)
Cardiomegaly	2 (1.8%)	0 (0.0%)
Gastrointestinal carcinoma	2 (1.8%)	0 (0.0%)
Colitis	2 (1.8%)	0 (0.0%)
Rhinitis	2 (1.8%)	0 (0.0%)
Arthritis	2 (1.8%)	0 (0.0%)
Confusion	2 (1.8%)	0 (0.0%)

In the clinical trials the following definitions were used:

[1]*Suspected Wound Infection:* a wound with at least some clinical signs and symptoms of infection such as increased exudate, odor, redness, swelling, heat, pain, tenderness to the touch, and purulent discharge; quantitative culture was not required.

[2]*Non-study site event* – An adverse event occurring on either extremity, but not located at or involving the study ulcer.

[3]*Cellulitis:* a non-suppurative inflammation of the subcutaneous tissues extending along connective tissue planes and across intercellular spaces; widespread swelling, redness and pain without definite localization.

[4]*Positive wound culture:* reported as an adverse event, but not reported as a wound infection.

Table 2 lists all DFU infectious adverse events (i.e., wound infection, cellulitis, osteomyelitis, gangrene, abscess, and fungal infection) as well as resections and amputations occurring on the study limb by first occurrence.

Table 2
Infectious Adverse Events and Amputations Occurring on the Study Limb in Diabetic Foot Ulcers by Number of Apligraf Applications

# Applications	# Patients n=112	# Closed	Days to Closure	# First Infections on Study Limb	# Amputations and Resections on Study Limb
1	10 (8.9%)	9/10 (90.0%)	15 (7-57)	1	0
2	11 (9.8%)	8/11 (72.7%)	15 (8-36)	2	0
3	15 (13.4%)	10/15 (66.7%)	22 (22-29)	5	0
4	17 (15.2%)	9/17 (52.9%)	36 (29-78)	6	1
5	59 (52.7%)	27/59 (45.8%)	51 (36-88)	24	6
Total Apligraf Patients	112	63 (56%)	36 (7-88)	38/112 (34%)	7
Total Control Patients	96	36 (38%)	50 (15-92)	36/96 (38%)	15

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VII. MARKETING HISTORY

In the United States, Apligraf was approved on May 22, 1998 for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy. In Canada, Apligraf was approved for the same patient population on August 12, 1997.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

The testing performed in the original application was adequate to support the safety and effectiveness of the device for the treatment of patients with venous insufficiency ulcers. Table 3 summarizes the new preclinical studies submitted in Supplement 16 in support of device use on diabetic foot ulcers.

Table 3
Apligraf Pre-Clinical Studies

Development & Characterization Studies (cont.)	
Study	Results/Conclusions
Tissue Remodeling and Cellular Persistence in Skin Construct Implants	Both keratinocytes and fibroblasts persisted for at least one year after grafting onto athymic mice. Matrix remodeling was a slow and steady process similar to uninjured skin. Rapid maturation of normal barrier function and basement membrane was demonstrated. The results demonstrated the biological potential for long-term persistence of HEPs and HDFs on nude mice which is in contrast with clinical studies where the persistence of Apligraf is not observed for more than 4 weeks.
Remodeling of a Bioengineering Living Skin Construct Grafted onto Athymic Mice	At 365 days post graft, human cells are still present and biologically active at the wound site. Myofibroblasts disappear by apoptosis and therefore there is no development of a hypertrophic scar. No signs of abnormal skin development or hyper- inflammation were found.
Response of Apligraf to Physical Injury In Vitro	After *in vitro* injury, re-epithelialization and differentiation of Apligraf placed on a dermal substitute was observed. Cytokine gene expression was similar to human skin during wound repair.

Table 3 (cont.)
Apligraf Pre-Clinical Studies

Immunology Studies	
Characterization of Primary and Secondary Allogenic T Cell Responses after Priming with HLA-Matched Professional and Non-Professional APC	Keratinocytes and fibroblasts do not prime allogenic T cells nor do they activate T cells primed by HLA matched dendritic cells.

