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

MEMORANDUM

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Subject:	Annual Safety Update for the Pediatric Advisory Committee (PAC)
Sponsor:	Vericel
Product:	Epicel (cultured epidermal autografts)
STN:	HDE# BH990200/86
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, Feb. 18, 2016). From 1989 to 1996, each patient received and 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

- 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 will be followed by subsequent annual safety updates for the PAC.)

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 represents 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 2020: (b) (4) Epicel grafts, including 2,305 grafts in pediatric patients.
- Calendar year 2021: Not yet available, however, from January 1, 2021 through September 30, 2021, Vericel distributed (b) (4) Epicel grafts, including 1,888 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, 2020 to September 30, 2021, 36 pediatric and (b) (4) adult patients were treated with Epicel for burn injuries.

VII. LABEL CHANGES IN REVIEW PERIOD

There were no label changes related to safety concerns during the annual review period.

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;

- o adverse events associated with vulnerable populations;
- o 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 2, 2021 to identify postmarket adverse event reports associated with the use of the Epicel submitted to FDA during the annual review period, October 1, 2020 to September 30, 2021. The search identified 8 MDRs, including 3 reports with fatal outcomes and 5 reports of device malfunction. No report involved a pediatric patient. All 8 reports were submitted by the manufacturer. The three patients with fatal outcomes were victims of burn injury; two cases involved extensive burn injuries (TBSA were 90% and 80%) and extent of burn injury was not reported in the remaining case. As per the manufacturer's assessment, these deaths were unrelated to the use of Epicel and the cause of death for each case is displayed in Table 1.

Table 1. Summary of Death Reports (n=3)

Case ID	Age (Yrs.) Sex	Event	TBSA* (%)	Grafting Units	Time from Graft to Death	Cause of Death
(b) (6)	64 Male	Death	90	96 units	5 days	Small bowel rupture

Case ID	Age (Yrs.) Sex	Event	TBSA* (%)	Grafting Units	Time from Graft to Death	Cause of Death
(b) (6)	52 Female	Death	Unknown	144 units	15 days	Myocardial infarction and multi-organ failure
	63 Male	Death	80	367 units	187 days	Cardio-pulmonary failure and sepsis

* total body surface area

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

Device malfunction reports: The five reports of device malfunction involved media leakage in the graft bags. Table 2 provides a summary of 5 device malfunction reports. Most of these grafts (except 6 grafts in patient (b) (6)) were used and no adverse events were reported in these cases. Of note, two additional malfunction reports were submitted to the MDR database on October 20, 2021 (after the data lock point of September 30, 2021 for the annual PAC review period). All malfunction events occurred between December 2020 and May 2021.

Table 2. Summary of Device Malfunction Reports (n=5*)

Case ID	Event	Graft Units	Lot	Description of event
(b) (6)	Malfunction	49 units	EE02651A	Media leakage in two graft pouches
	Malfunction	72 units	EE02711	Media noted in the bags
	Malfunction	62 units	EE02705	Media leakage in the bag
	Malfunction	41 units	EE02728A	Media leakage in the bag
	Malfunction	48 units	EE02787	Media leaking from grafts

*Two additional reports submitted to MDR database after the data lock point.

Reviewer comment: In response to an information request, the sponsor provided additional information on malfunction reports related to media leakage. The sponsor's investigation of media leakage issues determined that the root cause was multifactorial and related to both method ((b) (4)) and manpower (training). The sponsor stated that additional work is ongoing related to preventative maintenance, new (b) (4) parameters, and engineering studies to evaluate the (b) (4) . FDA will continue routine surveillance for device malfunction reports.

IX. ANNUAL REPORT REVIEW

The sponsor's most recent annual report (September 1, 2020 to August 31, 2021) was reviewed. During the reporting period, the sponsor received 29 AE reports (28 patients/38 events). There was an increase in the number of AE reports received during this reporting period compared to the previous reporting period (29 vs 13 case reports). The sponsor stated: "This may be due to the greater number of patients treated during this reporting period compared to the previous reporting period ((b) (4) patients vs (b) (4) patients)." The most frequently reported adverse events (AEs) by system organ class (SOC) category during this reporting period were: Product Issues (34.2%;13/38), General Disorders and Administration Site Conditions (23.7%; 9/38), Infections and Infestations (21.1%; 8/38), and Cardiac Disorders (13.2%; 5/38). Of the 29 reports, 17 reports involved fatal outcomes, of which there were 12 adult reports, 2 pediatric reports, and 3 reports that occurred in patients of unknown age.

Pediatric Death Reports: The sponsor received 2 reports involving fatal outcomes in pediatric Epicel recipients. These 2 cases are displayed in Table 3.

Table 3: Pediatric Case Reports with a Fatal Outcome Received by the Sponsor during this Reporting Period

Case Identifier	Age; Sex	TBSA (%)	Grafting Units	Time from Graft to Death	Cause of Death/PTs
(b) (6)	3 years; Female	Unknown	125 units	5 days	Unknown
	16 years; Unknown	90	457 units	184 days	Sepsis

Adult Death Reports: The sponsor received 15 reports involving fatal outcomes in adult or Epicel recipients of unknown age during the reporting period of the Annual Report. These 15 cases, which include 2 cases identified in the MDR database (described in section VIII.B), are displayed in Table 4.

