

### **3. SUMMARY OF SAFETY AND EFFECTIVENESS**

#### **3.1 General Information**

**Device Generic Name:** Interactive Wound and Burn Dressing

**Device Trade Name:** Composite Cultured Skin

**Applicant's Name and Address:** Ortec International, Inc.  
3960 Broadway, 2<sup>nd</sup> Flr.  
New York City, NY 10032

**Date of Panel Recommendation:**

**Date of Notice of Approval of Application:**

#### **3.2 Indications For Use**

Composite Cultured Skin is indicated for use in accelerating wound closure of split thickness donor site wounds in burn patients.

#### **3.3 Device Description**

Composite Cultured Skin is composed of a collagen matrix in which allogeneic human skin cells, (i.e., epidermal keratinocytes and dermal fibroblasts) are cultured in two distinct layers. The collagen cross-linked sponge consists primarily of Type I bovine collagen laminated on one side with a thin gel layer of acid-soluble bovine collagen.

The device is manufactured under aseptic conditions from human neonatal male foreskin tissue. The donor's mother is tested and found to be negative for syphilis and for human viruses, including HTLV I&II, Hepatitis B&C, HIV 1&2, EBV and HHV-6. The donor's fibroblast and keratinocyte cells are tested for human viruses (and found to be negative for HTLV I&II, Hepatitis B, HIV 1&2, EBV, and HHV-6), retroviruses, bacteria, fungi, yeast, mycoplasma, karyology, isoenzymes, tumorigenicity, normal growth and morphology. The final product is tested for morphology, cell viability, sterility, mycoplasma, and physical container integrity. Product manufacture also includes animal-derived reagents, which are tested and found to be negative for viruses, retroviruses, bacteria, fungi, yeast, and mycoplasma before use and all bovine material is obtained from countries free of Bovine Spongiform Encephalopathy (BSE).

The device measures approximately 6 cm x 6 cm (minimally 36 cm<sup>2</sup>). A non-adherent mesh (N-Terface® (Winfield Laboratories, Inc., Dallas, Texas)) is placed on both aspects

of the device to protect the cells. The device is packaged in a plastic tray with protein-free packaging medium containing DMEM, water for irrigation, sodium bicarbonate, folic acid solution, HEPES buffer, L-Glutamine, MEM non-essential amino acids, and sodium hydroxide to maintain cell viability during storage and shipping.

The plastic tray is sealed within a peelable inner pouch to provide a sterile barrier against moisture and gas. The inner pouch is, in turn, sealed inside a heavier-gauge outer pouch that protects the inner pouch sterility barrier and the product against damage during shipment. The multi-stage packaged product is packed with pre-chilled gel packs and shipped to the destination in a padded and insulated shipping container that maintains a temperature of 11-18° C (for up to 72 hr.).

### **3.4 Contraindications**

- Composite Cultured Skin is contraindicated for use on clinically infected wounds (see Precautions).
- Composite Cultured Skin is contraindicated in patients with known allergies to bovine collagen.

### **3.5 Alternative Practices And Procedures**

Split thickness skin grafting is a frequently used technique in the management of serious skin injuries requiring skin replacement, such as burns. Once it has been determined that a patient will require split thickness autografting, the creation of a donor site is automatically necessitated. Donor sites are areas of healthy, non-injured skin, which are harvested for autograft use, thereby leaving an open wound requiring coverage. CCS treatment of donor sites is the subject of this application.

There are many dressing options for donor sites in the postoperative period. The type of dressing selected depends on the size of the donor site created, the anatomic location on the body surface, and the proximity to other wounds. Types of dressings include biologic and biosynthetic wound dressings, and synthetic skin substitutes which permit wound healing in a moist environment.

An alternative technique is to use a dry, fine-meshed gauze or gauze impregnated with petrolatum or antimicrobial agents to cover these donor sites. These dressings are more painful to the patient and, when dry, prolong wound healing and do not permit motion of involved areas as effectively as moist or occlusive dressings.

