

# Epicel

## HDE# BH990200

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# Presentation Outline

- Device Description & Indications for Use
- Regulatory History
- Premarket Data Summary
- Pediatric Use & Annual Distribution Number (ADN)
- Medical Device Report Review – focusing on pediatric reports
- Literature Review
- Conclusions and Recommendation
- Question to the PAC

# Device Description

- Epicel, also referred to as cultured epidermal autograft, is an aseptically processed wound dressing composed of the patient's own (autologous) keratinocytes grown *ex vivo*
- Consists of sheets of proliferative, autologous keratinocytes, ranging from 2 to 8 cell layers thick
- Each Epicel graft is attached to petrolatum gauze backing and measures approximately 50 cm<sup>2</sup>
- Epicel is defined by the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation and FDA as a xenotransplantation product, because it is manufactured by co-cultivation with proliferation-arrested mouse fibroblasts (Epicel grafts consist of less than 1% mouse fibroblasts.)

# 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.*

# Regulatory History

- 1988: Genzyme marketed Epicel as unregulated product
- 2007: CDRH approved Epicel as a Humanitarian Use Device
- 2013: Regulatory responsibility transferred from CDRH to CBER
- 2014: Approval of label change to include the risk of squamous cell carcinoma  
Epicel ownership transferred from Genzyme to Vericel
- 2016: Approval of pediatric labeling

# Premarket Data

## Safety and Probable Benefit

- **Genzyme Biosurgery Epicel Clinical Experience:**
  - 1989 – 1996: 552 Epicel treated patients; 86.6% survival (478/552)
  - 1997: 55 Epicel treated patients; 87.3% survival (48/55)
  - 1998 – 2006: 734 Epicel treated patients; 91% survival (669/734)
  
- **Munster Study (Munster, 1996):** an independent, physician-sponsored study that compared the outcome of therapy in patients with massive burns with or without Epicel. The survival rate was 90% (18/20) in Epicel group vs. 37.5% (9/24) in control group.

# Premarket Data

- **Adverse Events (AEs):**

Death, colonization/infection, graft shear, graft detachment, blister, drainage, improper hemostasis, sepsis, renal AEs, grafts debrided with dressing, multi-organ failure

- **CDRH Decision:**

The data collected in the Genzyme Biosurgery databases regarding patient mortality and the rates of burn-associated AEs demonstrated that Epicel met the requirements of relative safety and probable benefit in the treatment of large TBSA burn injuries



# Pediatric Use

(age < 22 years)

- Since 2007 approval, 30% of Epicel recipients are pediatric patients
- **February 2016:** FDA approved pediatric labeling and the Annual Distribution Number
- Revised label displays separate safety and probable benefit data for adult and pediatric patients





# Annual Distribution Number (ADN)

- The Food, Drug, and Cosmetic Act 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
  - $90.1 \times 4000 = 360,400$  Epicel grafts
  - 90.1 = the average number of Epicel grafts used per patient per year from 2008 through 2014
  - 4000 patients = the target population per the HDE definition at the time of approval (Feb. 2016)
- Epicel sales have not exceeded the ADN

