Clinical Review of Supplement 34, HDE BH990200, Request for Pediatric Label

Reviewer: Yao-Yao Zhu

Team Leader: Bruce Schneider

Branch Chief: Ilan Irony

Date of Review Completion: February 17, 2016

Receiving Date: December 7th, 2015; **Mid-cycle**: January 14, 2016; **Due Date**: February 19, 2016.

Executive Summary: Epicel, a cultured epidermal autograft, was approved in 2007 as Humanitarian Device Exemption (HDE) for use in patients who have deep dermal or full thickness burns in ≥30% of body surface area. Since its approval, 1740 patients received Epicel and 30% of these are pediatric patients (age≤21 per FDA definition). Although children have been treated with Epicel, there is no clear labeling for pediatric use and there are no supportive pediatric data in the Indication for Use. To seek specific pediatric labeling for Epicel to be exempted from the profit prohibition, in June 2015, the applicant requested a pre-submission meeting to discuss labeling revision to specify use in both adult and pediatric patients, to add pediatric labeling data, and to request an exemption from the profit prohibition. The applicant justified this request with two recent FDA draft guidance on HDE and on clinical data extrapolation to pediatric use of medical device (see Reference below). Both guidance documents were drafted to encourage pediatric indication and labeling as a result of the enactment of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012.

In Supplement 34, the applicant proposed a new pediatric labeling (Table 2) with three existing supportive database (Genzyme Original HDE Application Clinical Data, Epicel Medical Device Tracker, and Pharmacovigilance Data) obtained from pre- and post- approval period (Table 3). In the revised label, applicant displayed the safety and probable efficacy data with separated pediatric and adult information as derived from the three databases. Based on general principle of labeling guidance (see references #1-5), the clinical team, in consultation with CBER Advertising and Promotional Labeling Branch (APLB) team, revised the proposed label extensively (see Table 1). Applicant agreed with most FDA' s revision but with three questions. FDA communicated with the applicant and resolved all the issues in the labeling changes (see Appendix A).

To estimate the number of device eligible for profit, applicant proposed an annual distribution number (ADN) as 360,400, based on average Epicel shipment per Epicel recipient per year from the annual report 2008 through 2014. FDA agreed with the proposed ADN based on FDA guidance on HDE (Reference #2).

Recommendation: approval of pediatric labeling change after all issues are resolved; approval of proposed ADN.

Table 1: FDA's Revision of Proposed Epicel DFU

Sections	**Reviewer's Comments for Revision and its Rationale, in Consultation with APLB**
Contraindications	Simplify and clarify the language for increasing readability
Warnings	Move the content of squamous cell cancer from Precautions to Warnings; add subheading to each warning for clarity
Precautions	Re-organize this section by moving many items to Storage, Handling, and Administration or by deletion if there are repetitions in the related sections
Adverse Reactions	Rewrite a preamble to summarize two safety databases in new Tables 1 and 2; delete original Table 1 because it overlaps with the original Table 2; delete items in Table 2 that are not adverse reactions but medical practice/wound management; remove "death" from list of adverse reactions, and stated number of deaths or mortality in preamble and in the beginning statement; remove "reports of skin cancer" to Warnings; emphasize underreporting of database 2 (table 2), and add more adverse event items to new Table 2 based on Table 16 in the supplement.
Clinical Studies	Rewrite a preamble to summarize three databases in new Tables 3, 4, 5 to support the probable benefit; to retain Table 5 (deleted by applicant): Munster Study, because this is the only prospectively controlled study, even it is a small study.
How Supplied	clarify Storage and Handling with bullets and command language for enhancing readability

Reference:

1. FDA Draft Guidance for Industry and FDA Staff Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices 2015
2. FDA Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff Humanitarian Device Exemption (HDE): Questions and Answers 2014
3. Guidance for Industry Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements, 2013
4. Regulatory Requirements for Medical Devices, 1989 (CDRH)
5. "Blue Book" Memorandum on Labeling, 1991 (CDRH)

Clinical Review of Supplement 34

Applicant: Vericel Corporation

HDE BH990200 (Class III, approved as HDE by CDRH in 2007)

Device Description

Epicel, a cultured epidermal autograft, is an aseptically processed wound dressing composed of the patient's own (autologous) keratinocytes grown ex vivo in the presence of proliferation-arrested, murine 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. Among the cells, there is less than 1% Mouse 3T3 fibroblast feeder cells used in the co-culture with autologous keratinocytes.

