SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name:	Cultured Epidermal Autografts (CEA)
Device Trade Name:	Epicel®
Applicant's Name and Address:	Genzyme Biosurgery 64 Sidney Street Cambridge, MA 02139
Humanitarian Device Exemption Number:	H990002
Date of Humanitarian Use Device Designation:	November 30, 1998
Date of Panel Recommendation:	None
Date of GMP Inspection:	March 18, 22-24, 1999 and April 4-7, 2005

Date of Notice of Approval to the Applicant: October 25, 2007

II. INDICATIONS FOR USE

Epicel® is indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns.

III. CONTRAINDICATIONS

Epicel® is contraindicated in patients with known hypersensitivity to agents used in the manufacture of Epicel® (please see the How Supplied section of the Epicel® product label for a complete listing of manufacturing reagents).

Epicel® is cultured in media containing vancomycin and amikacin (and if clinically indicated from the patient's history, amphotericin B is added). Trace quantities of these anti-infective agents may remain in the Epicel® autograft. Therefore, Epicel should not be used in patients with a known history of anaphylaxis to these agents.

Epicel® should not be used in patients with known sensitivities to materials of bovine or murine origin. The cell culture medium used in the culture of Epicel® contains bovine serum and the cells are co-cultured with murine 3T3 fibroblasts. The medium used to package and transport Epicel® does not contain serum; however, trace quantities of bovine derived proteins may be present.

Epicel® is contraindicated for use on clinically infected wounds (see also Precautions).

IV. WARNINGS AND PRECAUTIONS

A. Warnings

Although Epicel® is composed of autologous human cells from the patient, it is manufactured by co-cultivation with murine (mouse) cells and contains residual murine cells. Because Epicel® is co-cultivated with, and contains murine cells, FDA considers it a xenotransplantation product. Certain safety measures identified in the PHS Guideline on Infectious Disease Issues in Xenotransplantation regarding xenotransplantation recipients were recommended by the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee (BRMAC) which met on January 13, 2000. The PHS and FDA recommend that xenotransplantation recipients and their intimate contacts should not donate whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans. However, the murine fibroblasts used in producing Epicel grafts were not considered by the subcommittee or FDA to represent the same type of risk posed by many other xenotransplantation products. The murine cells have been extensively tested for viruses. Consistent with the discussion at the BRMAC Xenotransplantation Subcommittee, Epicel® recipients, but not their intimate contacts or healthcare providers should defer from donation. For more detailed information, the transcript of the BRMAC Xenotransplantation Subcommittee meeting may be accessed at the following FDA address: http://origin.www.fda.gov/cber/xap/trans.htm.

The Epicel® product is intended solely for autologous use. Patients undergoing the surgical procedure associated with Epicel® are not routinely tested for transmissible infectious diseases. Therefore, the Epicel® biopsy and the autologous Epicel® product may carry the risk of transmitting infectious diseases to health care providers handling these tissues. Accordingly, health care providers should employ universal precautions in handling the biopsy samples and the Epicel® product.

Discontinue use of Epicel® if the patient shows evidence of an allergic reaction. Allergic reactions or hypersensitivity reactions may manifest themselves as classical Type I-IV immune responses, e.g., anaphylaxis, hemolysis, antigen/antibody complex formation or a cell-mediated/delayed immune response.

B. Precautions

Caution: Do not use Epicel® past its expiration date (24 hours).

Caution: Do not use Epicel® if package is opened or damaged.

Caution: Epicel® should be stored in its shipping container until ready for use.

Caution: Do not reuse, freeze, refrigerate, or sterilize after opening.

Caution: Do not allow the grafts to dry prior to application to the wound bed.

Caution: Do not refrigerate, freeze or incubate the Epicel® shipping container or its contents. The Epicel® product consists of viable, autologous cells packaged and labeled for use within specified time limits. The Epicel® transport container should remain closed and be kept at cool room temperature (13 to 23° C, 55 to 73° F). Epicel® should be kept out of the operating room until ready for application.

Caution: Do not use cytotoxic agents with Epicel®. Hibiclense® (chlorhexidine gluconate) should not be used to treat wound bed infections in patients who have received, or are expected to receive, Epicel®. Anti-infective agents that have been used clinically and have not been observed to cause significant inhibitory effects on keratinocytes *in vitro*, or for which limited clinical experience has been obtained are listed in the Pre-grafting considerations section in the Epicel® product Directions for Use.

