Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

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To:	Craig Zinderman, MD, MPH Associate Director for Medical Policy, OBPV, CBER
Through:	Meghna Alimchandani, MD Acting Director, DPV, OBPV, CBER
Subject:	Annual Safety Update for the Pediatric Advisory Committee (PAC)
Sponsor:	Vericel
Product:	Epicel (cultured epidermal autografts)
STN:	HDE# BH 990200/101
Indication:	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.

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this is an annual safety update for the Pediatric Advisory Committee (PAC), 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 memorandum documents FDA's complete evaluation, including review of postmarket medical device reporting (MDR) of adverse events, annual reports from the manufacturer, and the peer-reviewed literature associated with the device.

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

Depending on the surface area requiring coverage, more than one graft may be used per patient. For example, 90.1 was the average number of Epicel grafts used per patient during the period from 2008 through 2014 (Review Memo BH990200/34, February 18, 2016). From 1989 to 1996, each patient received an average of 104 grafts (Epicel Directions for Use [February 2016], Clinical Studies section).

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

IV. REGULATORY HISTORY

a. 1988: Genzyme Tissue Repair began marketing Epicel as an unregulated product.
b. 1998: FDA designated Epicel as a combination product and as a Humanitarian Use Device (HUD).
c. 2007: FDA's Center for Devices and Radiologic Health (CDRH) approved Epicel under the HDE regulatory statute.
d. 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 CDRH to CBER.
e. 2014: FDA approved a labeling supplement to revise Directions for Use and Patient Information to describe the risk of squamous cell carcinoma (SCC).
f. 2014: Epicel ownership was transferred from Genzyme to Vericel.
g. 2016: FDA approved a pediatric labeling supplement, which specified use in both adult and pediatric patients, added pediatric labeling information, and granted an exemption from the profit prohibition.
h. 2017: First Annual Review of Pediatric Safety for Epicel was presented to PAC in March 2017. (This has been followed by subsequent annual safety updates for the PAC.)
i. 2022: FDA approved a labeling supplement (BH990200/89) to update the Warning section under Squamous Cell Carcinoma (SCC) of the Instructions for Use (IFU) following an updated sponsor assessment (see section VII).

V. PEDIATRIC USE

In 2007, Epicel received marketing approval under Humanitarian Device Exemption (HDE) regulations, for use in patients who have deep dermal or full thickness burns in ≥30% of body surface area. Since marketing approval in 2007 to 2015, approximately 29% of patients treated with Epicel worldwide were pediatric patients (age < 22 years). In 2016, FDA approved a pediatric labeling supplement, which specified use in both adult and pediatric patients, added pediatric labeling information, and granted an exemption from the profit prohibition. The Directions for Use (DFU) summarizes adverse reaction report information for 205 pediatric patients treated with Epicel from 1989 to 1996, and an additional 589 pediatric patients treated from 1998 to 2015. These were also summarized in the pediatric safety memo dated March 7, 2017, for PAC review.

VI. ANNUAL DISTRIBUTION NUMBER/ANNUAL SALES NUMBERS

Section 520(m)(6)(A)(ii) of the 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).
The currently approved ADN for Epicel is 360,400 grafts. 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 from 2008 through 2014 (Review Memo BH990200/34, ADN calculation, Feb. 18, 2016); 4000 individuals represent the target population per the HDE definition at the time the pediatric labeling was approved (February 2016).

The number of Epicel grafts distributed has not exceeded the ADN. The number of Epicel grafts distributed during:

- Calendar year 2023: (b) (4) Epicel grafts, including 2171 grafts in pediatric patients.
- Calendar year 2024: Not yet available, however, from January 1, 2024, through September 30, 2024, Vericel distributed (b) (4) Epicel grafts, including 2066 grafts in pediatric patients.

Note: These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.
During the annual review period, October 1, 2023, to September 30, 2024, 37 pediatric (b) patients, (b) (4) adult patients, and (4) patients of unknown age were treated with Epicel for burn injuries.

VII. LABEL CHANGES IN REVIEW PERIOD

There were no safety related label changes during the PAC review period (October 1, 2023, to September 30, 2024).

VIII. MEDICAL DEVICE REPORTS (MDRs)

a. Strengths and Limitations of MDR Data

The FDA receives MDRs of suspected device-associated deaths, serious injuries, and malfunctions from 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 potential device-related safety issues, and contribute to benefit-risk assessments of these products.

