FDA Executive Summary

Prepared for the
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FDA's Pediatric Advisory Committee

Epicel
(cultured epidermal autografts)
HDE# BH990200

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I. INTRODUCTION

The Pediatric Advisory Committee (PAC) annually reviews all Humanitarian Use Devices (HUDs) approved under an Humanitarian Device Exemption (HDE) that are labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs, and that are exempt from the profit prohibition, in accordance with section 520(m)(6) of the Food Drug and Cosmetic (FD&C) Act.

In accordance with section 520(m)(8) of the FD&C Act and the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update for the Pediatric Advisory Committee, based on the postmarket experience with the use of a humanitarian use device, Epicel (cultured epidermal autografts), manufactured by Vericel.

This review provides updated postmarket safety data, so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This executive summary will include summaries of the premarket clinical study, postmarket follow-up of the premarket clinical study, the peer-reviewed literature associated with the device, and postmarket medical device reporting (MDR) for adverse events.

II. INDICATIONS FOR USE

Epicel is indicated for use in adult and pediatric patients who have deep dermal or full thickness burns comprising a total body surface area (TBSA) 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. DEVICE DESCRIPTION

Epicel 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 titanium 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 and FDA[1] as a xenotransplantation product, because

[1] Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans

it is manufactured by co-cultivation with proliferation-arrested mouse, 3T3 fibroblast feeder cells.

According to the Epicel Directions for Use (DFU), the mouse 3T3 fibroblast feeder cells have been extensively tested for the presence of infectious agents, including sterility testing for bacterial and fungal contamination, testing for mycoplasma 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. During manufacturing, Epicel is evaluated for sterility via a pre-release sterility assessment, which is verified using a post-release, standard 14-day sterility assessment. Reagents used in the manufacture of Epicel are also tested for sterility and endotoxin content. The manufacturing process is 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.

IV. REGULATORY HISTORY

- 1988: Genzyme Tissue Repair began marketing Epicel as an unregulated product.
- 1996: The Manipulated Autologous Structural (MAS) cell guidance included products such as Epicel, and announced FDA's decision to require regulatory review and approval of these products. FDA requested that Genzyme submit an application for Epicel.
- 1997: Genzyme requested the Office of Chief Mediator and Ombudsman designate the lead FDA center for the regulatory review of the Epicel marketing application.
- 1998: FDA designated Epicel as a combination product and as a Humanitarian Use Device (HUD). The Tissue Reference Group recommended that the Center for Devices and Radiologic Health (CDRH) have lead review responsibility for the Epicel application.
- 1999: Genzyme submitted a humanitarian device exemption (HDE) application (H990002) to CDRH.
- 2006: Genzyme submitted supplemental safety data from the pharmacovigilance database covering the period June 1998 through August 2006.
- 2007: CDRH approved Epicel under the HDE regulatory statute indicated for patients who have deep dermal or full thickness burns comprising a total body surface area of greater than or equal to 30%.
- 2013: Lead regulatory responsibility for the Epicel HDE was transferred to the Center for Biologics Evaluation and Research (CBER) based on an assessment of the primary mode of action under the Combination Products regulations. This change was part of a transfer of oversight responsibilities for certain wound care products containing live cells from the CDRH to CBER. This consolidation initiative provided the opportunity to further develop and coordinate scientific and regulatory activities between CDRH and CBER. The transfer was announced in a Federal Register notice (Docket No. FDA-2013-N-0842). A new HDE number, BH990200, was assigned.
- 2014: Genzyme submitted special labeling supplements 19 and 21 to request revising the labeling language in three documents (a. Directions for Use; b. Patient

Information; and c. Dear Health Care Provider Letter) regarding new reports of cutaneous squamous cell cancer (SCC). The Directions for Use document and Patient Information were revised with new language regarding risks of squamous cell cancer in Epicel exposed burn wounds. The revised labeling change was approved in June 2014.
Epicel ownership was transferred from Genzyme to Vericel.

- 2015: The applicant requested a pre-submission meeting to discuss labeling revision to specify use in both adult and pediatric patients, to add pediatric labeling data, and to request an exemption from the profit prohibition
- 2016: HDE supplement 34 to include pediatric labeling was approved.