### **3.6 Marketing History**

Composite Cultured Skin has been approved under a Humanitarian Device Exemption for use in patients with mitten hand deformity due to Recessive Dystrophic Epidermolysis Bullosa (RDEB) as an adjunct to standard autograft procedures (i.e., skin grafts and flaps)

for covering wounds and donor sites created after the release of hand contractions (i.e., “mitten” hand deformities).

No launch date has been set as of the cut-off date for this PMA.

CCS is not marketed nor has it been withdrawn from marketing in any other country.

### **3.7 Summary of Studies**

#### **3.7.1 Summary of Nonclinical Laboratory Studies**

To establish the efficacy of CCS and the safety of the collagen sponge coated with collagen gel, Ortec International has conducted a series of studies. Wound healing was examined in severe combined immuno-deficient (SCID) mice, athymic nude mice, and swine. Cytokine production was examined *in vitro*, and biocompatibility studies were performed in rabbits, mice, and guinea pigs. An overview of the nonclinical studies conducted on CCS and the acellular collagen sponge is presented below.

CCS is designed to enhance wound healing in part by release of cytokines. In an *in vitro* assay, CCS stimulated the release of cytokines into culture media. *In vivo* wound healing was examined in male severe combined immuno-deficient (SCID) mice and female athymic nude mice. For male SCID mice, CCS produced approximately 60% wound contracture and complete epithelialization in eight of twelve animals. In a range-finding study using CCS with different cell densities, a trend toward greater wound healing was observed in nude mice treated with medium and high cell density CCS than with acellular or low cell density CCS.

The collagen sponge coated with collagen gel was shown to be biocompatible in *in vitro* cytotoxicity and *in vivo* tests under the conditions of the studies. There was no evidence of cytotoxicity when extracted material from the coated collagen sponges was incubated with mouse connective tissue NCTC 929 cells (elution and agar diffusion assays). An extract of the coated collagen sponge was not a hemolytic agent when tested in rabbit red blood cells. In guinea pigs, undiluted extracted material from the coated collagen sponge did not produce sensitization. Intracutaneous and acute systemic toxicity studies performed in rabbits and mice, respectively, resulted in comparable responses between extracts of the collagen sponge coated with collagen gel and control materials. Similarly, intramuscular implantation of the coated sponge into rabbits with observations up to 90 days post-implantation resulted in no significant differences between the control material and coated sponge. Both produced negative to mild reactivity, but the collagen sponge coated with collagen gel was more rapidly resorbed. The coated sponge was not mutagenic, and an extract of the coated collagen sponge did not produce a pyrogenic response in rabbits.

A full thickness skin wound study was conducted in swine comparing the healing rates for the collagen sponge and control material. Skin wounds made in swine revealed

similar rates of healing for collagen sponges and the control material; complete resorption of the sponge was reported by day 30.

Data collected in murine models of full-thickness wound healing revealed 60% wound contracture and complete epithelialization in 67% of male SCID mice at 14 days post-treatment with CCS, and a trend toward greater wound healing with higher cell densities of CCS in female nude mice. In an *in vitro* assay, several of the cytokine expression levels measured in CCS, such as GM-CSF and VEGF, lead to accumulated concentrations in CCS culture medium in the nanogram per milliliter level, which is significant.

With respect to biocompatibility, *in vitro* assays confirmed a lack of cytotoxicity and hemolysis. And, extracted material from the coated sponge did not produce sensitization, mutagenicity, pyrogenicity, or adverse intracutaneous, acute systemic, or sustained intramuscular effects. In a swine model, comparable resorption and healing were observed between control materials and the collagen sponge.