Caution: If clinical signs of infection (pain, edema, erythema, warmth, drainage, odor and/or unexplained fever) are present or develop, do not apply Epicel® until the infection is adequately treated. Epicel® is more susceptible to wound bed conditions and bacterial colonization than meshed split-thickness autografts. All infections should be evaluated and treated according to standard clinical practice.

Caution: The recipient wound bed is believed to influence the success of keratinocyte graft application. Spontaneous blister formation may occur in patients grafted with keratinocytes alone and result in graft loss. The use of a dermal substitute may improve final graft take, however the use of Epicel® with dermal substitutes has not been studied.

Caution: The anatomic site intended for graft application may also influence graft success. Mechanical stress has been implicated as one reason for graft blister formation.

Caution: Epicel® has been used since 1988. The long term safety of Epicel® is unknown. Preclinical information of the 3T3 cells and the final product, and clinical data collected to date, have not revealed a tumorigenic potential of the product. However, the long term potential of skin cancers arising from these cells is unknown.

Caution: Although the murine cells used in the manufacture of Epicel have been tested and found to have no detectable bacteria, fungi and viruses, the possibility of an infection can not be excluded. The risk of infection is unknown. It is also possible that symptoms of an infection may not be seen for months or years. To date, Genzyme Biosurgery is not aware of any infections related to murine cells.

Caution: Men and women who intend to have children should be advised that the effects, if any, of Epicel® on fetal development have not been assessed. In addition, the safety of Epicel® has not been studied in pregnant and nursing women.

V. DEVICE DESCRIPTION

Epicel® cultured epidermal autograft (CEA) is an aseptically processed wound dressing composed of the patient's own (autologous) keratinocytes grown *ex vivo* in the presence of proliferation-arrested, murine (mouse) fibroblasts. Epicel® consists of sheets of proliferative, autologous keratinocytes, ranging from 2 to 8 cell layers thick and is referred to as a cultured epidermal autograft. Each graft of Epicel® is attached to petrolatum gauze backing with stainless steel surgical clips and measures approximately 50 cm^2 in area.

Epicel® is defined by the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation (http://www.fda.gov/cber/gdlns/xenophs0101.htm) and the FDA Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (http://www.fda.gov/cber/gdlns/clinxeno.htm) as a xenotransplantation product because it is manufactured by co-cultivation with proliferation-arrested mouse, 3T3, fibroblast feeder cells. For recommendations regarding Epicel® recipient blood and tissue donation please refer to the Patient Counseling Information section of the Epicel® product label.

The mouse 3T3 cells have been extensively tested for the presence of infectious agents. Those tests include sterility testing for bacterial and fungal contamination, testing for mycoplasmal contamination, and screening for viral and retroviral contaminants. Additional evaluations regarding the proliferative potential of the mouse 3T3 cells, their potential to undergo transformation and their karyology have been conducted. Epicel® is evaluated for sterility via a pre-release sterility assessment and is verified for sterility by a standard 14 day sterility assessment, post-release. Reagents used in the manufacture of Epicel® are tested for sterility and endotoxin content. The manufacturing process is periodically monitored for the possibility of mycoplasma contamination. Product manufacture includes reagents derived from U.S. herd animal sources and is tested for sterility and viruses. Patients and the biopsy tissue (autologous cells) harvested from them (to manufacture Epicel®) are not routinely tested for transmissible infectious agents.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

A. Deep Dermal or Full Thickness Burns

The conventional treatment for burn wound closure is excision of the eschar or removal of the necrotic material and placement of a split thickness skin graft (STSG). A STSG is harvested from an area of the individual's unburned skin. It includes the epidermal layer, which regenerates, and a very thin portion of the dermal layer, which does not regenerate. This autograft is placed upon the freshly excised burn wound and closure ensues. This may occur fairly rapidly in patients with small TBSA burns where there is abundant unburned skin to harvest. The donor site may be used again after it heals which can range from 6 - 10 days, depending on the thickness of the harvested graft.

In burn injuries, sparing autograft dermis is a therapeutic goal. Harvested with conventional methods, autograft has a total thickness of approximately 0.010-0.016 inches and contains a significant amount of dermis with the epidermal layer. This is in contrast to thin epidermal autograft which is approximately one half that of conventional autograft and consists of the epidermis and a very small amount of dermis. Although conventional autograft donor wound sites heal in approximately three weeks, the dermal tissue is non-regenerative. The total number of harvests of conventional autografts that can be obtained from unburned parts of a patient's body is limited to approximately one to three procedures. Limited availability of autograft, especially in large burns, can be managed by thin autograft harvesting techniques that reduce the amount of dermal tissue harvested with the autograft.