MDR reports can be used to:

- Establish a qualitative snapshot of adverse events for a device or device

- type
- Detect actual or potential device problems including:
    - rare or unexpected adverse events;
    - adverse events that occur during long-term use;
    - adverse events associated with vulnerable populations;
    - off-label use; and use error.

Although MDRs are a valuable source of information, this Medical Device Reporting is a passive surveillance system and has limitations, including the submission of incomplete, inaccurate, untimely, unverified and/or additionally biased data. In addition, the incidence of an event cannot be determined from MDRs alone due to under- reporting of events and lack of information about frequency of device use.

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 an event can be difficult based solely on information provided in MDRs. 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 due to, reporting practices, 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 November 4, 2024, to identify postmarket adverse event reports associated with the use of Epicel submitted to FDA during the annual review period, October 1, 2023, to September 30, 2024. The search identified nine MDRs including six reports with fatal outcome, three reports of malfunction (one of the malfunction reports included a fatal outcome), and one report with serious injury. One report involved pediatric patients. All nine reports were submitted by the manufacturer. The six patients with fatal outcome(s) had extensive third degree burns and died after grafting. As per the manufacturer's assessment, the deaths were probably related to the underlying condition. The summary of death and injury reports is displayed in Table 1.

Table 1. Summary of Death and Injury Reports (n=7)

Case ID	Age (year)	Sex	Event	Time from Graft to Event	PT
US-VCEL-(b) (6)	22	Female	Obstructive airway disorder	66 days	death
US-VCEL-(b) (6)	26	Male	Multiple organ failure	unknown	death
US-VCEL(b) (6)	41	Male	Multiple organ failure	unknown	death
US-VCEL-(b) (6)	24	Male	Multiple organ failure	unknown	death
US-VCEL-(b) (6)	11	Male	Mesenteric ischemia, abdominal compartment syndrome	unknown	serious injury
US-VCEL-(b) (6)	40	Male	Succumbed injuries	34 days	death
US-VCEL-(b) (6)	33	Female	Multiple organ failure	17 days	death

Reviewer comment: The reported causes of deaths are consistent with complications experienced by severe burn trauma patients in the intensive care setting. No new safety concerns were identified.

The three reports of device malfunction involved media leakage in the graft bags. Table 2 provides a summary of three device malfunction reports.

Table 2. Summary of Device Malfunction Reports (n=3)

Case ID	Event	Lot	Description of event
US-VCEL	Malfunction	EE03095-23	The grafts were detached from the gauze backings. No grafts were used on the patient. Patient expired before the grafts were implanted due to a compromised airway.
US-VCEL	Malfunction	EE03094-32	One graft skin detached from the backing, two grafts with a media leak outside of the self-seal pouches, and a scratch on the foil with a possible break in the seal. 41 grafts were not implanted. No adverse events were reported for this patient.
US-VCEL-	Malfunction	EE03308-31	Some pink liquid (media leak) observed in one sleeve of trays. 21 grafts were not implanted. No adverse events were reported for this patient.

*Reported in previous period

Reviewer comment: Two of these three cases were updates on cases that were initially reported in the previous reporting period. The defected grafts were not implanted, and no adverse events were reported for the patients except one patient died before graft implanted.

IX. ANNUAL REPORT REVIEW

The sponsor's most recent annual report (September 1, 2023, to August 31, 2024) was reviewed. During the reporting period, a total of 62 events (32 serious events, 30 nonserious events) were reported in 30 patients.

The most frequently reported system organ class (SOC) categories during this reporting period were Product Issues (45.2%; 28/62); General Disorders and Administration Site Conditions (16.1%, 10/62); and Gastrointestinal disorders (9.7%, 6/62). Of the 62 reports, 10 reports involved fatal outcomes, of which there were nine adult reports, and one report that occurred in a patient of unknown age.

Pediatric Death Reports: There were no case reports with fatal outcome in pediatric Epicel recipients.

Adult Death Reports: The sponsor received 10 reports involving fatal outcomes in adult Epicel recipients or Epicel recipients of unknown age during the reporting period of the Annual Report. Six of these ten cases were identified in the MDR database and are described above in Section VIII.B; the remaining four cases are displayed in Table 3.