Indication for Use

Epicel is indicated for use in patients who have deep dermal or full thickness burns comprising a total body surface area of 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.

Review Team

- RPM: Ron Chamrin
- Clinical: Yao-Yao Zhu, Bruce Schneider, Ilan Irony, Wilson Bryan
- APLB: Loan Nguyen an Lisa Stockbridge
- CMC: Andrea Gray and Kim Benton
- Regulatory: Ted Stevens

Regulatory History

- 1988: Genzyme Tissue Repair began marketing Epicel as an unregulated device
- 1996: The Manipulated Autologous Structural (MAS) cell guidance included prodcuts such as Epicel. FDA requested that Genzyme submit an application for review of Epicel
- 1997: Genzyme requested the Office of Chief Mediator and Ombudsman designate the lead FDA center for review of Epicel
- 1998: Epicel was designated as a combination product and as a HUD. The Tissue Reference Group designated CDRH with lead review responsibility for Epicel.

- 1999: Genzyme submitted an HDE application (BH990002) to CDRH.
- 2006: Genzyme submitted supplemental safety data from the pharmacovigilance database covering the period June 1998 through August 2006.
- 2007: CDRH approved Epicel under the HDE regulations.
- 2010: Initial discussions between Genzyme and CDRH regarding pediatric use of Epicel.
- 2013: Lead regulatory responsibility for the Epicel HDE was transferred to CBER based on an assessment of the primary mode of action under the combination products regulations. A new HDE number, BH990200, was assigned.
- 2014: Genzyme submitted special labeling supplement 21 to request revising the labeling language in three documents (a. Directions for Use; b. Patient Information; and c. Dear Health Care Provider Letter) regarding new reports of four cases of cutaneous squamous cell cancer (SCC). Direction for Use was revised with new language regarding risks of squamous cell cancer in Epicel exposed burn wound.

  Epicel ownership was transferred from Genzyme to Vericel.
- 2015: Vericel met FDA in a face to face pre-submission meeting to discuss issues regarding proposed pediatric labeling and an exemption from profit prohibition under FDASIA 2012.

Proposed Labeling Revision

Table 2: Summary of Applicant's Proposed Labeling changes in the Direction for Use (DFU)

Labeling Section	Proposed Revision	Reviewer comments
Introduction and Indication (Page 1, 2)	• Substitute "patients" with "adults and children"	
Adverse Reactions (Page 5, 6, 7, 8)	• New Table 2: to summarize adverse events for both Pediatric and adult from the original Genzyme Tissue Repair database 1989-1996 • New Table 3: to summarize adverse events for both pediatric and adult groups from database 1998-2015 • Reports of skin cancer section: to include the pediatric patients	Original Table 1, a summary of adverse events for all subjects, may be removed because it overlaps with new Table 2, a summary of adverse events for pediatric and adult from the same database as in Table 1. New Table 3 may need to be revised because the main database reflects spontaneous reporting.
Clinical Information (Page 8. 9, 10, 11. 12)	• New Table 4: to update pediatric demographics and survival rate from original Genzyme Tissue Repair database, 1989-1996	Original Table 4 from Munster Study should not be removed because it is a physician-sponsored prospective study with a control group. Although it is a small study, it showed a probable efficacy that 7 year survival in Epicel

	• New Table 5: to provide pediatric demographic and survival information from post-approval database, 2007-2015 • Munster Study (original Table 4): to remove a physician-sponsored study (Epicel, n=20; control, n=24), from label as there is a substantial Epicel experience since approval.	group (n=20) was 90% as compared with 37% in control group (n=24).
DIRECTIONS FOR USE: pre-grafting consideration, Graft application, and postoperative treatment	• No new information	Language may be revised to increase readability

Data Source, which was used to generate pediatric information in the revised label, is summarized in Table 3.

