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

MEMORANDUM

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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
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. 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. During manufacturing, Epicel is evaluated for sterility via sterility assessments conducted pre-release and 14-days post-release. Reagents used in the manufacture of Epicel are also tested for sterility and endotoxin content.

[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.

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 2017: (b) (4) Epicel grafts
- Calendar year 2018: Not yet available, however, from January 1, 2018 through September 30, 2018, Vericel distributed (b) (4) Epicel grafts.

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, 2017 to September 30, 2018, 13 pediatric and (b) (6) adult patients were treated with Epicel for burn injuries.

VII. 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 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 October 5, 2018, 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, 2017 to September 30, 2018. The search resulted in the identification of a single MDR, that was submitted by the manufacturer, involving a 32-year-old male patient who died 8 months after treatment with 144 grafts of Epicel (Lot number: EE01842) for 90% total body surface area (TBSA) full thickness burn injuries. The cause of death was unknown. No details on clinical presentation, diagnosis, or autopsy were provided.

Pediatric MDRs: There were no pediatric MDRs submitted during the review period.

VIII. ANNUAL REPORT REVIEW

The sponsor's most recent annual report (reporting period September 1, 2017 to August 31, 2018) was reviewed. During the reporting period, the sponsor received 13 initial case reports, which included a total of 37 serious and 2 non-serious adverse event preferred terms (PTs).

The most common PTs (excluding Death) in these cases were multiple organ dysfunction syndrome (N= 4), sepsis (N = 2) and transplant failure (N = 2). Of the 13 reports, 11 reports involved fatal outcomes, including 1 pediatric and 10 adult cases.

Pediatric Death Reports: The sponsor received 1 report involving a fatal outcome in a pediatric Epicel recipient during the reporting period of the Annual Report. This case involved a 17-year-old male patient who died from acute respiratory distress syndrome 434 days after being treated with 96 grafts of Epicel (Lot number: EE02104) for 95% TBSA full thickness thermal burns sustained from a car crash.

Adult Death Reports: The sponsor received 10 reports involving fatal outcomes in adult Epicel recipients during the reporting period of the Annual Report. These 1o cases, which include the 32-year-old patient identified in the MDRs (described in section VII.B) are displayed in Table 1.

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

Case Identifier	Patient Demographics	TBSA (%)	Grafting Units	Time of Graft to Death	Cause of Death/ PTs
(b) (6)	31 years; Male	92%	not reported	22 days	Organ failure; Circulatory Collapse; Respiratory Failure; Transplant Failure; Infection
(b) (6)	32 years; Male	90%	144 units	254 days	Unknown**/Death
(b) (6)	28 years; Male	80%	48 units	10 days	Multiple organ dysfunction syndrome
(b) (6)	46 years; Male	85%	35 units	27 days	Death
(b) (6)	23 years; Male	72%	72 units	19 days	Multiple organ dysfunction syndrome; Septic Shock; Transplant Failure
(b) (6)	44 years; Male	not reported	48 units	18 days	Multiple organ dysfunction syndrome
(b) (6)	64 years; Male	64%	48 units	254 days	Multiple organ dysfunction syndrome
(b) (6)	24 years; Male	61%	75 units	500 days	Unknown/Death
(b) (6)	36 years; Male	85%	46 units	24 days	Renal failure, Sepsis
(b) (6)	29 years; Male	not reported	140 units	6 months	Sepsis

* Case has been reported to MDR
** Based on the limited information available on the possible cause of death, the company assessed the event of death as possibly related to Epicel.

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 DFU. The AEs reported are consistent with those experienced within the natural course of severe burn trauma patients in intensive care settings.

IX. POSTMARKET LITERATURE REVIEW

A PubMed literature search conducted on November 5, 2018 using the search term "Epicel" OR "cultured epithelial autografts" OR "cultured epidermal autografts" for articles published between 10/1/2017 and 9/30/2018 retrieved 4 articles. Titles and abstracts were reviewed for relevance to safety information specifically for the Epicel device and its labeled indication. None of the articles were specific to Epicel and none of the articles contained reports of adverse events or other safety information for Epicel.

X. 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 November 7, 2018. (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). 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.

XI. 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.