In a larger TBSA burns, usually >30%, the donor skin must be meshed and expanded in an attempt to cover a larger surface area with a smaller amount of available skin. If the patient does not have enough donor skin to cover the wound, the physician may need to consider other means of permanent wound closure in order to treat the patient's wounds.

VII. MARKETING HISTORY

Epicel® was considered a banked human tissue until 1996. In 1996 regulatory oversight was deemed appropriate for human tissue that underwent more than minimal manipulation in vitro. Outside of the United States, Epicel® has been used primarily in France, Germany, Italy, and Greece. Epicel® has been distributed in Canada under Compassionate Use regulations for medical devices.

Epicel® has never been withdrawn from marketing in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Since 1988, Epicel® has been used for the treatment of patients with third degree burn injuries. Genzyme Biosurgery has maintained an Epicel® database containing patient information supplied by attending burn teams. The database contains patient information collected from 1989 to 1996.

Table 1 summarizes the frequency of adverse events reported in ≥ 1% of third degree burn patients who received treatment (n=552) with Epicel® from 1989 to 1996, without an assessment of causality.

Table 1
Adverse Events Reported in ≥ 1% of Third Degree Burn Patients (n=552) Treated with Epicel®
1989-1996 [1]

Event	Number of Patients (%)	Number of Events
Death	74 (13)	74
Colonization/Infection	76 (14)	84
Graft shear [2]	43 (8)	45
Blister	23(4)	25
Drainage	18(3)	18
Improper hemostasis	19(3)	19
Sepsis, septic shock	17(3)	17
Graft detachment [2]	14(3)	14
Renal failure/disorder/dialysis	12(2)	12
Grafts debrided with dressing [3]	11(2)	11
Slow wound healing	7(1)	8
Allergy [4]	5(1)	5
Decreased vascular flow	5(1)	5
Improper takedown [3]	6(1)	6
Amputation of extremity	4(1)	5
Contractures	3(1)	3
Fever	3(1)	3
Hypothermia	4(1)	4
Hematoma	3(1)	3
Multi-system failure	6(1)	6
Blood pressure (low, high)	4(1)	4

1. Attending burn teams reported Adverse Events in a non-standardized manner. Due to insufficient details, there is no knowledge of long-term sequelae.

2. A review of reports indicates that, in the majority of cases, "Graft Shear" and "Graft Detachment" were used to describe the partial or complete detachment of the graft due to mechanical trauma or friction during the procedure or early postoperative period.

3. A review of reports indicates that, in the majority of cases, "Grafts debrided with dressing" and "Improper takedown" described technical procedural errors in the care of the graft.

4. A review of reports indicates that "Allergy" was an event experienced due to an agent other than the Epicel graft.

One lower extremity amputation not included in the database occurred in an epidermolysis bullosa dystrophica (DEB) patient treated with Epicel® that developed an invasive squamous cell carcinoma (SCC). A specimen of the patient's graft did not cause tumor formation in nude mice. SCC is a known complication of DEB. Although the role of Epicel® in the causation of SCC can not be excluded, there is no information to suggest that such a causal relationship exists.

A review of the adverse event data received by Genzyme and reported to FDA from June 1998 through August 2006 revealed that the events were similar to the previously identified adverse events. Table 2 summarizes the frequency of adverse events that occurred in ≥ 1% of third degree burn patients (n=734) who received treatment with Epicel® during the period reviewed. The relationship of these events to Epicel® has not been established.

Table 2
Adverse Events Reported and Occurring in ≥ 1% of Third Degree Patients (n= 734) Treated with Epicel® from June 24, 1998 through August 31, 2006

Event	Number of Patients (%)	Number of Events
Death[1]	65 (9%)	65
Sepsis	27 (3.7%)	27
Multi-organ failure	24 (3.3%)	24
Skin graft failure/Graft complication	10 (1.3%)	10

1. In accordance with standard coding conventions, after August 2000, death was collected as an outcome and was not coded as an event term unless no other term was provided. Combining the n for the adverse event coded term death [n=30] and the n for death as an outcome only [n=35], the death total is n=65 (9%).