# Medical Device Report Analysis

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# Limitations of MDR Data

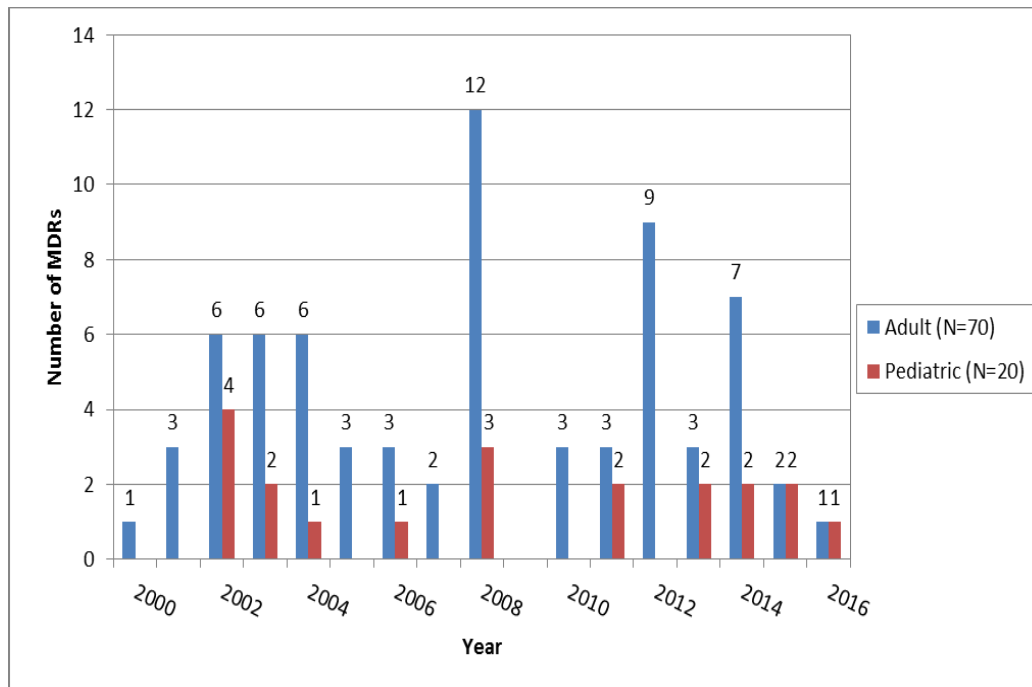
- **Under-reporting**
  - Users unfamiliar with reporting or fear of unintended consequences if they report
  - Confusion about HIPAA privacy and reporting
  - Malfunction or injury may not be clinically apparent
- **Data Quality**
- **Limitations of MDR Regulation:** Certain device malfunctions may not meet MDR reporting requirements
  - Therefore, lack of MDRs  $\neq$  lack of problems
- **Inability to Establish Causality**
  - Cannot determine link/causality between the use/malfunction of the device and the negative clinical adverse event or outcome in that report

# Methods

- FDA Medical Device Adverse Event Database
- MDR Search Inclusion Criterion:
  - The search was conducted on October 16, 2016 using the parameter of device brand name “Epicel”, with no date restrictions.
- Search Results: 90 MDRs associated with the use of Epicel

# MDR Results

**Number of MDRs by the Year received for Adults and Pediatric Patients**



- MDRs were received by FDA between the years of 2000 and 2016.
- All MDRs were submitted by the manufacturers.
- 84 MDRs were submitted by Genzyme Biosurgery
- 6 MDRs by Vericel Corp
- Increase in reports received in 2008.
- No reports received in 2009.

# MDR Event Types (n=90)

- 76 Deaths, 12 Injuries, and 2 Malfunctions
- MDRs reported several complications for each patient
- Top 3 adverse events in order of their frequency were:
  - Multi-organ failure in 38 patients
  - Sepsis in 28 patients
  - Cardiac problems in 11 patients (i. e., cardiac arrest, cardiogenic shock, cardiopulmonary failure, etc.)
- 20 of the 90 reports related to pediatric patients

# Pediatric MDRs (n=20)

- 20 MDRs describe the use of Epicel on pediatric patients
- Age range from 2-21 years (mean of 13.4)
- 6 female, and 14 male patients
- These were reported as 15 deaths, 4 injuries and 1 malfunction
- TBSA range was between 35% and 99% (Mean of 85% & Median 91.5%)

# Pediatric Death MDRs (n=15)

- 15 death reports involved pediatric patients
- Multiple clinical issues were described in each MDR
- The most reported adverse event was:
  - Multi-organ failure, in a number of which sepsis or infection was the underlying cause
  - Other adverse events:
    - Squamous Cell Carcinoma, Cardiac arrest, Focal Dermal Hypoplasia, Mixed drug interaction, Complications of the full thickness burns



# Pediatric Injury & Malfunction MDRs (n=5)

- The 4 injury reports involving pediatric patients included:
  - 3 reports of infection
  - 1 report of foot amputation
  
- Type of event in 1 report was submitted as a malfunction

# MDR Summary

- Since 2000, 90 MDRs have been received for Epicel
- Twenty MDRs involved pediatric patients – including 15 deaths, 4 injuries, and one malfunction
- The most commonly reported adverse event noted was multi-organ failure
- The mean TBSA was 85% in pediatric patients