- Genzyme Tissue Repair (GTR) database, 1989-1996
- The Epicel Medical Device Tracker (EMDT) database, 2007-June 2015
- The pharmacovigilance (PV) database, 1998-2015

Table 3: Available Data Sources for Epicel-Treated Patients

	Years Data Collected	#Patients (pediatric/adult) Total	Type Data Collected			
			Demographics/ Outcome	Graft Take	Survival	Adverse Events
Original HDE Application in 1998						
GTR database	1989-1996	205/347 552	Age, region, %TBSA burn, sex, inhalation injury	Yes	Yes	Yes
Tracking Data						
EMDT database	2007- 22 June 15[a]	120/281 402[d] 434 total	Age, region, %TBSA burn, sex	No	Yes	No
Pharmacovigilance Database						
(b) (4)	1998- 01 SEP 15[a]	133/40 204 total	Age, gender where available[b]	No	No	Yes
Literature and Other						
PubMed Search	1988-2015	Not applicable	Age, gender, %TBSA burn, sex where available	Where available	Where available	Where available

EMDT = Epicel Medical Device Tracker; GTR = Genzyme Tissue Repair; %TBSA = percent total body surface area; SEP = September.
[a] Data cutoff date
[b] Age and gender were not reported for all spontaneous events.
[c] Excludes 1 patient who did not have age reported.
[d] Excludes off-label use and ex-US.

Reviewer's Comments: none of the three databases is derived from outcome of clinical trials, but acceptable for HDE with favorable benefit-risk ratio and probable benefit. The probable benefit is provided by a published physician sponsor controlled study with increased survival in Epicel recipient as compared with standard treatment. The survival benefit is further confirmed with Tracking Data post approval.

Justification for Proposed Annual Distribution Number (ADN)

Applicant proposes ADN as 360,400 as calculated by 90.1x4000=360,400

Where 90.1=the average number of Epicel grafts used per patient per year from 2008 through 2014 (Table 22); 4000= target population by HDE definition

The table 22 shows that the average number of Epicel grafts used per patient per year from 2008 through 2014 is 90.1. This is the first multiplier used to estimate the ADN. The second multiplier is always 4000 so the proposed ADN for Epicel is 360,400.

The applicant pointed out that some patients are counted twice as they may have undergone multiple surgeries occurring in different years. The number of grafts shipped is used to calculate the number of grafts used; it is not possible to know the actual number of grafts used as this information is not available.

Table 22: Number of Patients and Epicel Grafts by Year

Annual Report Year	Patients	Grafts	Grafts/patient
2008	(b) (4)		
2009			
2010			
2011			
2012			
2013			
2014			
TOTAL:			
AVERAGE:	(b) (4)		90.1

Source: Annual Reports, 2008 through 2014

Reviewer's Comments: As per HDE guidance, ADN is defined as "the number of devices per year reasonably needed to treat, diagnose, or cure an individual ("first multiplier") and multiplies that value by 4,000 ("second multiplier")." The reviewer agreed with applicant estimation of the multiplier based on annual shipment of the grafts and number of recipients.

Appendix A. FDA Communication with Applicant Regarding Revised Pediatric labeling

Ron,

Please send the following to the applicant.

We have two additional suggestions for the revised DFU in your February 9th submission.

1. Please replace "CEA" with Epicel, located in Table 1, row 3. CEA is an abbreviation for Cultured Epithelial Autografts, which was omitted from your latest revision.

2. Please replace the term "Adverse Events" with "Adverse Reactions" under the Section of Adverse Reactions. For consistency with regulatory convention, the term "Adverse Reaction" is used in all drug or device labelling to define an undesirable effect, reasonably associated with the use of the device or drug. Please refer to FDA devices labeling guidance, the 1989 "Regulatory Requirements for Medical Devices" and a 1991 "Blue Book" memorandum on labeling, Section VIII.

Please revise your label and submit your final version. Please let us know any further questions.

Bruce, Ilan, and Lisa: Please let Ron know if you have further changes to this response. The deadline is tomorrow 9AM.