IX. SUMMARY OF PRECLINICAL STUDIES

A. Safety

The following tables summarize the preclinical safety testing conducted on the murine 3T3 fibroblast cell banks and the Epicel® final product.

Table 3
3T3 fibroblasts – Identification and Characterization

Cell Bank Tested	Test	Test Method	Results
Master Cell Bank (MCB)	Cell Culture Identification and Characterization	Isoenzyme analysis: Lactate Dehydrogenase, Glucose-6-Phosphate Dehydrogenase, Malate Dehydrogenase, Nucleoside Phosphorylase, Peptidase B	Confirmed Species of Origin as Mouse.
MCB, Working Cell Bank (WCB), Production Cell Bank (PCB)	Presence of Bacterial and Fungal Contaminants	Direct Inoculation according to 21 CFR 610.12	No evidence of fungal or bacterial contamination.
MCB, WCB, PCB	Presence of Mycoplasma	Agar Isolation and Vero Cell Culture Assay (Hoechst Stain)	Negative for presence of agar-cultivable and non-cultivable mycoplasmas.
MCB, WCB	*In Vitro* Assay for the Presence of Viral Contaminants	Inoculation and Observation of indicator cells for cytopathic effects (CPE), Hemadsorption (HAD) and Hemagglutination (HA)	Adventitious viral contaminants were not detected.
MCB, WCB	Test for the Presence of Inapparent Viruses	Inoculation of test article into adult mice, guinea pigs suckling mice and embryonated hens' eggs	No evidence of contamination with adventitious viral agents was observed.
MCB	Presence of Murine Specific Adventitious Agents	Mouse Antibody Production (MAP) Test	Sample free of all 16 murine viruses for which it was examined.
MCB	*In Vitro* Assay for the Presence of Bovine Viruses	Bovine Turbinate Cells inoculated with cell lysate prepared from test article	Bovine viruses (Bovine Viral Diarrheal Virus, Bovine Adenovirus type 3, Bovine Parvovirus, Infectious Bovine Rhinotracheitis virus, Bovine Parainfluenza Virus Type 3) were not detected.
MCB, End of Production stage (EOP)*	Presence of xenotropic murine retrovirus	Extended S^+L^- Assay	Negative for murine retrovirus.
MCB, EOP*	Cell Morphology and Presence of Virus-Like Particles	Transmission Electron Microscopic examination of a fixed cell pellet	No identifiable virus-like particles.
MCB, EOP*	Presence of Ecotropic Murine Retroviruses	Extended XC Plaque Assay	Negative for the presence of murine retrovirus
MCB, EOP*	Presence of Retrovirus	*In Vitro* assay for retroviral derived reverse transcriptase activity	No evidence for the presence of type C or type D retrovirus reverse transcriptase activity
MCB, EOP	Tumorigenicity	Growth of Mammalian Cells in Soft Agarose	Test article did not form viable colonies in soft agar
EOP	Karyology	Cytogenetic Analysis	Cells of mouse origin: unidentifiable chromosomes numerous and

			rearrangements observed, polyploidy, Chromosome 18 and the Y chromosome absent in all karyotypes

*These tests were done with EOP 3T3 cells that had been lethally-irradiated in accordance with the co-culture cell culture protocol. For additional information regarding preparation of the feeder cells for co-culture see the Radiation Validation below.

Table 4
Characterization of Epicel® Final Product

Test	Test Method	Results
Tumorigenicity	Growth of Mammalian Cells in Soft Agarose	Negative
Tumorigenicity	Tumor formation in Nude (*nu/nu*) Mice	Negative.
Karyology	Cytogenetic Analysis	Cells of human origin: few unidentifiable chromosomes observed, 3 chromosomal aberrations observed in 3 different karyotypes analyzed
Antibiotic, anti-infective sensitivity of Epicel®	Colony Forming Efficiency (CFE) assay	Small subset of the total tested were found to have a significant inhibitory effect; most were found not to inhibit cell proliferation or differentiation

A1. Radiation Validation Experiments

A feeder layer of irradiated murine fibroblasts (3T3 cells) is used to support keratinocyte growth in the Epicel® (cultured epidermal autografts) production process. The feeder layer is prepared by exposing the 3T3 cells to 6000 rads of gamma (γ)-radiation to render them proliferation-arrested. Studies were conducted to validate that 6000 rads of γ-radiation is a sufficient dose to inhibit proliferation of the 3T3 cells. In addition, analysis of the periodic validation of the irradiator used in preparing the cells was conducted. The evaluations included:

Radiation dose validation

- A non-irradiated cell spiking study to determine sensitivity of detection and proliferation-arresting effects of radiation dose;
- A radiation dose validation study was conducted to ensure that the amount of radiation was sufficient to proliferation-arrest the 3T3 cells
- A large confirmatory study in which no colony formation was observed with flasks irradiated with 6000 rads of radiation.
- ^{3}H-thymidine incorporation cell proliferation studies demonstrated that irradiated 3T3 cells did not proliferate over a 100 hour time frame, i.e., the doubling time of 3T3 cells is approximately 24-30 hours.

Irradiator validation

- Semi-annual preventive maintenance in accordance with manufacturer specifications;
- Semi-annual dosimeter evaluation;
- Monthly evaluation of the timer with a certified NIST stopwatch;
- Evaluation of the irradiator's timer with the stopwatch prior to each use; and
- Monthly adjustment of the irradiation time based upon ^{60}Co decay rate,

A2. Quantitation of 3T3 cells contained in Epicel®

Although the 3T3 cells are rendered proliferation-arrested, it is important to know if, and to what extent, patients would be exposed to mouse fibroblasts. Using an immunostain for mouse MHC I antigen, flow cytometric analysis determined that <1% (i.e., limit of detection) of the cells contained within the Epicel product were of mouse origin. Using a PCR-based methodology, Epicel was determined to have between 0.24-0.84% murine DNA.

B. Efficacy

A variety of *in vitro* and *in vivo* techniques have been employed to demonstrate that Epicel® will attach or engraft to a suitable substrate and form a stratified epithelium. In particular, Epicel® has been investigated for its performance after transplantation onto full-thickness wounds created on the dorsa of athymic mice ("surface grafts"); or after transplantation onto the vascularized inner surface of a skin flap ("flap grafts"). The results of the surface grafting studies established that cultured epidermal autografts generated using the Rheinwald and Green[1] technique were capable of regenerating an epithelium that remained for the duration of the study, 108 days. The results of the flap-grafting studies confirmed the surface grafting observations although the studies described were of shorter duration (28 days).

The results of the cell expansion, surface and flap grafting studies cited above suggest that Epicel® autografts have the potential to form permanent epithelium when grafted onto full-thickness wounds.

C. Sterility, Mycoplasma and Endotoxin assessments of Epicel®

Sterility

Sterility of the product is determined by the following methods and procedures:

- 72 hour pre-release sterility– the samples will be continued out to 14 days – sterility test is conducted via USP <71> Sterility Test
- 48 hour visual flask inspection
- Time of graft preparation sentinel flask sterility evaluation in which the sample includes cells – 14 day USP <71> Sterility Test endpoint
- Time of graft preparation visual inspection of flasks
- Gram stain on positive flasks
- Reporting requirement within 24 hours to end-user

- Reporting requirement within 5 days to FDA with follow-up of subsequent evaluations and patient outcomes via reports to the HDE

Mycoplasma

A consecutive series of product lots were assessed for mycoplasma contamination and were found to be consistently negative. In addition, quarterly evaluations of the manufacturing process are conducted.

Endotoxin

Epicel® samples, including cells taken from a sentinel flask at time of graft preparation, are tested in accordance with FDA's 1987 "*Guideline on Validation of the Limulus Amebocyte Lysate (LAL) Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices."*

D. Transportation regulatory oversight

The Epicel® biopsy transport kit is designed and tested according to International Air Transport Association (IATA) 650 packaging regulations for the transport of diagnostic specimens. Each package must state "Diagnostic Specimen Packed in Compliance with IATA Packing Instruction 650." The kits also comply with the Code of Federal Regulations Title 49, Part 173 and Title 29, Part 1910. Finally, each kit is labeled, "Not Tested for Biohazards."

E. Antibiotics/Anti-infective agents and effect on keratinocyte growth

Antibiotics and anti-infective agents commonly used on grafts in burn care were assessed for potential inhibitory effects on cell proliferation and differentiation of human keratinocytes. Reagents were tested in cell culture using a colony forming efficiency (CFE) assay. Keratinocytes were cultured with irradiated 3T3 feeder cells in media containing the desired concentration of antibiotic. After 12 days, the cultures were stained and cell colonies were evaluated and scored.