V. PREMARKET DATA

Epicel grafts consist of a combination of the patient's own keratinocytes and murine fibroblasts (less than 1%). The use of autologous cells potentially mitigates the intrinsic disease risks associated with donor or allogeneic cells. The percentage of mouse cells, (i.e., <1%), has not been associated with adverse events observed to date, in either the individual being treated with Epicel, or his immediate contacts (e.g., family member or healthcare provider) that would suggest an infectious, xenogeneic agent is transferred to individuals. In the premarketing testing, reagents used in the culturing process and manufacturing of Epicel were tested for sterility and for the presence of endotoxin. Epicel was 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. From a preclinical and manufacturing standpoint, Epicel had been demonstrated to be safe for use in the target population.

Summary of clinical information

Safety and probable benefit

A review of the clinical literature showed that Epicel has been 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 patient mortality[2][3][4][5][6][7].

[2] Carsin H et al. Cultured epithelial autografts in extensive burn coverage of severely traumatized patients: a five year single-center experience with 30 patients. Burns. 2000 Jun;26(4):379-87.
[3] Compton CC et al. Acceleration of skin regeneration from cultured epithelial autografts by transplantation to homograft dermis. J Burn Care Rehabil. 1993 Nov-Dec;14(6):653-62.
[4] Hickerson WL et al. Cultured epidermal autografts and allodermis combination for permanent burn wound coverage. Burns. 1994;20 Suppl 1:S52-5; discussion S55-6.
[5] Loss M et al. Artificial skin, split-thickness autograft and cultured autologous keratinocytes combined to treat a severe burn injury of 93% of TBSA. Burns. 2000 Nov;26(7):644-52
[6] Still JM Jr et al. Use of cultured epidermal autografts in the treatment of large burns. Burns. 1994 Dec;20(6):539-41.

Clinical data for burn patients treated with Epicel was presented from two sources: 1) Genzyme Biosurgery Epicel Clinical Experience and 2) The "Munster Study": a physician-sponsored evaluation conducted by Dr. Andrew Munster at Johns Hopkins Burn Center, Baltimore, Maryland.

Genzyme Biosurgery Epicel Clinical Experience (database, 1989-1996)
From 1988 to 1996, Genzyme Biosurgery had 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 had collected information from 1989 to 1996 on patients receiving Epicel and had entered the information into a database, relying on information supplied by the attending burn team(s). 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 had a survival rate of 86.6% (478/552) at 3 months, post initial surgery. A summary of this data is shown in Table 5 of Epicel Summary of Safety and Probable Benefit[8] .

Genzyme Biosurgery Epicel Clinical Experience (database, 1997 - 2006)
During 1997, only survival data was collected (55 patients treated, 7 deaths (13%)). From 1998 to 2006, data collected on patients treated with Epicel was limited in scope, e.g., serious adverse events, total body surface area (TBSA), number of grafts used and mortality. For this time period, Genzyme's database contains data for 734 burn patients and Table 2 summarizes the frequency of adverse events that occurred in ≥ 1% of third degree burn patients. These patients had a survival rate of 91% (669/734). 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.

Munster Study (Munster, 1996)
This published article[9] reported on an independent, physician-sponsored study that compared the outcome of therapy in patients with massive burns with or without Epicel. 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 Epicel. All patients had to satisfy the following entry 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 64 patients in this study, including 20 of

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[7] Theopold C et al. Graft site malignancy following treatment of full-thickness burn with cultured epidermal autograft. Plast Reconstr Surg. 2004 Oct;114(5):1215-9.
[8] http://www.accessdata.fda.gov/cdrh_docs/pdf/H990002B.pdf
[9] Munster AM. Cultured skin for massive burns. A prospective, controlled trial. Ann Surg. 1996 Sep;224(3):372-5; discussion 375-7.

the 22 treated with Epicel. Twenty- two (22) patients with an average burn size of 71.8% were treated with cultured keratinocytes and compared with a group of 42 controls with an average burn size of 61.6%. A summary of this data is shown in Table 6 of Epicel Summary of Safety and Probable Benefit[8].