### **3.7.2 Summary of Clinical Studies**

#### **Donor Site Pilot Study in Burn Patients**

*Protocol #97-002/OR “A Controlled Randomized Pilot Study of the Effects of a Composite Cultured Skin Containing a Collagen Matrix Seeded with Allograft Cells on the Management of Split Thickness Donor Sites”.*

#### **Study Design**

This study was a prospective, single-center, open, randomized and controlled trial in patients requiring split thickness skin autografting for the management of burn injuries. This was a matched-pairs design (i.e., each patient had two designated donor sites of equivalent surface area). Each site was randomized to receive a single application of either CCS or the control dressing. Patients were followed through post-treatment Day 28.

#### **Patient Assessment**

The primary outcome measure was the time (days) to wound closure (100% re-epithelialization). Re-epithelialization was defined as the visible presence of a dry, opalescent-pink external surface representing the newly formed outer cornified layer of the epidermis, which, in the Investigator’s assessment, no longer required a dressing or protective covering. Wound closure was evaluated using computerized planimetric analysis and validated through photographic review. Photographs were assessed by two blinded independent burn experts to determine if clinical re-epithelialization was present.

The secondary outcome measures included the time to complete wound closure (Investigator’s assessment), the rate of healing, and the time to readiness for recropping.

This latter measure reflected the quality of healing (i.e., the time at which reharvesting would be clinically possible).

Safety was assessed by recording adverse events, donor site pain and itching assessments, and the incidence of infection, wound cultures, and laboratory measurements.

### **Disposition of Patients/Demography**

A total of eight subjects were enrolled into a single center. Seven patients completed the study and one patient had a serious adverse event, which resulted in death and that was judged by the Investigator to be unlikely related to study treatments.

Five (62.5%) patients were African American, and three (37.5%) were Caucasian. Mean age of the patients was 41.3 years (range 10 to 84 years); mean height was 66.8 inches (range 51 to 72 inches); and mean weight was 145.1 pounds (range of 83 to 221 pounds).

### **Analysis and Results**

#### Efficacy Results

*Healing at graft site- Planimetric Analysis and Investigator's Assessment.* The Kaplan-Meier estimates of the percent of healed patients from computerized planimetric analysis and from the Investigator's assessment showed a statistically significant difference in healing time between CCS and the control treatment ( $p=0.034$ ), with shorter healing times observed with CCS. At least 50% of the patients were healed by both planimetric analysis and Investigator's assessment by Day 12 with CCS, while 50% of the patients were healed by Day 25 with the control treatment.

The healing rate from the Investigator's assessment of the percent of healing at each visit was calculated. At each time point, the mean percentages of CCS donor site healing were larger than the mean percentages for the control site. At Days 14 and 21, these differences were statistically significant ( $p=0.014$  and  $0.026$ , respectively).

*Readiness for recropping assessments.* At the end of the study, the Investigator assessed the CCS sites to be ready for recropping. CCS sites were ready for recropping before the control sites in three patients, for one patient, both sites were ready at the same time, and for two patients, neither site was ready.

*Photographs.* The photographs were evaluated by blinded reviewers. Overall, the majority of the validation and inter-observer correlation results indicated substantial agreement between the various assessment methods (computerized planimetric analysis, the Investigator's assessments, and the blinded review of the photographs).

#### Safety Results

All eight patients had at least one adverse event. One patient died and 12 serious adverse events were reported and all were considered by the Investigator to be unlikely related to study treatment. The highest incidences of adverse events were fever and constipation (each with 3 patients (37.5%)).

There were no statistically significant differences in donor site pain or itching between the two treatments at any of the study time points.

### **Donor Site Pivotal Study in Burn Patients**

*Protocol #98-004/OR: “Controlled Randomized Multi-Center Study of the Effects of a Composite Cultured Skin Containing a Collagen Matrix Seeded with Allograft Cells on the Management of Split Thickness Donor Sites in Burn Patients”.*

### **Study Design**

This was a prospective, active controlled, randomized multi-center study involving patients requiring conventional split thickness skin autografting for the management of burn injuries. The study incorporated a matched pairs design (i.e., each patient had two designated donor sites of equivalent surface area and depth). Each donor site was randomized to receive a single treatment of either the control dressing or investigational device (CCS).