A small subset of the reagents that were assessed, were found to have a significant inhibitory effect. Please refer to tables 5 and 6 of the product instructions for use for more information.

X. SUMMARY OF CLINICAL INFORMATION

Clinical data of burn patients treated with Epicel® is presented from two sources:

1. Genzyme Biosurgery Epicel® Clinical Experience (database)

2. Munster Study: a physician-sponsored evaluation conducted by Dr. Andrew Munster at Johns Hopkins Burn Center, Baltimore, Maryland (Ann Surg. 1996; 224(3):372-5)[2].

A. Clinical Data

1. A. Genzyme Biosurgery Epicel® Clinical Experience (database, 1989-1996)

Since 1988, Genzyme Biosurgery has supplied Epicel® for the treatment of approximately 1300 patients with burn injuries. The product had been considered a banked human tissue until 1996 when FDA announced that manipulated autologous cell-based products used for structural repair or reconstruction (MAS cell products, http://www.fda.gov/cber/gdlns) required regulatory oversight. Genzyme Biosurgery has collected information from 1989 to 1996 on patients receiving Epicel® and has entered the information into a database, relying on information supplied by the attending burn team. For this time period, Genzyme's database contains data for 552 patients. Demographic, clinical outcome (survival), and adverse event data were recorded for patients who were treated with Epicel® (mean number of grafts = 104, range of 4-408). These patients show a survival rate of 86.6% (478/552) at 3 months, post initial surgery. A summary of this data is shown in **Table 5** (refer to Table 1 for adverse events reported for these patients).

Table 5
Epicel® Database:
Patient Demographics and Characteristics

	Total Treated Patients n	Survived n (%)
Number of Patients	552	478 (86.6)
Sex		
Male n (%)	409 (74.1)	355 (74.3)
Female n (%)	116 (21.0)	98 (20.5)
No Data n (%)	27 (4.9)	25 (5.2)
Mean 3rd Degree Burn[1] (%)	56.1 ± 21.2	54.4 ± 20.9
Mean Age (yrs)	28.7 ± 18.1	27.9 ± 17.4
Mean TBSA[2] (%)	68.6 ± 17.4	67.6 ± 17.1
Inhalation Injury[3] n (%)	195 (35.3)	159 (33.3)

1. 3rd Degree Burn: also referred to as full-thickness burns, are characterized by total irreversible destruction of all skin, dermal appendages, and epithelial elements. Spontaneous regeneration of epithelium is not possible.
2. TBSA: Total Body Surface Area including third degree burn area.
3. Based on available recorded information for "moderate" or "severe" inhalation injury.

B. Clinical Information (database, 1997 to 2006)

Data collected on patients treated with Epicel® from 1998 to 2006 was limited in scope, e.g., serious adverse events (see Table 2, AEs from 1998-2006), TBSA,

number of grafts used and mortality. During 1997, only survival data was collected (55 patients treated, 7 deaths (13%)). The incidence of adverse events observed from 1998-2006 appears similar, if not lower, than the incidence of adverse events observed in the 552 patients treated from 1989 to 1996.

2. Munster Study (Munster, 1996)

This published article reported on an independent, physician-sponsored study that compared the outcome of therapy in patients with massive burns with or without cultured epidermal autografts. Two groups of patients were studied over a seven year period. One group received standard care (excision plus allografting and/or split thickness autografting) and the other group received standard care plus cultured epithelial autograft (CEA), i.e., Epicel®. All patients for entry into the study had to satisfy the following criteria: 1. a minimum burn size of 50% with a substantial third-degree component, and 2. survival beyond the first operative procedure for excision and initial coverage. Genzyme Biosurgery was able to collect data from the medical records of 44 of the patients in this study. A summary of this data is shown in **Table 6**.

Table 6
Available Data from Munster Study

Parameter	Epicel®	Control
Number of Patients (n)	20	24
Sex		
Male n (%)	15 (75.0)	22 (91.7)
Female n (%)	5 (25.0)	2 (8.3)
Mean 3rd Degree Burn (%)	41.4 ± 20.92	38 ± 25.37
Risk Factors		
Mean Age (yrs)	29.6 ± 13	44.0 ± 18.5
Mean TBSA (%)	69.1 ± 15.03	62.9 ± 13.16
Inhalation Injury n (%)	18 (90.0)	19 (79.2)
Final Status at 7 years		
Survival n (%)	18 (90.0)	9 (37.5)
Death n (%)	2 (10.0)	15 (62.5)

B. Conclusions Drawn from the Preclinical and Clinical Studies

The studies indicate that Epicel® is a treatment option in the care of patients with severe, life threatening burns. Adverse events reported with the use of Epicel® are typical of those seen with burn injuries and skin grafting procedures, in general. It is well understood that permanent wound closure must be achieved in a timely fashion to avoid the many complications of the burn injury. The studies demonstrate that Epicel® is a viable adjunct to

conventional closure with split thickness skin grafts, particularly in the treatment of those severely burned patients who do not have sufficient skin to graft the entire burn.