Adverse events recorded in Genzyme Biosurgery Epicel database (1989 – 2006)
Genzyme Biosurgery maintained a database containing information supplied by attending burn teams on patients treated with Epicel 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*

Event	Number of Patients (%)	Number of Events
Death	74 (13)	74
Colonization/Infection	76 (14)	84
Graft shear#	43 (8)	45
Blister	23(4)	25
Drainage	18(3)	18
Improper hemostasis	19(3)	19
Sepsis, septic shock	17(3)	17
Graft detachment#	14(3)	14
Renal failure/disorder/dialysis	12(2)	12
Grafts debrided with dressing^	11(2)	11
Slow wound healing	7(1)	8
Allergy&	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

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

\# 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.

^ 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.

& 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.

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 was not established.

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

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

* 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%).

CDRH decision

The data collected in the Genzyme Biosurgery databases regarding patient mortality and the rates of burn-associated adverse events demonstrated that Epicel met the requirements of relative safety and probable benefit in the treatment of large TBSA burn injuries. The published burn injury literature supported this interpretation as well. Adverse events reported with the use of Epicel were typical of those seen with burn injuries and skin grafting procedures, in general. It was well understood that permanent wound closure must be achieved in a timely fashion to avoid the many complications of the burn injury. The studies in the literature demonstrated that Epicel was a viable adjunct to conventional closure with split thickness skin grafts, particularly in the treatment of those severely burned patients who did not have sufficient skin to graft the entire burn. Based on the data provided, FDA determined that Epicel is a relatively safe product with probable benefit to individuals suffering burns in extent greater than 30% TBSA.

CDRH determined that, based on the preclinical and limited clinical data submitted in this HDE application, Epicel would not expose patients to an unreasonable risk or significant risk of illness or injury, and the probable benefit to health from using the

device outweighed the risk of illness or injury. Monitoring controls, e.g., reporting requirements, database archiving, and tissue archiving, were in place for assessment of the risks to safety due to the product's xenogeneic component.

VI. PEDIATRIC USE

Since marketing approval in 2007, as Humanitarian Device Exemption (HDE), for use as wound covering in patients who have deep dermal or full thickness burns in >30% of body surface area, (b) (4) patients with burn wounds worldwide received Epicel and 29% of these were pediatric patients(age<22). Although children had been treated with Epicel, there was no specific labeling for pediatric use and no supportive pediatric data appeared in the Directions for Use.

In Supplement 34 to the HDE, the applicant proposed new pediatric labeling with three existing supportive databases (Genzyme Original HDE Application Clinical Data, Epicel Medical Device Tracker, and Pharmacovigilance Data) obtained from the pre- and post- approval periods. In the revised label, the applicant presented safety and probable benefit data with separated pediatric and adult information as derived from the three databases. Based on general principle of labeling guidance, the clinical team, in consultation with the CBER Advertising and Promotional Labeling Branch (APLB) team, revised the proposed label extensively. Vericel and FDA agreed on the revised labeling, and the supplement was approved in February 2016.

VII. ANNUAL DISTRIBUTION NUMBER/ANNUAL SALES NUMBERS

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the Annual Distribution Number (ADN).

To estimate the number of devices eligible for profit, the applicant proposed an annual distribution number (ADN) as 360,400, based on average Epicel shipment per Epicel recipient per year from 2008 through 2014.

The ADN was calculated as 90.1 x 4000 = 360,400 Epicel grafts, where 90.1 was the average number of Epicel grafts used per patient per year from 2008 through 2014 (Review Memo BH990200/34, ADN calculation, Feb. 18, 2016); 4000 represents the target population per the HDE definition.

FDA agreed with the proposed ADN based on FDA guidance on HDE. The pediatric label and ADN were approved in February 2016. The currently approved ADN remains at 360,400 Epicel grafts.

In 2016, through October, (b) (4) Epicel grafts were shipped in the U.S.

