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

MEMORANDUM

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To: Brendan Day, MD, MPH
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Subject: Annual Safety Update for the Pediatric Advisory Committee (PAC)

Sponsor: Vericel

Product: Epicel (cultured epidermal autografts)

STN: HDE# BH 990200/112

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,

[1] Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans https://www.fda.gov/regulatory-information/search-fda-guidance-documents/source-animal-product-preclinical-and-clinical-issues-concerning-use-xenotransplantation-products

February 18, 2016). From 1989 to 1996, each patient received an average of 104 grafts (Epicel Directions for Use [February 2016], Clinical Studies section).

IV. REGULATORY HISTORY

- 1988: Genzyme Tissue Repair began marketing Epicel as an unregulated product.
- 1998: FDA designated Epicel as a combination product and as a Humanitarian Use Device (HUD).
- 2007: FDA's Center for Devices and Radiologic Health (CDRH) approved Epicel under the HDE regulatory statute.
- 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.
- 2014: FDA approved a labeling supplement to revise Directions for Use and Patient Information to describe the risk of squamous cell carcinoma (SCC).
- 2014: Epicel ownership was transferred from Genzyme to Vericel.
- 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.
- 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.)
- 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 2024: (b) (4) Epicel grafts, including 2,679 grafts in pediatric patients.
- Calendar year 2025: Not yet available, however, from January 1, 2025, through September 30, 2025, Vericel distributed (b) (4) Epicel grafts, including 1,469 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, 2024, to September 30, 2025, 20 pediatric patients and (b) (4) adult patients 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, 2024, to September 30, 2025).

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 January 5, 2026, to identify postmarket adverse event reports associated with the use of Epicel submitted to FDA during the annual review period, October 1, 2024, to September 30, 2025. The search identified six MDRs including five reports with fatal outcome and two reports of device malfunction (one MDR had fatal outcome and device malfunction). One report involved pediatric patients. All six reports were submitted by the manufacturer. The five 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 reports is displayed in Table 1.

Table 1. Summary of Death Reports (n=5)

Case ID	Age (year)	Sex	TBSA	Event	Time from Graft to Event	Cause of Death
US-VCEL-(b) (6)	23	Male	90%	Disseminated intravascular coagulation (DIC)	69 days	DIC
US-VCEL-(b) (6)	32	Male	30%	Thrombocytopenia, sepsis, pulmonary hemorrhage, atrial fibrillation	30 days	Pulmonary hemorrhage
US-VCEL-(b) (6)	61	Male	74%	Intestinal ischemia	18 days	Intestinal ischemia
US-VCEL-(b) (6)	85	Female	30%	Septic shock, cardiac arrest, product leakage	18 days	Cardiac arrest
US-VCEL-(b) (6)	4	Male	79%	Gastrointestinal necrosis	46 days	Gastrointestinal necrosis

***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.

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

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

Case ID	Event	Lot	Description of event
US-VCEL-(b) (6) *	Malfunction	EE03423-31	Liquid media was noted in cellophane pouch in Box#2 (full pack of 24 grafts), but the sheet grafts were intact with no drainage or seromas observed. These grafts were implanted with no adverse events reported.
US-VCEL-(b) (6)	Malfunction	EE03432-32	Eight grafts were floating/not confluent. These grafts were not implanted, and no adverse events were reported for this patient.

*Reported in Table 1.

Reviewer comment: The defected grafts were not implanted, and no adverse events were reported for the patients except one patient died due to cardiac arrest.

IX. ANNUAL REPORT REVIEW

The sponsor's most recent annual report (September 1, 2024, to August 31, 2025) was reviewed. During the reporting period, a total of 27 events (16 serious events, 11 non-serious events) were reported in 16 patients. The number of patients treated with Epicel during this reporting period was (b) (4) compared to (b) (4) in the previous reporting period.

The most frequently reported system organ class (SOC) categories during this reporting period were Product Issues (9/27); General Disorders and Administration Site Conditions (5/27); Infections and infestations (5/27); Gastrointestinal disorders (2/27); Blood and lymphatic system disorders (2/27), and Cardiac disorder (2/27). Of the 27 reports, 9 reports involved fatal outcomes, including eight adult death reports and one pediatric death report.

Pediatric Death Reports: There was one case report with fatal outcome in a pediatric Epicel recipient (US-VCEL(b) (6)). This case was identified in the MDR database and is described above in Section VIII.B

Adult Death Reports: The sponsor received eight reports involving fatal outcomes in adult Epicel recipients during the reporting period of the Annual Report. Four of these eight 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)	38	Wound fungal infection, Death	unknown	Multiple organ failure
US-VCEL(b) (6)	33	Sepsis	unknown	Sepsis
US-VCEL(b) (6)	48	Lung injury, GI bleed	unknown	Multiple organ failure
US-VCEL(b) (6)	28	Infection, organ failure	unknown	Infection, organ failure

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 eight cases associated with nine reports of product Issues in the Annual Report. Two of these reports were identified in the MDR database and are described above in Section VIII.B; the remaining six cases are displayed in table 4 below.

Table 4. Summary of Product Issue Reports (n=6)

Argus#	Lot#	# Shipped	# Utilized	#Not Utilized	# Impacted	Product Issue Reported
US-VCEL-(b) (6)	EE03329-31	144	143	1	1	One graft were reported to be scalloping
US-VCEL-(b) (6)	EE03343-31	101	64	37	37	37 grafts were reported to be detached from backings.
US-VCEL-(b) (6)	EE03352-21	45	33	12	12	12 grafts were reported to be detached from backings.
US-VCEL-(b) (6)	EE03505-22	105	104	1	1	One graft was reported to be detached from backings.
US-VCEL-(b) (6)	EE03506-33	79	70	9	9	Nine grafts were reported to be detached from backings and floating in media.
US-VCEL-(b) (6)	EE03526-21	57	49	8	8	Eight grafts were reported to be detached from backings and floating in media.

Reviewer comment: All six 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.

Graft detachment and media leakage have been reported in previous annual reports. The FDA has issued information requests seeking the root causes of these issues and the corresponding corrective actions. The manufacturer stated that these issues are attributable to multiple factors, including the manufacturing process, the (b) (4) grafts, and potential damage during transportation. The manufacturer has implemented several corrective actions over the past three reporting periods, resulting in a significant reduction in the percentage of total grafts affected by product quality issues from the 2023 Annual Report to the 2025 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." The number of product issue reports in the current reporting period was significantly lower than in the previous reporting period (9 reports in this reporting period vs. 19 reports in prior reporting period). We will continue to closely monitor these product quality issues.

X. POSTMARKET LITERATURE REVIEW

A PubMed literature search conducted on January 7, 2026, 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, 2024, and September 30, 2025, retrieved 16 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)

SCC is the most common skin cancer to develop from burn wound scars. The label (please see Appendix A) 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."

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

[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.

0.56% of Epicel patients. As noted in Section IV, the manufacturer revised the Epicel labeling to include updated information on SCC.

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 (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, 2024, to September 30, 2025, 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

[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

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.

Appendix A: 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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