Table 4: Adult Case Reports with a Fatal Outcome Received by the Sponsor during this Reporting Period

Case Identifier	Age; Sex	TBSA (%)	Grafting Units	Time from Graft to Death	Cause of Death/ PTs
(b) (6)	Unknown; Unknown	Unknown	Unknown	5 days	Unknown
	26 years; Male	Unknown	136 units	116 days	Renal failure
	39 years; Male	Unknown	72 units	18 days	Cardiac arrest failure
	24 years; Male	90	70 units	4 days	Sepsis
	44 years; Male	Unknown	44 units	10 days	Multi-organ failure
	26 years; Female	Unknown	72 units	2 days	Unknown
	63 years; Female	63	129 units	128 days	Tracheitis, sepsis
	65 years; Male	Unknown	60 units	13 days	Respiratory failure, sepsis
	54 years; Female	Unknown	75 units	4 days	Pulmonary/cascading organ failure
	Unknown; Unknown	Unknown	120 units	21 days	Sepsis
	52 years; Female	Unknown	144 units	15 days	Myocardial infarction, multi-organ failure
	63 years; Male	80	367 units	187 days	Cardiopulmonary failure, sepsis
	51 years; Male	Unknown	233 units	59 days	Cardiac arrest
	Unknown; Unknown	Unknown	Unknown	40 days	Unknown
	43 years; Female	96	318 units	54 days	Multi-organ failure

* Case reported to MDR database

Reviewer comment: Most reports of death following Epicel were related to multiple organ dysfunction, cardiac events or sepsis. According to the reporter in each case, none of the deaths were reported as related to use of Epicel. A review of the AE data revealed that the nature and type of reported AEs received during this reporting period were similar to those reported in the previous Epicel Annual Reports and those listed in the Epicel Directions for Use (DFU). The AEs reported are consistent with complications experienced by severe burn trauma patients in the intensive care setting.

Product Issues Reports: Thirteen (13) Product Issue reports, which included 7 malfunction reports previously submitted to the MDR database (described in section VIII), are summarized in the table 5 below. Five reports involved pediatric patients; eight reports involved adult patients. Two reports ((b) (6)) in one patient involved adverse events (sepsis and death) that had been discussed in pediatric death report above ((b) (6)), while the remaining reports had no adverse events.

Table 5. Summary of Product Issues Reports (n=13)

Case ID	Event	# Grafts Utilized	# Graft(s) Not Utilized	Lot No	Description of event
(b) (6)	Malfunction	70	26 (not needed)	EE02643D	Dry Graft
	Malfunction	99	0	EE02643E	Media Leak
	Malfunction	55	16 (not needed)	EE02715	Media Leak
	Malfunction	49	0	EE02651; EE02651A	Media Leak
	Malfunction	72	0	EE02711	Media Leak
	Malfunction	62	0	EE02705	Media Leak
	Product complaint	96	9 (not needed)	EE02704B	Box Damage
	Malfunction	22	11 (impacted)	EE02597I	Graft Shearing
	Malfunction	41	0	EE02728A	Media Leak
	Malfunction	48	6 (impacted)	EE02787	Media Leak
	Malfunction	66	6 (not needed)	EE02778A	Graft Shearing
	Physical property issue	45	27 (impacted)	EE02847	Graft Shearing
	Malfunction	52	20 (impacted)	EE02848	Graft Shearing

*Case reported to MDR database

Reviewer comment: In response to an information request, the sponsor provided additional information on Product Issue reports. Media leakage issues were previously discussed in section VIII. The sponsor's investigation identified the root cause of graft shearing to be related to method (petrolatum application). The petrolatum allows the gauze backing of Epicel graft to adhere to the graft dish during transportation, and avoids motion of the Epicel graft within the graft dish which may lead to potential shearing. The sponsor stated that additional work is ongoing related to possible inconsistencies in the amount of petrolatum that is applied to the graft dish during the manufacturing process. The remaining Product Issue reports (Dry Graft and Box Damage) were isolated events.

X. POSTMARKET LITERATURE REVIEW

A PubMed literature search conducted on November 5, 2021 using the search term "Epicel" OR "cultured epithelial autografts" OR "cultured epidermal autografts" for articles published between October 1, 2020 and September 30, 2021 retrieved 13 articles. Titles and abstracts were reviewed for relevance to safety information specifically for the Epicel device and its labeled indication. No article relevant to adverse events for Epicel was identified.

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. The label for Epicel includes information on the risk of SCC (Directions for Use –Warnings section, and Patient Information). There have been no new cases of SCC in Epicel-treated patients reported to Vericel or reported in the literature since the data-lock date of the initial PAC presentation for Epicel (September 30, 2016), up through October 31, 2021. (The 6 cases of SCC observed in Epicel-treated patients since the first use of Epicel in 1988 were reviewed and discussed during the initial PAC presentation dated March 7, 2017). 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). For the EMDT, Vericel contacts patients at least annually to update their contact and survival information for all patients treated with Epicel since 2007.

XII. SUMMARY

The number of death reports and types of AEs observed during this annual review period are similar to those observed during the previous PAC evaluations and those listed in the DFU, and do not suggest new safety concerns. Infection and multi-organ failure are common in severe burn injuries, and the 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 any 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.