Table 3: Summary of Case Reports with Fatal Outcome Received during the Reporting Period – All Age Groups

Case ID	Age, Sex	Event	Time from Graft to Event	Cause of Death
US-VCEL-(b) (6)	52	Death	unknown	Multiple organ failure
US-VCEL-(b) (6)	60	Death	unknown	Unknown
US-VCEL(b) (6)	45	Sepsis	unknown	Sepsis
US-VCEL(b) (6)	60	Death	unknown	Sepsis

Reviewer comment: The reports of death for which information on cause of death was available were related to multiple organ failure or sepsis, which are known complications with underlying severe burn injuries.

Product Issue Reports: There were 19 reports of product Issues in the Annual Report. Three of these 19 reports were identified in the MDR database and are described above in Section VIII.B; the remaining 16 cases are displayed in table 4 below.

Table 4. Summary of Product Issue Reports (n=16)

Case ID	Lot #	# Shipped	# Utilized	# Not Utilized	Product Issue Reported
US-VCEL	EE03184-21	106	36	70	The grafts were detached from the gauze backing.
US-VCE	EE03206-21	93	91	2	The grafts were detached and bunched to an area of the graft tray.
US-VCE	EE03206-32	73	71	2	The grafts were detached and bunched to the side.
US-VCE	EE03228	113	102	11	The gauze backings were partially or completely lifted. Cells were scalloped and hanging off when lifted from the backing.
US-VCE	EE03227-31	144	125	19	The grafts were detached and scalloped from the gauze backing.
US-VCE	EE03215-23	49	37	12	The grafts were detached from the gauze backing.

US-VCE	EE03233-22	44	37	7	The grafts were detached from the gauze backing.
US-VCE	EE03227-22	27	0	27	The grafts were detached from the gauze backing.
US-VCE	EE03257-21	48	34	14	The grafts were detached from the gauze backing.
US-VCE	EE03258-21	99	92	7	The grafts were detached from the gauze backing.
US-VCE	EE03261-31	144	128	16	The grafts were detached from the gauze backing.
US-VCE	EE03263-21	95	88	7	The grafts were detached from the gauze backing.
US-VCE	EE03262-21	81	40	41	The grafts were detached from the gauze backing. Some grafts were reported to be lighter in color than usual and the skin thinner than usual.
US-VCE	EE03244-31	79	74	5	The grafts were detached from the gauze backing.
US-VCE	EE03323	144	143	1	The graft was detached and scalloped in the dish.
US-VCEL	EE03308-32	96	88	8	The grafts had scalloped edges.

Reviewer comment: Fourteen of 16 product issue events were related to graft floating/detachment from the backing. The defected grafts were not used on patients, and no clinical adverse events were reported for these patients.

FDA requested additional information from the manufacturer about the quality issue reports, including information on the manufacturer's review and any corrective actions. The manufacturer clarified that "several corrective actions have taken over the last two reporting periods including updates to manufacturing processes and training related to: (b) (4) , and the percentage of total grafts impacted by product issues was reduced from 2023 Annual Report to 2024 Annual Report". The sponsor also stated that: "some patients' cultured keratinocyte cells routinely generate grafts that are (b) (4) . The (b) (4) grafts was a contributing factor in several cases that cannot be addressed through additional corrective actions by Vericel. Damage to Epicel grafts that has occurred during transit is easy for the surgeon to identify visually, and these grafts can be discarded so that there is no patient exposure."

X. POSTMARKET LITERATURE REVIEW

A PubMed literature search conducted on November 6, 2024, using the search term "Epicel" OR "cultured epithelial autografts" OR "cultured epidermal autografts" OR "cultured epithelial autograft" OR "cultured epidermal autograft" for articles published between October 1, 2023, and September 30, 2024, retrieved 10 articles. Titles and abstracts were reviewed for relevance to safety information specifically for Epicel device and its labeled indication. No article relevant to Epicel AEs was identified.

XI. ADVERSE EVENT OF SPECIAL INTEREST: Squamous Cell Carcinoma

SCC is the most common skin cancer to develop from burn wound scars. The label (please see Appendix B) for Epicel includes information on the risk of SCC[2] (Instructions for Use [IFU] –Warnings section, and Patient Information). As stated in the label, "Although SCC is a known complication of burn scars and DEB, the role of Epicel in the causation of SCC cannot be excluded."