VIII. POSTMARKET LITERATURE REVIEW

A search of the U.S. National Library of Medicine's PubMed.gov database for peer-reviewed literature published from October 25, 2007 (date of initial U.S. approval) to September 30, 2016 with the search term "Epicel" OR "cultured epithelial autografts" OR "cultured epidermal autografts" retrieved 32 articles. Titles and abstracts were screened for relevance to safety information specifically for the Epicel device and its labeled indication. There was 1 case report of graft site malignancy involving squamous cell carcinoma (described below). Safety-related label changes to describe risk of SCC with Epicel use were approved in 2014. Additional new safety issues were not identified from review of the remaining 31 publications, which included articles on experimental or other cellular therapies including foreign products (N = 19), basic science/methodology (N = 7), off-label use (N = 3), general subject review (N = 1) and unrelated topic (N = 1).

A single literature case report pertinent to Epicel was described by Singh[10] et al; providing long term follow-up on a previously described case report for the same patient. Previously in 2004, Theopold[11] had described a case report of graft site malignancy involving SCC. A 34-year-old man was involved in a gas explosion while working in a manhole, sustaining full-thickness burns to 95% TBSA. In 1989, he received multiple cultured epithelial autografts (CEAs). (Note that on follow-up, the physician confirmed that the CEA received by the patient was Epicel.) He developed SCC at multiple graft sites (5 different locations of the left lower extremity) which manifested about 13.5 years after the initial treatment with CEAs. The paper by Singh et al. provided long-term follow up on this patient, who developed 8 additional SCCs in his lower extremities over the next 9 years (October 2005–April 2015). The patient survived and is closely monitored with a low threshold for excisional biopsies of any suspicious lesions. (Note: This case is included as Case 2 in Table 8).

IX. MEDICAL DEVICE REPORTS (MDRs)

A. Strengths and Limitations of MDR Data

Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect

[10] Singh et al. Invasive Squamous Cell Carcinoma in Full-thickness Burn Wounds After Treatment with Cultured Epithelial Autografts. Plast Reconstr Surg Glob Open. 2015 Aug 10;3(7):e460.
[11] Theopold et al. Graft site malignancy following treatment of full-thickness burn with cultured epidermal autograft. Plast Reconstr Surg. 2004 Oct;114(5):1215-9.

potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:
  - rare, serious, or unexpected adverse events;
  - adverse events that occur during long-term device use;
  - adverse events associated with vulnerable populations;
  - off-label use; and
  - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified and/or additionally biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

B. MDRs Associated with EPICEL

The MDR database was searched on Oct. 26, 2016, to identify all existing post market adverse event reports associated with the use of the Epicel Cultured Autograft (ECA). The searches resulted in the identification of 90 unique MDRs.

Overall Data
The 90 reports were received between 12/21/2000 and 07/15/2016; all of which were submitted by the manufacturer. Patient age information was reported in 78 MDRs and ranged from 2 to 74 years (mean=34.6 years), with pediatric patients comprising 20 (25%) of the reports. Patient sex information was reported in 84 MDRs of which 22 (27%) were female and 62 (74%) were male.

The event types in the 90 reports were 76 deaths, 12 injuries and 2 malfunctions. All patients were victims of burn injury except one who was grafted with ECA for treatment of chronic open wounds of Goltz Syndrome/Focal dermal hypoplasia (FDH). The Total Body Surface area (TBSA) burned was specified in 59 reports with a range between 35% and 99% and a mean of 76% (median 80%). The three top reported types of adverse events were multi-organ failure (41%), followed by sepsis (16%), and cardiac problems (11%), such as cardiac arrest and cardiogenic shock. The manufacturer reported five cases of Squamous Cell Carcinoma (SCC) , one of which was a pediatric patient. SCC patients developed non-healing lesions/ulcers many years post ECA implant.

Note:
The 90 MDRs include reports submitted prior to the approval of the HDE on 10/25/2007. At the time of the HUD designation in 1998 and subsequent submission of the HDE application in 1999, the manufacturer chose to "report serious cases assessed as possibly, probably or definitely related to Epicel as 30 day Medical Device Reports (MDRs)." Between December 2000 and January 2007 Genzyme reported 37 MDRs. Fifty-three MDRs were received by CDRH since the HDE approval (See Tables 3 and 4 below).