### **Patient Assessment**

The primary efficacy variable was time to complete wound closure (complete re-epithelialization) as determined by photography.

The secondary efficacy variables were time to complete wound closure as determined by computerized planimetric assessment of unhealed wounds, time to complete wound closure as determined by investigator through clinical assessment, the rate of wound healing as determined by the percent change in wound area from baseline as determined by planimetric data, time to readiness for recropping as assessed by the investigator, and time to actual recropping of an original donor site.

Safety variables that were compared between the two treatments were: incidence of donor site specific adverse events, scar outcome, pain and itching scores, and incidence of donor site infection and breakdown, time to actual recropping, and recrop outcome. Adverse events were tabulated by preferred term, body system and severity (mild, moderate, severe, life-threatening or fatal).

### **Disposition of Patients/Demography**

A total of 82 patients were enrolled among 12 study sites. All 82 patients were included in the intent-to-treat and safety populations. The per-protocol population consisted of 74 patients (90.2%). Sixty patients (73%) completed the study, 22 patients (26.8%) discontinued study before the week 24 visit, and 8 patients were excluded from the per protocol analysis.

The population receiving randomized treatment was composed of 63 men (76.8%) and 19 (23.2%) women. Mean age of all patients was 31.7 years (range: 1 to 88 years). The

population was 53.7% Caucasian, 24.4% African-American, 15.9% Hispanic, 2.4% Asian/Pacific Islander and 3.7% other.

### Analysis and Results

All patients who were randomized and received treatment with the study devices, regardless of study completion, and had at least one post-treatment efficacy evaluation were included in the intent-to-treat (ITT) population. The population included in the safety analysis was the subset of the intent-to-treat population who received treatment with a study device, regardless of study completion. Included in the per-protocol population were patients who received treatment with a study device and who had no major protocol violations.

### Efficacy Results

Primary efficacy data (i.e., time to 100% wound closure) are presented in Table 3.7.2.1 for the ITT and PP populations and the three methods of assessment.

**Table 3.7.2.1: Median and Mean Days to 100% Wound Closure**

	Median Days to Wound Closure*				Mean (SD) Days to Wound Closure			
	Source	CCS	CON	p-value**	Source	CCS	CON	p-value+
Investigator ITT	E18.3	12.0	16.0	<0.0001	E18.1	13.2(4.87)	18.4(7.86)	<0.0001
Investigator PP	E19.3	12.0	16.0	<0.0001	E19.1	12.9(4.16)	17.9(7.51)	<0.0001
Planimetric ITT	E1.3	12.0	17.0	<0.0001	E1.1	13.7(5.83)	19.3(8.37)	<0.0001
Planimetric PP	E2.3	12.0	16.0	<0.0001	E2.1	13.4(5.14)	18.7(8.02)	<0.0001
Photographic ITT	E9.3	15.0	22.0	0.0006	E9.1	18.0(7.12)	22.4(8.48)	<0.0001
Photographic PP	E10.3	15.0	21.0	0.0009	E10.1	17.8(6.64)	22.1(8.25)	<0.0001