# Literature Review

- Literature was reviewed to evaluate adverse events following the use of Epicel for burn patients
  - PubMed search using the terms "Epicel" OR "cultured epithelial autografts" OR "cultured epidermal autografts" for articles published between October 25, 2007, to September 30, 2016, retrieved 32 articles.
  - 1 case report of graft site malignancy involving squamous cell carcinoma
  - No new safety issues were identified from review of the remaining 31 publications
    - included articles on experimental or other cellular therapies including foreign products (N = 19), basic science/methodology (N = 7), off-label use (N = 3), general subject review (N = 1) and unrelated topic (N = 1)

# Literature Review Results

<b>Article</b>	<b>Singh et al. Plast Reconstr Surg Glob Open. 2015</b>
Type	case report
Adverse Event	graft site malignancy involving squamous cell carcinoma (SCC)
Description	34-year-old man with 95% TBSA burns received multiple cultured epidermal autografts (later confirmed to be Epicel). 13.5 years after grafting, he developed SCC at five graft sites (initially described by Theopold in 2004). Singh provides long-term follow up on this patient, who developed 8 additional SCCs over the next 9 years (October 2005 – April 2015). Patient survived and is closely monitored .

## Literature Review Conclusion

No new safety issues were identified.



# Reports of Squamous Cell Carcinoma (SCC) after Epicel

(N = 6)

Reports	Source (report date)	Description	Outcome
Case 1	Pre-market data	A dystrophic epidermolysis bullosa (DEB) patient developed SCC a few days following Epicel grafting in 1994. (Note: off-label use)	Below the knee amputation
Case 2	Literature case report (2004)	34-year-old man with 95% TBSA burns developed multiple SCCs in grafted areas 13.5 years after Epicel grafting.	Recovered; SCC resections
Case 3	MedWatch (2011)	8-year-old child with 99% TBSA burns developed multiple SCCs (abdomen, knee, foot) with atypical features, 12 years after Epicel grafting.	Death
Case 4	MedWatch (2012)	Patient of unknown age and unknown burn size, developed SCC 15 years after Epicel grafting	Recovered
Case 5	MedWatch (2012)	Patient of unknown age and unknown burn size, developed SCC 19 years after Epicel grafting	Death
Case 6	MedWatch (2014)	46-year-old man with 95% TBSA burns developed SCC 13 years after Epicel grafting	Recovered

# Postmarket Safety-related Label Change

- In 2014, FDA approved revisions to the Epicel label to include information on the risk of squamous cell carcinoma (SCC) in three documents:
  - (i) Directions for Use – Warnings section
  - (ii) Patient Information
  - (iii) Dear Health Care Provider Letter (issued in June 2014)

# Postmarket Safety-related Label Change

## Direction for Use – 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 **12 to 19 years** after Epicel grafting. A latency period of  $32 \pm 18$  years from the time of burn injuries to occurrence of SCC is described in the literature.*

*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 three 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.*

# Epicel Medical Device Tracking Data

- Epicel is a tracked medical device: demographics and survival information are collected under this database.

Direction for Use (DFU): Survival Data from Epicel Database  
(2007 – 2015)

	<b>Pediatric Patients</b>	<b>All Patients (Pediatric &amp; Adults)</b>
Deaths	14	75
Patients treated with Epicel	120	402
Survival	88.3% (106/120)	81.3% (327/402)



# Discussion and Conclusion

- 2014 label revision included the risk of SCC
- AEs in children and adults relatively constant over time and consistent with comorbidities in severe burn injury
  - U.S. data (National Burn Repository 2016 Report): greater than 65 – 70% TBSA burns associated with 50% case fatality
- FDA did not identify any new safety signals

# FDA Recommendation

- FDA will continue surveillance and report the following to the PAC in 2018:
  - Distribution numbers
  - MDR review results
  - Literature review results

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- Office of Communication & Education/CDRH
- Office of Surveillance & Biometrics/CDRH
- Office of Tissues & Advanced Therapies/CBER

# Question to the PAC

- Does the Committee agree with FDA's conclusions and recommendation?