Five cases of SCC observed in Epicel-treated burn patients were reviewed and discussed during the initial PAC presentation on March 7, 2017. No new cases of SCC in Epicel-treated patients were reported to Vericel or reported in the literature from the initial PAC presentation through 2021. In 2022, the Sponsor conducted an updated assessment for SCC, including spontaneous reports and literature case reports, and cumulatively identified a total of 13[3] cases of SCC in burn patients, including 5 pediatric patients, treated with Epicel (please see prior annual PAC update memo under BH 990200/92). All burn injuries were catastrophic burns involving a total body surface area (TBSA) ranging from 70% to 99%. The latency period from Epicel use to occurrence of SCC ranged from 11 to 23 years (median:15 years). The manufacturer calculated a cumulative reporting rate of SCC (based on the 13 SCC cases and (b) (4) patients treated as of June 2022) to be 0.56% of Epicel patients. As noted in Section IV, the manufacturer revised the Epicel labeling to include updated information on SCC. (Please see Appendix A for updated case count of SCC cases).

Vericel continues to monitor for the occurrence of AEs, including SCC, through their routine pharmacovigilance activities, including collection and analysis of spontaneously reported AEs, monitoring of published literature, and the Epicel Medical Device Tracker

[2] Note that Epicel label includes an additional case of SCC in a patient with epidermolysis bullosa dystrophica (DEB).
[3] Of the 13 cases, 5 were the old cases reviewed during the initial PAC presentation on March 7, 2017, one was a new case reported to Vericel in 2022, and 7 were literature cases from the literature review conducted by the sponsor in 2022.

(EMDT) database. For the EMDT, Vericel contacts patients at least annually to update their contact and survival information for all patients treated with Epicel since 2007. FDA is monitoring SCC occurrence in Epicel-treated patients through MDRs, annual reports from the manufacturer, periodic literature review, and annual PAC reviews.

Reviewer comments: The manufacturer's estimated reporting rate does not exceed the background rate of SCC in patients with burn wound scars, with an estimated 2% of burn scars undergoing malignant transformation.[4,5] Other sources have reported background rates of SCC in burn patients ranging from 0.24%[6] to 6.97%[7]. Based on the AE reports, the patient population treated with Epicel have sustained massive burn injuries (often >90% TBSA burn injuries), and it is unknown if the severity of the burn injuries and number of Epicel grafts used, have an impact on the occurrence of SCC.

In the current annual review period, October 1, 2023, to September 30, 2024, there were no additional reports of SCC.

XII. SUMMARY

The number of death reports and types of AEs observed during this annual review period are similar to those listed in the IFU, and do not suggest new safety concerns. Infection is common in severe burn injuries, and this as well as other AEs reported during this reporting period represent outcomes consistent with the known comorbidities seen in severe burn injury patients. Given the high fatality rate in patients with severe burns, the number of reported deaths after Epicel use does not suggest a concern for fatal outcomes related to the device itself, as opposed to the underlying injury. High TBSA burn injuries in these cases is associated with a high fatality rate, even among patients who survive long enough to receive Epicel grafts.

FDA did not identify new safety signals during this comprehensive safety review of the manufacturer's Epicel HDE annual report, the MDRs received by FDA, and the literature published during the annual review period. The HDE for this device remains appropriate for the adult and pediatric populations for which it was granted. FDA will continue routine monitoring of the safety and distribution data for this device.

[4] Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. Burns. 2005 Jun;31(4):403-13.
[5] Gül U, Kiliç A. Squamous cell carcinoma developing on burn scar. Ann Plast Surg. 2006 Apr;56(4):406-8.
[6] Bernt Lindelöf, Britta Krynitz, Fredrik Granath et al. Burn Injuries and Skin Cancer: A Population-based Cohort Study. Acta Derm Venereol 2008; 88: 20–22
[7] Khalifa E. Sharquie and Raed I. Jabbar. The Frequency of Squamous Cell Carcinoma Among Patients with Long Standing Burn Scars. J Turk Acad Dermatol 2021;15(3):65-68

Appendix A

Table A. Cases of Squamous Cell Carcinoma After Epicel-Treated Burn Injury (n=14)