XI. RISK/PROBABLE BENEFIT ANALYSIS

Epicel® grafts consist of a combination of the patient's own keratinocytes and, to a very small extent, i.e., less than 1%, murine fibroblasts. The use of autologous cells avoids the intrinsic disease risks associated with donor or allogeneic cells. The murine fibroblasts, i.e., swiss mouse embryo cells referred to as 3T3 cells, have been used for medical research purposes for greater than 30 years. The murine cells have been characterized at various cell banking stages for identity (i.e., isoenzyme profile), the presence of bacterial, fungal or mycoplasmal contamination and for the presence of viruses. In addition, end of production (EOP) stage cells, i.e., cells cultured past the cell culture stage used for Epicel® graft production, have been evaluated for the presence of viruses and for tumorigenicity. All safety evaluations of the 3T3 cells and of the combined cell construct, i.e., 3T3 cells plus the patient's cells, have been found to be negative for the presence of viruses and for tumorigenic potential. The 3T3 cells used in Epicel® are proliferation-arrested by gamma irradiation. Validation experiments have been conducted to demonstrate that the irradiated 3T3 cells contained in the Epicel® grafts do not proliferate in cell culture. Epicel® has been in use in the burn wound medical community for approximately 20 years. The amount of mouse cells, (i.e., <1%), has not been associated with adverse events observed to date that would suggest an infectious, xenogeneic agent is transferred to individuals, whether the individual is being treated with Epicel®, or is an intimate contact (e.g., family member or healthcare provider) of the patient. Reagents used in the culturing process and manufacturing of Epicel® are tested for sterility and for the presence of endotoxin. Epicel® is tested via a sterility and endotoxin product release system, i.e., sterility checks at 72 hours and 14 days via USP sterility tests, that safeguard against the use of contaminated product. In addition, clinical safety information collected by the sponsor indicates an adverse event profile for Epicel® recipients similar to that expected of patients undergoing standard skin grafting treatment methods. From a preclinical and manufacturing standpoint, Epicel® has been demonstrated to be safe for use.

A review of the clinical literature shows that in most cases in which Epicel® is used, it is used in combination with other burn care products to treat patients with severe burns. The majority of investigations reviewed found that Epicel®'s performance was judged by physicians to be acceptable with respect to graft take, rates of complications, appearance and mortality. Today, over 50 percent of all patients with burns involving 80 percent of their total body-surface area survive[3-6]. The survival percentages of patients treated with Epicel®, as documented in Genzyme database's, were: 1) 87% in the 1989-1996 database; and 2) 91% in the 1998-2006). These low rates of mortality are notable, considering the life-threatening condition of the patient population.

It is important to recognize that these patients undoubtedly benefited from other therapies used in modern burn care. Nevertheless, the data from the Munster study and the perception of the treatment team in the review of a case series by Carsin et al.[7], also suggest that burn

mortality might potentially be improved by the use of Epicel®. Carsin et. al reported on the use of Epicel® in 30 patients with burn wound injuries with a mean TBSA of 37 +/- 17% in a single hospital, in France. The patients, treated from 1991 to 1996, had 78+/-10% average burn size, 65+/-16% average third-degree burn size. Epicel® provided for comparable permanent burn –wound coverage vs. conventional autograft treatment (26 +/- 15% vs. 25% +/- 10%) with younger aged patients showing a statistically significant CEA-take better than conventional treatment. They also noted a 90% survival rate in using the device and stated that Epicel® had a high beneficial value in the management of burns exceeding 60% TBSA. They believed the device to very likely have been life-saving.

The one comparatively-controlled study by Munster was admittedly a small study but the mortality findings, i.e., 10% Epicel® recipients vs. 62% standard of care demonstrate a probable benefit from using Epicel®. In review of all available literature, there were no large case series investigating the performance of Epicel® found, nor any studies that suggested an increased mortality for patients treated with Epicel®.