Thanks,
Yao-Yao

From: Chamrin, Ronald
Sent: Thursday, February 11, 2016 1:40 PM
To: Zhu, Yao-Yao; Hoque, Atm S.; Yong, Carolyn; Nguyen, Loan; Gray, Andrea
Cc: Schneider, Bruce; Bryan, Wilson; Riggins, Patrick; Oh, Steven; Stevens, Ted; Robinson, Becky; Bailey, Alexander; Serabian, Mercedes; Benton, Kimberly; Puri, Raj K. (FDA/CBER); Stockbridge, Lisa L; Haudenschild, Changting; Riggins, Patrick; Tull, Lori; McFarland, Richard; Gray, Andrea; Irony, Ilan
Subject: RE: FDA Information Request - BH990200.34 - response is attached

Hi All,
Below is the link to official submission now located in the EDR.

If there are any major issues that need to be conveyed to the Sponsor please let me know by 9 am, Friday, February 12, 2016 or sooner.

Select the link to login to the EDR and access the submission:
(b) (4)

Thanks,
Ron

Ron Chamrin
Regulatory Project Manager
Consumer Safety Officer
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Cellular, Tissue, and Gene Therapies
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 240-402-8269
Fax: 301-595-1303
ronald.chamrin@fda.hhs.gov

From: Chamrin, Ronald
Sent: Tuesday, February 09, 2016 12:22 PM
To: Zhu, Yao-Yao; Hoque, Atm S.; Yong, Carolyn; Nguyen, Loan; Gray, Andrea
Cc: Schneider, Bruce; Bryan, Wilson; Riggins, Patrick; Oh, Steven; Stevens, Ted; Robinson, Becky; Bailey, Alexander; Serabian, Mercedes; Benton, Kimberly; Puri, Raj K. (FDA/CBER); Stockbridge, Lisa L; Haudenschild, Changting; Riggins, Patrick; Tull, Lori; McFarland, Richard; Gray, Andrea; Irony, Ilan
Subject: FW: FDA Information Request - BH990200.34 - response is attached

Dear All,
Please see the attached documents from the document.

1. The cover letter has a clear table which denotes the edits made by the Sponsor when compared to our most recent version.
2. Word document with tracked changes from the Sponsor from our most recent version.
3. .pdf incorporating all the changes

If there are any major issues that need to be conveyed to the Sponsor please let me know by 9 am, Friday, February 12, 2016 or sooner.

Thanks,

Ron

Ron Chamrin
Regulatory Project Manager
Consumer Safety Officer
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Cellular, Tissue, and Gene Therapies
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 240-402-8269
Fax: 301-595-1303
ronald.chamrin@fda.hhs.gov

From: Deborah Ladenheim [mailto:deborah.ladenheim@(b) (4) .com]
Sent: Tuesday, February 09, 2016 11:59 AM
To: Chamrin, Ronald
Subject: RE: FDA Information Request - BH990200.34 - response is attached

Ron,

Thank you for providing this clarification – it is helpful.

We are compiling the formal response today and it should arrive at the FDA tomorrow.

Per your request, I have attached the key components of the submission to this message. We have made a few minor changes to the DFU you have sent and these are marked as tracked changes in the attached Word document. A clean copy of the DFU is also provided as a pdf incorporating these changes. I have also attached a copy of the cover letter that is included in the submission which provides a summary of the changes we propose as well as a rationale for each.

Let me know if you have any questions and please advise on the next steps for this submission.
Please confirm receipt of this message.

Kind regards,
Debbie

From: Chamrin, Ronald [mailto:Ronald.Chamrin@fda.hhs.gov]
Sent: Monday, February 08, 2016 9:51 AM

To: Deborah Ladenheim
Subject: RE: FDA Information Request - BH990200.34 - response requested February 11, 2016
Importance: High

Hi Debbie,
Thanks for taking my call today. As we discussed we (FDA) are conducting our review of your submission dated December 4, 2015 and received by CBER on December 7, 2015.

Thank you for your feedback regarding the revisions made by FDA for Directions for Use (DFU). In addition to pediatric labeling, we have made several changes in the DFU, to improve clarity.

To clarify our revisions, please see the following responses to your three questions. In addition, we provide Table A to explain other changes in the label. Please check the changes to ensure that the label is accurate and make further revisions if necessary. Please let us know if you would like to have a brief teleconference to discuss the revisions.