APC: antigen presenting cell; HDF: human dermal fibroblast; HEP: human epidermal keratinocyte.

IX. SUMMARY OF THE RESULTS OF THE CLINICAL INVESTIGATION

The clinical data provided in the original application were sufficient to support safety and effectiveness claims for device use in the treatment of chronic venous insufficiency leg ulcers. These data are summarized in the package labeling which is available on the FDA Web site at *http://www.fda.gov/cdrh/pdf/p950032.pdf.* This section describes the new clinical submitted in Supplement 16.

The following is a summary of the large scale study designed to support approval, i.e., "Protocol 95-DUS-001, "A Multi-Center Prospective Randomized Controlled Clinical Trial of Graftskin for the Treatment of Diabetic Foot Ulcers".

Study Design:
A prospective, randomized, controlled, multi-center, unmasked study was conducted to evaluate the safety and efficacy of Apligraf in comparison to Control treatment, saline moistened gauze in the treatment of diabetic neuropathic foot ulcers. The study population included consenting patients who were between 18 and 80 years old, with a 0.4 cm^2 – 16.3 cm^2 full-thickness foot ulcer of neuropathic etiology of at least 2 weeks duration located on the plantar, medial or lateral surface of the foot which extended through the dermis, but without tendon, muscle or bone exposure. The study ulcer was also at least 2 cm away from any other ulcers on the same extremity. The study participants were required to be: diagnosed with type 1 or type 2 diabetes, a HbA1C between 6% and 12% and available for six-month follow-up. Patients were excluded for ulcers with tracts or tunnels, a clinical infection at the study ulcer site, ABI < 0.65, active Charcot's foot at the study extremity, a study ulcer that healed > 30% from post-debridement at Study Day –7 to Day 0, renal dialysis, history of alcohol or substance abuse within one year, acute or chronic hepatitis, receiving corticosteroids, immuno-suppressive agents, radiation therapy or chemotherapy one month prior to study enrollment, or enrollment in clinical studies evaluating a device within the past 30 days or within the past 3 months for pharmaceuticals or biologics.

Two hundred seventy-seven patients were entered into the screening phase of the study. Sixty-nine patients did not meet inclusion/exclusion criteria. After randomization and screening, 208 patients were treated in the study, i.e., 112 received Apligraf and 96 received Control therapy. Twenty-two patients per group were discontinued prior to the Study Month 6 visit. Patients received 12 weeks of treatment and 3 additional months of follow-up. Complete wound closure was evaluated by or on 12 weeks. Patients were evaluated weekly for the first 12 weeks with mid-week visits for dressing changes from Day 0 through Week 5 and follow-up visits at Months 4, 5 and 6.

Both treatment groups received good ulcer care consisting of sharp debridement, saline moistened dressings and a non-weight bearing regimen. All patients in the Apligraf treatment group received Apligraf at Day 0. At Study Weeks 1, 2, 3 and 4, if Apligraf coverage was less than 100% and the wound was not progressing to healing then an additional Apligraf unit was applied. A maximum of 5 Apligraf applications were allowed. Apligraf was dressed with saline-moistened non-adherent dressing, tape, dry gauze, petrolatum gauze and gauze wrap. The Control treated patients received saline-moistened non-adherent dressing, tape, saline moistened gauze, dry gauze, petrolatum gauze and gauze wrap from Day 0 through Study Week 4.

Patients in both treatment groups who did not heal by Study Week 5 were treated with saline-moistened gauze, dry gauze, petrolatum gauze and gauze wrap from Study Week 5 through Study Week 12. The patients were instructed to change this dressing two times per day.

Patients were instructed to avoid weight bearing on the affected foot throughout the duration of the study. During the first 6 weeks patients were instructed to use crutches or a wheelchair. Each patient was fitted with a customized tri-density sandal. These sandals were to be worn throughout the entire study.

In keeping with good medical practice, early detection and treatment of ulcer infection using standard procedures was advised.