Addressing issues of burn complications and whether they can lead to death, with regards to safety, is difficult without controlled data. However, the sponsor's two fairly large databases identifying patient complications show a fairly low rate of sepsis, a major concern for severely burned patients and a concern that strongly influences clinical outcome. Of almost 1300 patients reported in Tables I and II, the incidences of sepsis were 3.0% and 3.7% respectively. This rate compares favorably with literature cited by various authors reviewed by Macedo[8] and his co-workers who reported a sepsis rate of 19.4% in a Brazilian national burn center. Multi-organ failure, which can be independent of septicemia, is often the end stage cause of death in burns. Sheridan et al.[9], found that the most common cause of death at a large Shriner's Burn Center was multiple organ failure, despite the clinical absence of uncontrolled infection at the time of death. The two Genzyme Biosurgery databases identified rates of multi-organ failure of only 1% and 3.7% respectively. It is possible that the clinical use of Epicel®, combined with other state of the art treatments for burn care, may help lower the chances of multi-organ failure, but that has to be ultimately proven in larger trials. The sponsor's own collection of clinical data, including the adverse event incidences identified and the low incidence of mortality of patients treated with Epicel® support a conclusion that the device is clinically safe to use.

The data collected in the Genzyme Biosurgery databases regarding patient mortality and the rates of burn-associated adverse events demonstrates that Epicel® is at least equivalent to other methods for treatment of large TBSA burn injuries. The published burn injury literature supports this interpretation as well. Epicel®'s probable use in clinical settings will continue to be as a combination therapy with split thickness grafts from the patient and/or cadaver grafts. Epicel® has the potential to expand on these sources to provide for an acceptable graft status. Epicel® extends the array of burn care treatment products useful for patients who have suffered extensive burns and do not have sufficient quantities of undamaged skin for use in split-thickness skin grafts. Another probable benefit of the device is the reduction of donor site associated pain as well as a reduced risk of infection of the donor sites.

Based on the data provided, FDA has determined that Epicel® is a safe product with probable benefit to individuals suffering burns in extent greater than 30% TBSA.

XII. PANEL RECOMMENDATION

Review of the Epicel® application did not include Plastic and Reconstructive Surgery Advisory Panel consideration for device-related safety and probable benefit. However, issues regarding xenotransplantation guidelines identified by PHS (Guideline on Infectious Disease Issues in Xenotransplantation), and specifically, how the xenotransplantation guidelines should be applied to Epicel®, were discussed at the January, 2000, BRMAC Xenotransplantation Subcommittee meeting http://origin.www.fda.gov/cber/xap/trans.htm. Recommendations of the panel and FDA for Genzyme and patients treated with Epicel® were:

- Genzyme will obtain samples of the 3T3 mouse cells and the final patient product (Epicel®) will be archived.
- Genzyme will obtain baseline, i.e., pre-Epicel® treatment, samples of the patient's blood for archiving.
- Epicel® recipients, but not their intimate contacts, should defer from donating whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans.
- The patient label and physician label will communicate to the patient, or through the treating physician, the xenogenic nature of Epicel®.
- Epicel® will contain a peel-off label for the patient's medical chart history indicating that the patient was treated with a xenotransplantation product. The peel-off label states: This patient has been treated with Epicel® (cultured epidermal autografts), a product manufactured with murine cells.
- The patient label and physician label will communicate to the patient and through the treating physician that the patient should consider allowing an autopsy examination of their body upon death.
- Genzyme will construct a database to collect Epicel® patient information; this information will be provided to the National Xenotransplantation Database (NXD) when the NXD is completed.
- Genzyme will provide reports within 5 days to FDA regarding any clinical events that are suspicious of a xenogeneic cause.
- Epicel® recipients will be passively monitored with active investigation of any suspicious clinical events.

All of the recommendations provided by the Advisory Panel were adopted by FDA and all are being implemented by Genzyme Biosurgery.

XIII CDRH DECISION

CDRH has determined that, based on the preclinical and limited clinical data submitted in this HDE application, Epicel® will not expose patients to an unreasonable risk or significant

risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury. Monitoring controls, e.g., reporting requirements, database archiving, and tissue archiving, are in place for assessment of the risks to safety due to the product's xenogeneic component.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the Physician's Labeling.

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

Information for the Patient: See Patient Labeling

Postapproval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

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