Table 3: Reports Submitted Prior to HDE Approval by Event Type

Event Type	Pediatric Patients	Adult Patients	Total
Death	6	28	34
Injury	2	1	3
Malfunction	0	0	0
Total	**8**	**29**	**37**

Table 4: Reports Submitted After HDE Approval by Event Type

Event Type	Pediatric Patients	Adult Patients	Total
Death	9	33	42
Injury	2	7	9
Malfunction	1	1	2
Total	**12**	**41**	**53**

Pediatric Reports

Twenty of the 90 reports involved pediatric patients. Pediatric patient age and sex were reported in all 20 MDRs. The patient age ranged from 2 to 21 years, with an average age of 13.4 years. Patient sex was reported as 6 female, and 14 male patients. The reporting country of origin was available in 16 MDRs and included 15 from United States, and one from South Africa.

Event types in pediatric patients were 15 deaths, 4 injuries and one malfunction. The TBSA burned was specified in 14 pediatric reports, and ranged between 35% and 99%. The average pediatric TBSA was 85% (Median 91.5%).

Pediatric Death Reports

The most frequently reported cause of death in pediatric patients was multi-organ failure (n=8), three of which involved infection or sepsis. The other causes of death included squamous cell carcinoma (n=1), cardiac arrest (n=1), Goltz syndrome/Focal dermal hypoplasia (FDH) (n=1), mixed drug interaction, unrelated to the graft (n=1) and death due to complications of full thickness burns (n=1). Two MDRs did not disclose the cause of death. Table 5 provides a summary of the 15 pediatric death reports.

Table 5. Summary of Pediatric Death Reports (n=15)

Patient Age (Yrs)	Patient Sex	Type of Burns	TBSA Percentile	Grafting information	Graft to Death Time	Cause of Death/Adverse event
14	M	UNK	UNK	192 grafts in 2002	One hour after graft	Multiorgan failure
20	M	UNK	UNK	144 grafts in 2002	Same year (not specified)	Multiorgan failure
19	F	flame burn (Automobile accident)	62% (smoke inhalation injury)	50 grafts in 2002 (in 2 sessions)	Following year (not specified)	Multiorgan failure; Multiple invasive fungal infection & episode of sepsis, DIC, renal failure; BK amputation due to ischemia (Died after stopping life support)
10	F	UNK	UNK	80 grafts in 2001	2 days after graft	Cardiac arrest
21	M	flame burn (Self inflicting)	95%	168 grafts in 2004 (in 2 sessions)	Same year (not specified)	Multiorgan failure (no details)
20	M	military blast	92%	96 grafts in 2006	10 days after graft	Multiorgan failure (no details)
4	M	flame burn (gasoline fire)	79% (full thickness)	61 grafts in 2007 & 2008 (in 2 sessions)	7 days after the last graft	Multiorgan failure- Infection (*C. difficile* diarrhea, *Streptococcus pneumonia*)
7	M	gasoline fire	79% (full thickness)	52 grafts in 2007 & 2008 (in 2 sessions)	1 month after last graft	Complications of full thickness thermal burn; Infection *(Streptococcus pneumonia*), Pulmonary congestion

Patient Age (Yrs)	Patient Sex	Type of Burns	TBSA Percentile	Grafting information	Graft to Death Time	Cause of Death/Adverse event
2	M	thermal burn (house fire)	90%	72 grafts in 2008 (in 2 sessions)	8 days after last graft	Multiorgan failure (Respiratory problem prior to Epicel graft); hypotension; "brain dead" and Hypochloraemia
16	M	thermal burn	97%	UNK number of grafts in 2011	Same day after graft	Multiorgan failure; Septic shock; cardiopulmonary arrest
19	F	thermal burn	UNK	UNK number of grafts in 2013 (in 2 sessions) did fine with grafts and was discharged home	9 months after last graft	Pt was found unconscious at home. Autopsy results: due to mixed drug interaction including Methadone and Hydroxyzine-unrelated to grafting (one week before death had *C. difficile* infection. treatment in ER)
20	F	Goltz Syndrome/Focal dermal hypoplasia (FDH)	UNK	68 grafts in 2012 & 2013 (in 4 sessions) plus other treatment modalities-Off label use	9 months after last graft (limited engraftment due to poor wound bed)	Respiratory failure, Sepsis (*Serratia marcescens* infection). Death due to Goltz Syndrome/Focal dermal hypoplasia (FDH).
18	M	UNK	91%	96 grafts in 2015	11 days after graft	UNK Cause
8	F	UNK	85%	15 grafts in 2016	24 days after graft	UNK Cause