\*Kaplan-Meier estimates of the median days to 100% wound closure

\*\*Log-Rank test of the difference between median healing times

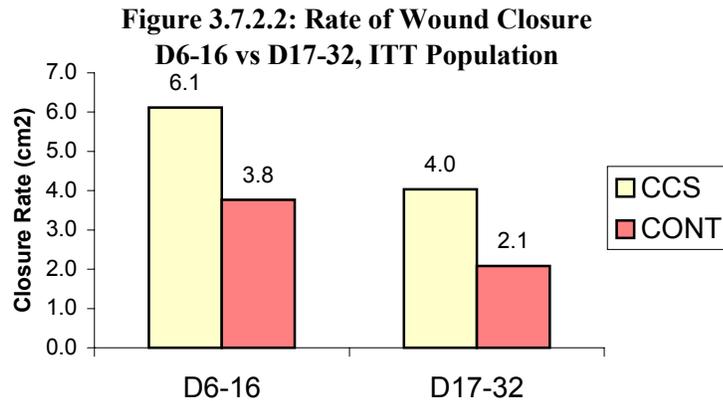
+Paired t-test

For the ITT population and median days to healing using photographic assessment, CCS treated sites healed seven days faster than the control treated sites (15 days vs. 22 days, respectively); this was statistically significant with p-value =0.0006. For mean days to healing by photographic assessment, CCS treated sites in the ITT population healed four days faster than the control treated sites (18 days vs. 22 days, respectively), also statistically significant (p<0.0001).

Results of ITT planimetric assessments support those obtained by photography, i.e., median and mean days to healing for CCS were 12 to 14 days, respectively, while those of the control treated sites were 17 and 19 days, respectively. These differences reflect a five-day shorter time to healing with CCS and are statistically significant (p<0.0001).

Results of the ITT investigator assessment also support those obtained by photography, i.e., median and mean days to healing for CCS were 12 and 13 days, respectively, while those of the control treated sites were 16 and 18 days, respectively, reflecting a four to five day shorter time to healing with CCS that is statistically significant (p<0.0001).

The Per Protocol (PP) population results obtained closely resemble those of the ITT population with statistically significant differences in time to wound closure for all three-assessment methods.



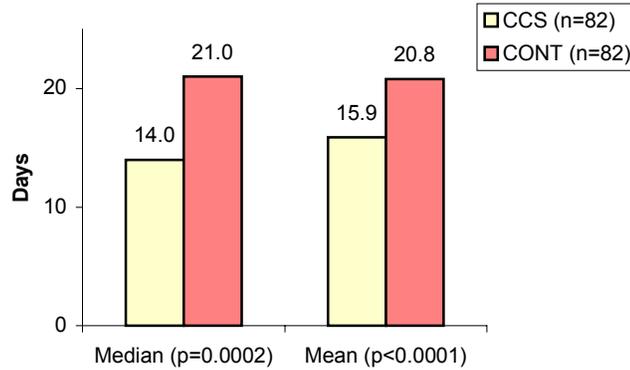
#### Rate of Wound Closure

Secondary efficacy parameters for the rate of Wound Closure in the ITT population is depicted in Figure 3.7.2.2. Clinically meaningful and statistically significant differences in the rates of wound closure per day, as measured by planimetry, were observed during the 32-day post surgical period. Results of analyses indicated that CCS promoted a faster rate of healing than did the control treated sites. The mean rate of wound closure for CCS on days 6 through 16 was 61% faster than the control treated sites during the same period (6.1 vs 3.8 cm<sup>2</sup>, respectively) and the mean closure time of CCS during day 17-32 was 90% faster than that of the control treated sites (4.0 vs. 2.1 cm<sup>2</sup>, respectively).

#### Time to Readiness for Re-Cropping

The time to readiness for re-cropping, as assessed by the investigator, is depicted for the ITT population in Figure 3.7.2.3. The median time required for re-crop of a CCS treated site was 7 days less than the median time required for the control treated site; i.e., 14 days CCS vs. 21 days control treated sites, (p=0.0002). Mean times to readiness for re-cropping were 5 days less for CCS (i.e., 16 days CCS vs. 21 days control treated sites [p<0.0001]).

