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

MEMORANDUM

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Through:	Meghna Alimchandani, MD Deputy Director, Division of Epidemiology (DE), OBE, CBER
From:	Shaokui Wei, MD, MPH Epidemiologist, Analytic Epidemiology Branch (AEB), DE, OBE, CBER
Subject:	Annual Safety Update for the Pediatric Advisory Committee (PAC)
Sponsor:	Vericel
Product:	Epicel (cultured epidermal autografts)
STN:	HDE# BH990200/74
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 review provides a 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.

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).

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

- 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.)
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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 per year from 2008 through 2014 (Review Memo BH990200/34, ADN calculation, Feb. 18, 2016); 4000 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 2019: (b) (4) Epicel grafts, including 2,724 grafts in pediatric patients.
- Calendar year 2020: Not yet available, however, from January 1, 2020 through September 30, 2020, Vericel distributed (b) (4) Epicel grafts, including 1,293 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, 2019 to September 30, 2020, 19 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;
    - 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 8, 2020 to identify all existing postmarket adverse event reports associated with the use of the Epicel submitted to FDA during the annual review period, October 1, 2019 to September 30, 2020. The search resulted in the identification of a single MDR with a fatal outcome. A 67-year-old female patient was treated with Epicel for 32.5% burn with mild inhalation injury on (b) (6) 2020. Seven days after Epicel implantation, the patient developed abdominal compartment syndrome with septic shock. Diffuse ischemic bowel with patchy areas of necrosis was found during abdominal surgery. Two days later ischemia and necrosis were more widespread and the patient died on (b) (6) 2020 due to respiratory failure. The manufacturer's narrative stated that the deaths/adverse events were unrelated to the use of Epicel.

Reviewer comment: The AEs reported are consistent with those experienced within the natural course of severe burn trauma patients in intensive care settings. No new safety concerns were identified.

IX. ANNUAL REPORT REVIEW

The sponsor's most recent annual report (reporting period September 1, 2019 to August 31, 2020) was reviewed. During the reporting period, the sponsor received 13 case reports.

The most common preferred terms (PTs) (excluding Death) in these cases were multiple organ dysfunction syndrome (N= 4), product complaint (N=3), and sepsis (N = 2). Of the 13 reports, 10 cases involved fatal outcomes, including 2 pediatric, 7 adult cases and 1 case involving a patient of unknown age.

Pediatric Death Reports: The sponsor received 2 reports involving fatal outcomes in pediatric Epicel recipients during the reporting period of the Annual Report. These 2 cases are displayed in Table 1.

Table 1: Pediatric Case Reports with a Fatal Outcome Received by the Sponsor during Reporting Period

Case Identifier	Patient Demographics	TBSA (%)	Grafting Units	Time from Graft to Death	Cause of Death/ PTs
(b) (6)	16 years; Male	90	289 units	54 days	Multi-organ failure
(b) (6)	17 years; Male	75	214 units	102 days	Hepatic failure, Sepsis

Adult Death Reports: The sponsor received 7 reports involving fatal outcomes in adult Epicel recipients during the reporting period of the Annual Report. These 7 cases, which include 1 case identified in the MDR database (described in section VII.B), are displayed in Table 2.

Additionally, the sponsor received a death report in a female patient of unknown age; cause of death was unknown and clinical details were not provided.

Table 2: Adult Case Reports with a Fatal Outcome Received by the Sponsor during Reporting Period

Case Identifier	Patient Demographics	TBSA (%)	Grafting Units	Time from Graft to Death	Cause of Death/ PTs
(b) (6)	34 years; Male	79.5	151 units	82 days	Multiple organ failure
	61 years; Male	unknown	107 units	10 days	Multiple organ failure
	32 years; Male	unknown	96 units	25 days	Multiple organ failure
	67 years; Female	32.5	unknown	10 days	respiratory failure, septic shock
	38 years; Male	67	131 units	185 days	Multiple organ failure
	29 years; Male	unknown	24 units	6 days	Sepsis
	64 years; Male	90	96 units	6 days	Multiple organ failure

* Case has been reported to MDR

Reviewer comment: Most reports of death following Epicel were related to multiple organ dysfunction 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 those experienced within the natural course of severe burn trauma patients in intensive care settings.

X. POSTMARKET LITERATURE REVIEW

A PubMed literature search conducted on November 8, 2020 using the search term "Epicel" OR "cultured epithelial autografts" OR "cultured epidermal autografts" for articles published between October 1, 2019 and September 30, 2020 retrieved 10 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 to October 31, 2020. (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 in 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 represent outcomes consistent with the known comorbidities seen with severe burn injuries. 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 population for which it was granted. FDA will continue routine monitoring of the safety and distribution data for this device.