DFU Study Endpoints:

The primary study endpoint was 100% study wound closure by or on Study Week 12. "Complete wound closure" was defined as full epithelialization of the wound with the absence of drainage. "Epithelialization" was defined as a thin layer of epithelium visible on the open wound surface.

The primary efficacy endpoint was examined using a time to 100% study wound closure analysis that evaluated the incidence of 100% study wound closure per unit time. A categorical analysis that evaluated the incidence of 100% study wound closure by or on Study Week 12 was also performed as a supporting analysis.

Secondary endpoint measurements included: undermining, maceration, exudate, granulation, eschar, fibrin slough, and overall assessment from baseline to the 6 month

visit.

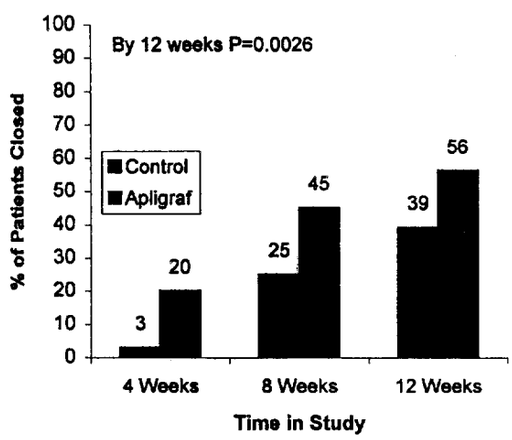
DFU Results:

DFU Baseline Demographics:
The baseline demographics in the Apligraf and Control arms were comparable for all parameters evaluated, including severity and type of diabetes, gender, race, age and ulcer area.

DFU Study Drop-outs:
The discontinuation rate for all patients prior to the 6 month evaluation was 44/208 (21%) including 22 Apligraf and 22 Control patients.

Incidence of 100% Wound Closure:
Apligraf used with standard dressings provided a statistically significant improvement in the incidence of ulcer closure per unit time when compared to Control therapy. The overall closure rate was 56.3% (63/112) for Apligraf and 37.5% (36/96) for Control patients by or on 12 weeks (p=0.0082 by the Fisher's exact test (2-tailed)). In the Kaplan-Meier analysis (Figure 1), the estimated frequency of wound closure at 12 weeks was 56% for Apligraf and 39% for Control (p=0.0026). In the Cox's Regression Analysis, which accounted for the healing pattern over the 12 week efficacy timeline, closure rates of 58% and 32% at week 12 were predicted for Apligraf and Control patients, respectively, (p=0.0001).

Figure 1
Frequency of Complete DFU Wound Closure as a Function of Time (Kaplan-Meier) (Treated Population n=208)



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DFU Incidence of Closure per Unit Time - In a Kaplan-Meier life table analysis, median times of 65 and 90 days were calculated for when 50% of the Apligraf and Control patients achieved wound closure, respectively, (p=0.0026). A Cox's Proportional Hazards Regression Analysis of these data determined that the covariables: pooled center, baseline ulcer area, and Charcot status had significant effects on the time to 100% wound closure. Adjusted median times to closure from this analysis were 66 and 90 days for Apligraf and Control patients, respectively (p=0.0001).

DFU Duration of Wound Closure - The durability of complete wound closure was calculated from the first and last study days in which a Wound Closure case report form (CRF) was checked closed. In this analysis, the mean number of days for wound closure for patients who attained complete closure by or on 12 weeks and completed the study was 114 days for Apligraf patients and 100 days for Control patients. Similarly, the mean number of days of ulcer closure for all patients showed no significant differences for Apligraf (108 days) and Control (95 days) patients.

DFU Ulcer recurrence - The incidence of DFU recurrence as a function of device applications is presented in Table 4.