Patient Age (Yrs)	Patient Sex	Type of Burns	TBSA Percentile	Grafting information	Graft to Death Time	Cause of Death/Adverse event
8	M	Flame burn	99%	UNK number of grafts in 1998 (in 3 sessions)	13 years after last graft	Squamous Cell Carcinoma

The only off-label use of ECA was reported in one pediatric patient; a 20 year old female who was treated for Goltz Syndrome/Focal dermal hypoplasia (FDH), a genetic disorder with chronic open wounds. The patient died of complications related to her open wounds.

Pediatric Injury Reports

There were four pediatric injury reports. Three patients developed infection, two of which were reported as *Aspergillus sp.* infection, and one was specified as *Candida parapsilosis*. One report with minimal information stated that a foot amputation surgery was performed on the patient. Table 6 presents a summary of the pediatric injury reports.

Table 6. Summary of Pediatric Patients' Injury Reports (n=4)

Patient Age	Patient Sex	TBSA Percentile	Grafting Information	Cause of Injuries
8	M	95% (full thickness)	43 grafts (UNK date)	*Aspergillus sp.* infection
21	M	92%	reported as "2400 cm^2" of graft	*Aspergillus sp.* infection
4	M	UNK	UNK	foot amputation (no details)
5	F	35%	UNK	Infection (grafts sample culture was positive for *Candida parapsilosis*). Patient developed infection. Affected grafts were removed.

Pediatric Malfunction Report

The one pediatric adverse event report that was submitted as a malfunction stated that the Epicel final product from one specific lot number was found to be positive for gram positive cocci. This result was subsequently confirmed through a gram stain of the retained sample which was also found to be positive for gram positive cocci. The patient received several grafts but had no adverse events.

Summary

Ninety reports associated with the use of Epicel were received by FDA between the years 2000 and 2016. Seventy reports were related to adult patients and 20 to pediatric patients. Event types in adult patients were 61 deaths, eight injuries, and one malfunction report. The most frequently reported cause of death in adult patients was multi-organ failure followed by infection/sepsis, and cardiac problems. The average TBSA in adult patients was 76%. Nine of the adult patients had TBSA of 90% and over.

Twenty of the 90 MDRs, representing 20 unique patients/events, were associated with the use of the Epicel in pediatric patients. Multi-organ failure was also the most frequently reported adverse events in pediatric patients followed by infection/sepsis. The average TBSA among the pediatric patients was 85% and seven of the patients had TBSA of over 90%. In the majority of the reports, the manufacturer's narrative stated that the adverse events were unrelated to the use of Epicel.

X. POST-APPROVAL SURVIVAL DATA REPORTED IN THE DIRECTIONS FOR USE (DFU)

Epicel Directions for Use (updated 2016) includes tracking data as per FDA requirement following Epicel approval in 2007. Demographics and survival information have been collected under this database. During the period from October 2007 to June 2015, a total of 402 patients received Epicel in the U.S. according to the labeled indication, with average age of 32 years; 73% were males, and the average burn size was 66% of TBSA. Of these 402, there were 120 pediatric patients with average age of 12 years; 71% were males, and the average burn size was 66% of TBSA. The survival rate in this pediatric population was 88.3% (106/120) as compared with the overall survival rate of 81.3% in the total population (327/402).(Table 7)

Table 7: Survival data from Epicel Database (October 2007 to June 2015)

	Pediatric Patients	**Total**
Deaths	14	75
Patients treated with Epicel	120	402
Survival	88.3% (106/120)	81.3% (327/402)

XI. ADVERSE EVENT OF SPECIAL INTEREST:

Squamous Cell Carcinoma (SCC)

Squamous cell carcinoma (SCC) is the most common skin cancer to develop from burn wound scars, with an estimated 2% of burn scars undergoing malignant transformation[12, 13] . As of September 30, 2016, 6 reports of SCC after Epicel treatment were submitted to the manufacturer or published in medical literature (Table 8). Review of these cases by FDA and the manufacturer noted that following Epicel grafts to treat burns, SCC has, in some cases, developed with shorter latency periods, and presented with more aggressive features and multi-focal growth when compared to SCC developing in burn patients who have not been treated with Epicel. In 2014, FDA approved revisions to the Epicel label (supplement BH990200/21) to include information on the risk of SCC and requested revision of the labeling language in three documents: (i) Directions for Use – Warnings section, (ii) Patient Information, and (iii) Dear Health Care Provider Letter. The manufacturer issued the Dear Health Care Provider letter in June 2014.