**Figure 3.7.2.3: Time to Readiness for Re-Cropping  
ITT Population**

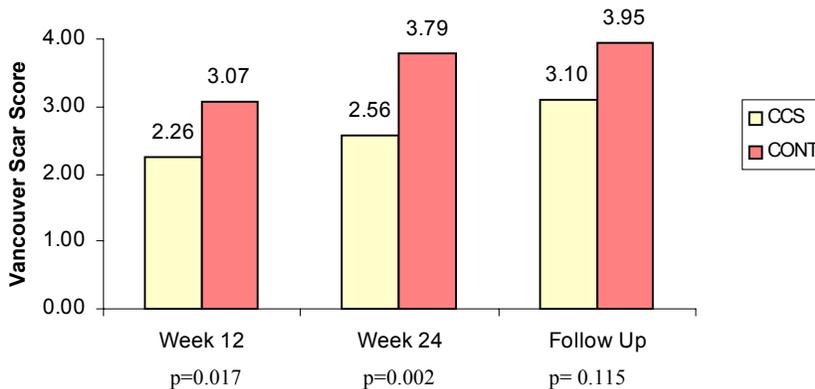


**Scarring Severity**

Scarring severity was assessed by two methods. Investigator assessments were conducted at weeks 12 and 24 and at the follow-up visit using the Vancouver Scar Scale. Assessments were also conducted via blinded review of photographs utilizing the Hamilton Burn-Scar Rating Scale. With both assessment methods, scarring severity at CCS treated sites was significantly lower ( $p < 0.05$ ) than the control treated sites at weeks 12 and 24.

Figure 3.7.2.4 depicts the mean Vancouver scores for the Safety Population, as assessed by the Investigator. At week 12, mean scarring severity at CCS treated sites was nearly 30% less than the control treated sites (2.26 versus 3.07, respectively,  $p = 0.017$ ). At week 24, mean scarring severity for the CCS sites was more than 30% less than the control treated sites (2.56 versus 3.79, respectively,  $p = 0.002$ ). At the follow up visit, no statistically significant difference was observed between the two treatments.

**Figure 3.7.2.4: Vancouver Scar Scale  
Investigator Assessment of Scarring Severity**



### Signs of Infection and Breakdown

Clinically meaningful differences were noted in signs of infection and site breakdown between the CCS and the control treated sites, in favor of CCS. The percentage of CCS donor sites exhibiting signs of infection was 1.2% versus 3.7% for the control treated sites. The percentage of CCS donor sites exhibiting signs of breakdown or blistering was 5.0% compared to 10.1% for the control treated sites.

### Itching

Severity and incidence of donor site itching was similar for the two groups (72.2% vs. 68.8%, CCS vs. the control treated site, respectively), with no clinically meaningful or statistically significant increase in itching for the CCS group.

### Safety Results

Of the 82 patients enrolled in the study, 64 (78.0%) had at least one adverse event. Overall, most of the adverse events were mild to moderate in severity, however there were three fatalities that were not related to treatment of the donor site. Sepsis, multiple organ system failure and dyspnea were the events associated with fatal outcomes. Serious adverse events without donor site involvement were reported by 23 (28%) of the patients. There were no serious adverse events involving the donor sites. There were 12 adverse events involving the CCS site and 13 adverse events involving the control treated site. All of the adverse events with donor site involvement were mild to moderate in severity.

Table 3.7.2.5 lists the adverse events without donor site involvement that had an incidence of  $\geq 5.0\%$  in one or more severity categories. Most of the adverse events were considered unlikely to be related to the study treatment. No severe, life threatening, or fatal adverse events occurred at an incidence of  $\geq 5.0\%$ .

**Table 3.7.2.5: Adverse Events Reported with an Incidence  $\geq 5.0\%$  by Severity**

	Mild to Moderate n=82		Severe n=82		Life Threatening / Fatal n=82	
	n	%	n	%	n	%
<b>Body System</b>						
Preferred Term	n	%	n	%	n	%
<b>Body As A Whole - General Disorders</b>						
Fever	8	9.8	0		0	
<b>Gastro-Intestinal System Disorders</b>						
Constipation	16	19.5	0		0	
Nausea	8	9.8	1	1.2	0	
Vomiting	9	11.0	1	1.2	0	
<b>Metabolic And Nutritional Disorders</b>						
Hyperglycaemia	5	6.1	1	1.2	0	
Hypernatraemia	5	6.1	0		0	
<b>Platelet, Bleeding &amp; Clotting Disorders</b>						