Table 4

Ulcer Recurrence in Diabetic Foot Ulcers by Number of Applications

#Applications	# Patients n=112	# Closed	#Re-opened ≤ 4 Weeks	#Re-closed by 6 months	#Re-opened > 4 Weeks	#Re-closed by 6 months
1	10 (8.9%)	9	4/9 (44%)	4/4	0/9 (0%)	NA
2	11 (9.8%)	8	2/8 (25%)	2/2	1/8 (13%)	0/1
3	15 (13.4%)	10	4/10 (40%)	4/4	0/10 (0%)	NA
4	17 (15.2%)	9	1/9 (11%)	0/1	1/9 (11%)	0/1
5	59 (52.7%)	27	11/27 (41%)	9/11	1/27 (4%)	1/1
Apligraf Total	112	63	22/63 (35%)	19/22 (86%)	3/63 (5%)	1/3 (33%)
Control	96	36	13/36 (36%)	8/13 62%)	3/36 (8%)	2/3 (67%)

An additional analysis of ulcer recurrence for all patients healed by 12 weeks showed that the incidence of ulcer recurrence at four, five and six months was 12.5% (7/56), 2.0% (1/49), and 5.9% (3/51) in the Apligraf group and 10.3% (3/29), 3.4% (1/29), and 12.9% (4/31) in the Control group, respectively.

DFU Secondary endpoints - Between Study Day 0 and Study Week 12, both Apligraf and Control groups show statistically significant improvement in undermining, maceration,

exudate, granulation, eschar and fibrin slough. At Study Week 12, Apligraf showed statistically significant improvements when compared to control in maceration ($p=0.0233$), exudate ($p=0.0290$) and eschar ($p=0.0293$).

DFU Baseline status impact on wound closure - The impact of patient baseline status on wound closure was evaluated for Charcot joint deformity, diabetes type, and ulcer location. The results of these analyses are presented in Table 5.

Table 5
Pre-Treatment Status and Wound Closure
DFU Treated Population (n=208 patients)

	Pre-Treatment Status		Number and Percent of Wound Closure by 12 Weeks	
Patient Condition	No. and (%) Apligraf	No. and (%) Control	No. and (%) Apligraf	No. and (%) Control
Total	112 Patients	96 Patients	63 (56.3%)	36 (37.5%)
Charcot Joint Deformity				
Absent	95 (84.8%)	74 (77.1%)	60/95 (63.2%)	28/74 (37.8%)
Inactive	17 (15.2%)	22 (22.9%)	3/17 (17.6%)	8/22 (36.4%)
Diabetes*				
Type 1 (IDDM)	41 (36.6%)	26 (27.1%)	20/41 (48.8%)	6/26 (23.1%)
Type 2 (NIDDM)	69 (61.6%)	70 (72.9%)	42/69 (60.9%)	30/70 (42.9%)
Ulcer Location**				
Toes	22 (19.6%)	13 (13.5%)	14/22 (63.6%)	8/13 (61.5%)
Metatarsal heads	58 (51.8%)	49 (51.0%)	36/58 (62.1%)	20/49 (40.8%)
Midfoot	30 (26.8%)	34 (35.4%)	12/30 (40.0%)	8/34 (23.5%)
Age				
18 – 70 years	98 (87.5%)	91 (94.8%)	55/98 (56.1%)	34/91 (37.4%)
71 – 80 years	14 (12.5%)	5 (5.2%)	8/14 (57.1%)	2/5 (40.0%)
Gender				
Male	88 (78.6%)	74 (77.1%)	46/88 (52.3%)	30/74 (40.5%)
Female	24 (21.4%)	22 (22.9%)	17/24 (70.8%)	6/22 (27.2%)
Ulcer Area†				
≤ 177 (mm^2)	59 (52.7%)	45 (46.9%)	39/59 (66.1%)	20/45 (44.4%)
> 177 (mm^2)	52 (46.4%)	51 (53.1%)	23/52 (44.2%)	16/51 (31.4%)
Ulcer Duration				
≤ 6 months	61 (54.5%)	51 (53.1%)	38/61 (62.3%)	22/51 (43.1%)
> 6 months	51 (45.5%)	45 (46.9%)	25/51 (49.0%)	14/45 (31.1%)
Number of Ulcers on Study Foot				
Single	100 (89.3%)	90 (93.8%)	57/100 (57.0%)	33/90 (36.7%)
Multiple	12 (10.7%)	6 (6.2%)	6/12 (50.0%)	3/6 (50.0%)
HbA1c				
≤ 8.40	63 (56.3%)	42 (43.8%)	34/63 (54.0%)	12/42 (28.6%)
> 8.40	49 (43.8%)	54 (56.3%)	29/49 (59.2%)	24/54 (44.4%)