[12] Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. Burns. 2005 Jun;31(4):403-13. Epub 2005 Apr 1.
[13] Gül U, Kiliç A. Squamous cell carcinoma developing on burn scar. Ann Plast Surg. 2006 Apr;56(4):406-8.

Table 8: Reports of Squamous Cell Carcinoma following Epicel to date (N = 6)

Reports	Source	Diagnosis	Age at Grafting	Time to onset of SCC after graft	SCC	Outcome
Case 1	Pre-market data	dystrophic epidermolysis bullosa (DEB)*	Unknown age; grafted in 1994	A few days	Lower extremity	Below the knee amputation
Case 2	MedWatch (Mfr Report #: 1226230-2011-00003) of literature case report (Previously discussed in literature review section; Theopold, 2014; Singh, 2015)	95% TBSA burn	34-year-old male; grafted in 1989	13.5y	Multiple SCCs in grafted areas: 5 SCCs in L leg (onset 13.5y after Epicel); 8 additional SCCs developed 2005 to 2015.	Recovered; SCC resections
Case 3	MedWatch (Reported in 2011; Mfr Report #: 1226230-2011-00002)	99% TBSA burn	8-year-old male; grafted in 1998	12y (2010)	Multiple SCCs (abdomen, knee, foot); atypical features, altered p53.	Death
Case 4	MedWatch (Reported in 2012; Mfr Report #:1226230-20I2-00002)	unknown	Unknown age; grafted in 1997	15y	unknown	Recovered
Case 5	MedWatch (Reported in 2012; Mfr Report #:1226230-20I2-00003)	unknown	Unknown age; grafted in 1993	19y	unknown	Death
Case 6	MedWatch (Reported in 2014; 1226230-2014SA131512)	95% TBSA burn	46-year-old male; grafted in 1998	13y	left posterior lateral knee	Recovered

*Note that DEB is not an approved indication for Epicel and this was off-label use. Patients with recessive DEB have up to a 50-fold increased incidence of cutaneous squamous cell carcinoma[14].

The labeling revisions which reflect the new information regarding SCC are described as follows in the Directions for Use and the Patient Information document.

- Direction for Use – Warnings: Squamous Cell Carcinoma (SCC)

  Squamous cell carcinoma (SCC) has been reported in patients with burn injury after being grafted with Epicel. Distinctive features of these cases include multicentric location, large size, aggressive growth, local recurrence after resection, and fatal outcome in some of the cases. In the reported cases, the SCC

[14] Kim et al. Update on the pathogenesis of squamous cell carcinoma development in recessive dystrophic epidermolysis bullosa. Eur J Dermatol. 2015 Apr;25 Suppl 1:30-2.

occurred in the grafted areas 12 to 19 years after Epicel grafting. A latency period of 32 ± 18 years from the time of burn injuries to occurrence of SCC is described in the literature.

A patient with epidermolysis bullosa dystrophica (DEB) developed an invasive SCC a few days after grafting with Epicel. The patient underwent a lower extremity amputation within weeks of diagnosis.

Of the three patients diagnosed with SCC with known age, one was an eight-year-old child at the time of treatment with Epicel. The child was diagnosed with SCC in the area of the Epicel graft 11 years and 7 months after treatment, and the outcome was fatal.

Although SCC is a known complication of burn scars and DEB, the role of Epicel in the causation of SCC cannot be excluded.

- Patient Information
  What are the Potential Complications of Burns and Skin Grafting?
  Squamous Cell Carcinoma (SCC), one type of skin cancer, is a possible long-term complication of extensive burns. SCC was reported in a few patients who received grafting with Epicel. SCC in these cases developed in more than one area on the body approximately 12 to 19 years from the time of grafting.