Sponsor's Three Questions:

1. *Contraindications. We were surprised to see that the usual "hypersensitivity reactions" statement has moved from Contraindications in the original labeling to the Warnings section in the current version. Can you provide any background for this change?*

   FDA Response: We deleted the first paragraph under Contraindications because it overlaps with the next two paragraphs, which describe contraindications to specific antibiotics and bovine/murine products - the main components of the manufacturing reagents. We placed the original third paragraph under Warnings as the first warning to cover hypersensitivity reactions to the rest of other Manufacturing Reagents such as culture medium. These are potential hypersensitive reactions that should be placed under Warnings, but not Contraindications (see Reference 2, Section 9, Page 12).

2. *Precautions statement about use of Epicel in pregnancy and nursing women (end of section in the previous version). This statement appears to have been omitted from the current version. Is this an oversight or did you intentionally take it out?*

   FDA Response: It was an oversight. We moved the statement back to the PI, under Precautions.

3. *New Table 1 in the DFU differs from the corresponding Table 10 in the supplement with some reactions removed in the labeling compared with the supplement. Did you re-run*

the tables and come up with a different listing or have these reactions been removed intentionally?

FDA Response: Yes, we removed the following items from New Table 1 including "improper dressing," "improper or missing hemostasis," "excision improper/missing," "bed prep poor," and "surgery improper at bedside." Those items are removed because they appear to be relevant to the surgical practice rather than "adverse reactions."

Table A: FDA's Revision of Epicel DFU

Sections	Explanation of Revision
Contraindications	Simplify and clarify the language for increasing readability
Warnings	Move the content of squamous cell cancer from Precautions to Warnings; add subheading to each warning for clarity
Precautions	Re-organize this section by moving many items to Storage, Handling, and Administration or by deletion if there are repetitions in the related sections
Adverse Reactions	Rewrite a preamble to summarize two safety databases in new Tables 1 and 2; delete original Table 1 because it overlaps with the original Table 2; delete items in Table 2 that are not adverse reactions but medical practice/wound management; remove "death" from list of adverse reactions, and stated number of deaths or mortality in preamble and in the beginning statement; remove "reports of skin cancer" to Warnings; emphasize underreporting of database 2 (table 2), and add more adverse event items to new Table 2 based on Table 16 in the supplement.
Clinical Studies	Rewrite a preamble to summarize three databases in new Tables 3, 4, 5 to support the probable benefit; to retain Table 5 (deleted by applicant): Munster Study, because this is the only prospectively controlled study, even it is a small study.
How Supplied	clarify Storage and Handling with bullets and command language for enhancing readability

If you agree to our revisions please submit to the HDE 1) a cover letter describing the submission, 2) your proposed label in .docx format with track changes that you make from our most recent version to your version and 3) your proposed label in .pdf format.

If you notice any typos, pagination issues, or other corrections of our revisions please indicate this clearly in your submission.

Please submit your response to the document control center and e-mail me a courtesy copy by **9 am, Thursday, February 11, 2016 or earlier.**

Please let me know if you have any questions.

Thanks,
Ron

Ron Chamrin
Regulatory Project Manager
Consumer Safety Officer
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Cellular, Tissue, and Gene Therapies
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
Phone: 240-402-8269
Fax: 301-595-1303
ronald.chamrin@fda.hhs.gov

From: Deborah Ladenheim [mailto:deborah.ladenheim@(b) (4) .com]
Sent: Wednesday, February 03, 2016 12:05 PM
To: Chamrin, Ronald
Subject: FW: FDA Information Request - BH990200.34 - few clarification questions
Importance: High

Ron,

Thanks for doing such a thorough job on the labeling. Our team has a couple of questions and we are working on providing our revised proposed labeling and would appreciate some clarification.

1. Contraindications. We were surprised to see that the usual "hypersensitivity reactions" statement has moved from Contraindications in the original labeling to the Warnings section in the current version. Can you provide any background for this change?

2. Precautions statement about use of Epicel in pregnancy and nursing women (end of section in the previous version). This statement appears to have been omitted from the current version. Is this an oversight or did you intentionally take it out?

3. New Table 1 in the DFU differs from the corresponding Table 10 in the supplement with some reactions removed in the labeling compared with the supplement. Did you re-run the tables and come up with a different listing or have these reactions been removed intentionally?

Any information you can provide would be much appreciated.

Debbie