*Two patients in the Apligraf group did not have type of diabetes specified.
**Two patients in the Apligraf group had ulcers located not at the toes, metatarsal heads, or midfoot
†One patient in the Apligraf group did not have a baseline ulcer tracing available.

DFU Device Safety:

DFU Study Withdrawals:
15 patients withdrew from Study 95-DUS-001 due to adverse events or intercurrent illness. Per treatment arm the division was 6 Apligraf patients and 9 Control patients.

DFU Adverse events: are displayed in section VI.

There were no statistically significant differences in adverse events reported in this study except for the incidence of diarrhea and peripheral edema that occurred less frequently in the Apligraf group.

Additional safety parameters (amputations or resections on the study limb, hospitalizations, sepsis, life-threatening adverse events, and death) were comparable and discussed previously in Table 2 (i.e., Infectious Adverse Events and Amputations Occurring on the Study Limb in Diabetic Foot Ulcers by Number of Apligraf Applications) of the Adverse Events Section.

DFU Immune response:
In tests of patients' sera there were no observations of antibody responses against bovine type I collagen, bovine serum proteins or the Class I HLA antigens on human dermal fibroblasts and human epidermal cells. T-cell specific responses were not observed against bovine Type I collagen, human fibroblasts or human keratinocytes. There was also no clinical evidence of Apligraf rejection by any patient.

X. CONCLUSIONS DRAWN FROM THE STUDY

Protocol 95-DUS-001 (DFU)

This study provides reasonable assurance of the safety and effectiveness of Apligraf for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure. In specific the study demonstrated that:

- Apligraf provided a statistically significant advantage in the incidence of wound closure per unit time and the total incidence of wound closure by or at 12 weeks when used with standard dressings.

- Adverse events were comparable between Apligraf and Control groups. Serious infections at the study ulcer were comparable. Additional safety parameters (hospitalizations, sepsis, life-threatening adverse events, and death) were also comparable.

- There were no observations of antibody responses against bovine type I collagen, bovine serum proteins or the Class I HLA antigens on human dermal fibroblasts, and human epidermal cells. T-cell specific responses were also not observed against bovine type II collagen, human fibroblasts or human keratinocytes.

XI. PANEL RECOMMENDATION

On May 8, 2000, the General and Plastic Surgery Devices Panel recommended approval of Apligraf for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure with the following conditions:

1) Product labeling should indicate that device use is appropriate only after the failure of standard ulcer therapy.

2) Product labeling should accurately describe the safety and effectiveness of the device observed in clinical studies.

3) Product labeling should indicate that the control group in the neuropathic diabetic ulcer study received standard saline dressings and not human graft treatment.

XII. CDRH DECISION

Expedited processing was authorized on August 7, 1995 based on the potential of Apligraf to provide a clinically important advance over existing alternatives in the treatment of neuropathic diabetic foot ulcers.

Inspection of the sponsor's manufacturing facilities was completed on February 26, 1999 and was found to be in compliance with the device Good Manufacturing Practice regulations.

After the Panel meeting, FDA completed the review of the clinical data submitted immediately prior to the Advisory Committee meeting and worked with the sponsor to finalize product labeling. The product labeling was written to address the concerns discussed by the Advisory Panel.

FDA issued an approval order on June 20, 2000.

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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

Post Approval Requirements and Restrictions: see the Approval Order.