X. SUMMARY

Epicel is a Humanitarian Use Device that is indicated for use in adult and pediatric patients who have deep dermal or full thickness burns comprising a total body surface area (TBSA) of ≥ 30%.

Epicel's Directions for Use (updated 2016) includes tracking data as required by FDA following marketing approval in 2007. Demographics and survival information have been collected under this requirement. During the period from October 2007 to June 2015, the survival rate in the pediatric population was 88.3% (106/120) as compared with the overall survival rate of 81.3% in the total population (327/402) who received the device.

Ninety spontaneous adverse event reports associated with the use of Epicel were received by FDA between 2000 and 2016, including 20 pediatric reports. Of the 70 adult reports, there were 61 deaths, in which the patients had burns comprising a mean of 76% TBSA, and 9 of whom had burns involving ≥ 90% TBSA[15]. There were 15 pediatric deaths with burns comprising a mean of 85% TBSA. Multi-organ failure was the most frequently reported adverse event in pediatric patients followed by infection/sepsis.

[15] Of note, expedited reporting is required only for deaths that are related, as of February 25, 2009 and per HUD supplement S-005.)

In the majority of Epicel death cases, the patients experienced multi-organ failure and sepsis, both of which are well-known sequelae of severe burn wounds[16, 17]. A study in a pediatric burn center found that sepsis was the leading cause of death after burn injury[18]. Multi-organ failure, which can be independent of septicemia[19], is a common cause of death in burn patients. The risk of multiple organ dysfunction syndrome increases with burn wounds >20% TBSA[20].

Thus, the adverse events reported with the use of Epicel were either labeled or consistent with the known comorbidities seen with severe burn injuries. There is a high risk of mortality and morbidity in patients with severe burns. Overall mortality from a severe burn injury (involving >20% TBSA) ranges from 3 to 55%, depending upon the extent (e.g., size and depth) of the burn as well as the presence of inhalation injuries[21]. Recent U.S. data indicate that 50% case fatality occurs once burns are greater than 65 – 70% TBSA[22]. Major predictors of case fatality in burns include burn size, age, and the presence of inhalation injury.

At the time of initial approval in 2007, the FDA document on Summary of Safety and Probable Benefit (SSPB) noted that over 50% of all patients with burns involving 80% of their TBSA survive, and the survival percentages of patients treated with Epicel were were: 1) 87% in the 1989-1996 database; and 2) 91% in the 1998-2006 database. The SSPB stated that "These low rates of mortality are notable, considering the life-threatening condition of the patient population."

The relatively low percentage of patients with reports of death after Epicel treatment identified in this postmarketing safety review, covering the period since FDA approval in 2007 (initial approval) – 2016, suggests similar rates of survival and mortality as observed in the pre-approval databases. Additionally, the label was updated in 2014 to include the risk of squamous cell carcinoma after Epicel use. In conclusion, FDA did not identify any new safety signals during this comprehensive safety review. The HDE for this device remains appropriate for the adult and pediatric population for which it was granted. FDA will continue routine monitoring of the safety and distribution data for this device.

[16] Kraft et al. Burn size and survival probability in paediatric patients in modern burn care: a prospective observational cohort study. Lancet. 2012 Mar 17;379(9820):1013-21.
[17] Greenhalgh et al. American Burn Association consensus conference to define sepsis and infection in burns. J Burn Care Res. 2007 Nov-Dec;28(6):776-90.
[18] Williams et al. The leading causes of death after burn injury in a single pediatric burn center. Crit Care. 2009;13(6):R183. Epub 2009 Nov 17.
[19] Sheridan et al. Death in a Burn Unit – Sterile Multi-Organ Failure. Burns. 1998; 24(4):307-11.
[20] Gauglitz et al. Complications and long-term outcomes of a severe burn. Available on UpToDate; topic last updated Aug 10, 2016.
[21] Gauglitz et al. Overview of the management of the severely burned patient. Available on UpToDate; topic last updated Jul 25, 2016.
[22] 2016 National Burn Repository, Report of Data from 2006 – 2015. American Burn Association.