Case ID Date Report Received Source	Patient Age, Sex	Patient burn injury: TBSA	Year of CEA Graft	Skin Cancer Information: Age at Dx (Year)	Skin Cancer Information: Location	Latency	Outcome
VCEL-(b) (6) 25-Apr-2011 Literature (Theopold 2004)	34y Male	95%	1989	~47y	Left leg	13y6mo	Recovered (30-Sep-2015)
-VCEL(b) (6) 21-Apr-2011 Spontaneous	8y Male	99%	1998	~20y (10-May-2010)	L abdominal wall, L knee, foot	11y10 mo	Death ((b) (6)
VCEL(b) (6) 26-Apr-2012 Spontaneous	Unknown Female	Unknown	1997	Unknown	SCC	~15y	"Alive and well" (29-May-2012)
VCEL(b) (6) 26-A Spontaneous	Unknown Male	Unknown	1993	Unknown	SCC	~19y	Death (date unknown)
VCEL(b) (6) 17-S Spontaneous	46y Male	95%	1998	~58y (Feb-2011)	Left knee	12y8m o	Recovered (22-Sep-2014)
VCEL(b) (6) 23-Au Spontaneous	Unknow n (adult) Male	95%	2011	Unknown (Aug-2022)	Leg	~11y	Ongoing (Aug-2022)
VCEL(b) (6) 22-Ap Spontaneous	41y Male	Unknown	1999	41y (2023)	Right lower extremity anterior shin area	15y	Ongoing (Apr-2023)

Case ID Date Report Received Source	Patient Age, Sex	Patient burn injury: TBSA	Year of CEA Graft	Skin Cancer Information: Age at Dx (Year)	Skin Cancer Information: Location	Latency	Outcome
					Right lower extremity anterior shin area	24y	
NA 2022 Literature (Baus 2021)	~18y Male	92%	1992	32y (Jun-2006)	Left thigh	14y	Recovered
NA 2022 Literature (Baus 2021)	~21y Male	80%	1995	40y (Oct-2014)	Left thigh	19y	Recovered
FR-VCEL(b) (6) 2022 Literature (Baus 2021)	~17y Male	~70%	1998	33y (Feb-2014)	Left and right flank	16y	Death (Dec-2014)
NA 2022 Literature (Baus 2021)	~40y Male	90%	2001	54y (2015)	Right leg	~14y	Ongoing (Dec-2021)
					Left hip	~16y	
					Left thigh	~17y	
NA 2022 Literature (Bocchi 2013)	18y Female	95%, (87% 3rd degree)	~1990	41y (Apr-2012)	Knee	22-23y	Ongoing (2012)
NA 2022 Literature abstract (Finnerty 2012)	NA	NA	NA	NA	NA	NA	Unknown
NA 2022 Literature abstract (Finnerty 2012)	NA	NA	NA	NA	NA	NA	Unknown

Appendix B: Excerpt from Epicel Instructions for Use (Revision 11, dated November 2022)

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 occurred in the grafted areas 11 to 23 years after Epicel grafting. A latency period of 11 to 41 years (median 28) based on a systematic review of case series published in 2000 or later from the time of burn injuries to occurrence of SCC is reported in the literature.[8,9]

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 seven 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.

[8] Kowal-Vern A, Criswell BK. Burn scar neoplasms: literature review and statistical analysis. Burns. 2005. 31: 403-413.

[9] Abdi MA, Yan M, Hanna TP. Systematic Review of Modern Case Series of Squamous Cell Cancer Arising in a Chronic Ulcer (Marjolin's Ulcer) of the Skin. JCO Glob Oncol. 2020 Jun;6:809-818. doi: 10.1200/GO.20.00094. PMID: 32530749; PMCID: PMC7328103.

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Bocchi F, Zermani R. Report of a case of Marjolin's Ulcer in a patient with multiple burn scars during plastic surgical treatment: surgical resolution aimed at maintaining functional knee. Acta Biomed. 2013 Jun 1;84(1):61-63.

Finnerty C, McCauley R, Hawkins H, Herndon D. Genomic alterations in cultured epithelial autograft (CEA) associated with the development of squamous cell carcinoma. J Tissue Eng Regen Med. 2012; 6(suppl.1):94.

Theopold C, Hoeller D, Velander P, Demling R, Eriksson E. Graft site malignancy following treatment of full-thickness burn with cultured epidermal autograft. Plast Reconstr Surg. 2004 Oct;114(5):1215-1219.