**Table 3.7.2.5: Adverse Events Reported with an Incidence  $\geq 5.0\%$  by Severity**

	Mild to Moderate n=82		Severe n=82		Life Threatening / Fatal n=82	
	n	%	n	%	n	%
<b>Body System</b>						
Preferred Term						
Thrombocythaemia	5	6.1	0		0	
<b>Psychiatric Disorders</b>						
Agitation	6	7.3	0		0	
Anxiety	5	6.1	0		0	
Insomnia	12	14.6	0		0	
<b>Red Blood Cell Disorders</b>						
Anaemia	11	13.4	1	1.2	0	
<b>Reproductive Disorders, Female (N=19)</b>						
Vaginal Haemorrhage (N=19)	1	5.3	0		0	
<b>Respiratory System Disorders</b>						
Atelectasis	5	6.1	0		0	
Pharyngitis	8	9.8	0		0	
<b>Skin And Appendages Disorders</b>						
Pruritus	8	9.8	0		0	
<b>Body System Unclassified</b>						
Relaxation Of Scar	5	6.1	0		0	

n=Number of Patients

There were 12 mild to moderate adverse events involving the CCS treated donor sites and 13 mild to moderate adverse events involving the control treated donor sites. The events for each treatment, the severity of the event and its frequency are presented in Table 3.7.2.6

**Table 3.7.2.6: Adverse Events Reported With Donor Site Involvement**

Adverse Event	CCS (n=82)				Control (n=82)			
	Mild		Moderate		Mild		Moderate	
	n	%	n	%	n	%	n	%
Application site reaction	1	1.2	0		1	1.2	0	
Pain	2	2.4	2	2.4	2	2.4	2	2.4
Infection	1	1.2	0		1	1.2	0	
Surgical Site Reaction	1	1.2	0		1	1.2	0	
Bullous Eruption	0		0		1	1.2	0	
Pruritus	2	2.4	2	2.4	2	2.4	3	3.7
Rash Pustular	1	1.2	0		0		0	

n=Number of Patients

## Deaths, Other Serious Adverse Events Reported, and Other Significant Adverse Events Reported.

### Deaths

Three patients died during the study. None of the deaths were considered related to the study treatment.

### Other serious adverse events

Table 3.7.2.7 summarizes the serious adverse events reported during the study. The total number of subjects reporting one or more serious adverse events was 24. All of the serious adverse events were considered unlikely to be related to study treatment. There were no serious adverse events involving the donor sites.

**Table 3.7.2.7: Serious Adverse Events Reported**

<b>Body System Preferred Term</b>	<b>n</b>	<b>%</b>
<b>Application Site Disorders</b>		
Cellulitis	1	1.2
<b>Autonomic Nervous System Disorders</b>		
Hypotension	1	1.2
<b>Body As A Whole – General Disorders</b>		
Multiple Organ Failure	1	1.2
Scar	3	3.7
<b>Centr &amp; Periph Nervous System Disorders</b>		
Brain Stem Disorder	1	1.2
Convulsions	1	1.2
Neuropathy	1	1.2
<b>Gastro-Intestinal System Disorders</b>		
Achalasia Cardiae	1	1.2
<b>Heart Rate And Rhythm Disorders</b>		
Cardiac Arrest	1	1.2
<b>Musculo-Skeletal System Disorders</b>		
Bone Development Abnormal	1	1.2
<b>Red Blood Cell Disorders</b>		
Anaemia	1	1.2
<b>Resistance Mechanism Disorders</b>		
Healing Impaired	2	2.4
Infection Aggravated	1	1.2
Sepsis	3	3.7
<b>Respiratory System Disorders</b>		
Dyspnoea	4	4.9
Larynx Oedema	1	1.2
Pneumonia	1	1.2
Pneumothorax	1	1.2
<b>Secondary Terms</b>		
Ectropion	1	1.2

**Table 3.7.2.7: Serious Adverse Events Reported**

<b>Body System Preferred Term</b>	<b>n</b>	<b>%</b>
<b>Skin And Appendages Disorders</b>		
Skin Malformation	3	3.7
<b>Urinary System Disorders</b>		
Renal Failure Acute	1	1.2
<b>Vascular (Extracardiac) Disorders</b>		
Haematoma	1	1.2
<b>White Cell And Res Disorders</b>		
Lymphoedema	1	1.2
<b>Body System Uncategorized</b>		
Entropion/Ectrop Rep Nec	1	1.2
Lid Reconst W Skin Graft	1	1.2
Lid Reconstr W Graft Nec	1	1.2
Tot Nasal Reconstruction	1	1.2
Other Pleural Incision	1	1.2
Ext Fix Dev-Metacar/Carp	1	1.2
Remove Impltd Device Nos	1	1.2
Rotator Cuff Repair	1	1.2
Finger Amputation	1	1.2
Other Local Destruc Skin	3	3.7
Skin Suture Nec	2	2.4
Full-Thick Skin Graft Nec	1	1.2
Heterograft To Skin	1	1.2
Relaxation of Scar	4	4.9
Skin Repair & Plastic Nec	2	2.4
Rehabilitation Nec	1	1.2

n=Number of Patients

### 3.8 Conclusions Drawn from the Studies

The preclinical safety studies demonstrate that the device is composed of biocompatible components. The animal studies also demonstrate that the collagen sponge component of the device is rapidly resorbed and does not interfere with wound repair.

CCS wound dressing has demonstrated a positive benefit (100% re-epithelialization) in wound healing when evaluated in clinical investigations. With respect to human clinical investigations, CCS has been used in the treatment of over 186 patients in the U.S. and Australia.

#### *Safety*

The adverse effects observed during clinical evaluations of CCS in patients with donor sites, ~~EB, full and deep partial thickness burns, venous ulcers and diabetic ulcers~~ include a total of ~~eight~~ **71** deaths and ~~71~~ **71** non-fatal serious adverse events in ~~186~~ **186** patients. As judged by the treating investigator, none of these adverse events were definitely related to CCS.

Although few adverse events attributable to CCS have been reported, adverse events commonly associated with the treatment of acute and chronic wounds include, but are not limited to:

- Odor
- Pain
- Redness/erythema
- Pruritis/itching
- Cellulitis
- Infection
- Rash
- Scarring

Clinical investigations to date have not revealed any significant clinical manifestations of product-related immunological reactions. These clinical data include treatment of over 150 patients (i.e., 28 burn patients, 12 patients with chronic wounds from EB, 17 chronic venous stasis ulcer patients, 7 patients with diabetic foot ulcers and 90 patients with donor sites). Sera drawn from the patients in US studies revealed no antibody responses to bovine serum proteins. The sponsor has not determined the impact of device application on patients' humoral or cellular immune responses to the allogeneic human cellular components of CCS, i.e., keratinocytes and fibroblasts.

### *Efficacy*

The mean healing time to 100% wound healing in a large multicentered clinical evaluation of donor sites was significantly shorter for the CCS-treated donor sites than for the control-treated sites. The mean healing times reported for the three methods of measurement were: 1) 18 days for CCS compared to 22.4 days for the control by photographic analysis; 2) 13.7 days for CCS compared to 19.3 days for the control by planimetric analysis; and, 3) 13.2 days for CCS compared to 18.4 days for the control according to the investigator's evaluation. Median time to healing by Kaplan-Meier estimate was also significantly different favoring CCS-treated donor sites.

Based on this study as well as other studies summarized in this summary, CCS is effective as an interactive wound dressing in the management of split thickness donor sites.

### **3.9 CDRH Decision**

### **3.10 Approval Specifications**