



Our STN: BL [125603/0]

**BLA APPROVAL**

Vericel Corporation  
Attention: Margarita Aguilera  
Senior Regulatory Consultant  
64 Sydney Street, Cambridge MA 02139

December 13, 2016

Dear Ms. Aguilera:

Please refer to your Biologics License Application (BLA) for Autologous Cultured Chondrocytes on Porcine Collagen Membrane dated January 4<sup>th</sup> 2016 submitted under section 351(a) of the Public Health Service Act (PHS Act).

## **LICENSING**

We have approved your BLA for Autologous Cultured Chondrocytes on Porcine Collagen Membrane effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Autologous Cultured Chondrocytes on Porcine Collagen Membrane under your existing Department of Health and Human Services U.S. License No. 2010. Autologous Cultured Chondrocytes on Porcine Collagen Membrane is indicated for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults.

The review of this product was associated with the following National Clinical Trial (NCT) number(s): NCT00719576 and NCT01251588.

Under this license, you are approved to manufacture Autologous Cultured Chondrocytes on Porcine Collagen Membrane at your facility located at Cambridge, Massachusetts. You may label your product with the proprietary name MACI and market it in 3 x 5 centimeter cellular sheets.

We did not refer your application to the Cellular, Tissue, and Gene Therapies Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

## **DATING PERIOD**

The dating period for Autologous Cultured Chondrocytes on Porcine Collagen Membrane shall be 6 days from the date of manufacture, when stored at room temperature. The date of manufacture shall be defined as the date of primary packaging.

## **FDA LOT RELEASE**

You are not currently required to submit samples of future lots of Autologous Cultured Chondrocytes on Porcine Collagen Membrane to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2(a). We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

## **BIOLOGICAL PRODUCT DEVIATIONS**

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Document Control Center  
10903 New Hampshire Ave.  
WO71-G112  
Silver Spring, MD 20993-0002

## **MANUFACTURING CHANGES**

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Autologous Cultured Chondrocytes on Porcine Collagen Membrane, or in the manufacturing facilities.

## **LABELING**

We hereby approve the draft package insert labeling submitted under amendment 25, dated December 12, 2016 and the draft carton and container labeling submitted under amendment 25, dated December 12, 2016.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA [125603/0] at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST) as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Document Control Center  
10903 New Hampshire Ave.  
WO71-G112  
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

## **ADVERSE EVENT REPORTING**

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format – Postmarketing Safety Reports* at <http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm> and FDA's Adverse Event reporting System website <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm>.

## **PEDIATRIC REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and

effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study in patients 10 to 17 years of age until June, 2025 because the product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study is listed below:

1. Deferred pediatric study under PREA for the treatment of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in pediatric patients ages 10 to 17.

Final Protocol Submission: June 30, 2017

Study Completion Date: June 30, 2025

Final Report Submission: December 31, 2025

Submit the final study report to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as: **Required Pediatric Assessment(s)**

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B:**

We acknowledge your written commitment(s) as described in your letter of December 8, 2016 as outlined below:

2. To perform the following to implement (b) (4) testing as an ACI-Maix collagen membrane quality inspection item:
  - a. Develop a quantitative method and provide appropriate validation of the method by June 30, 2017;

- b. Provide an initial release specification by June 30, 2017 based on assessment of statistical tolerance intervals constructed from results of at least (b) (4) samples of (b) (4) lots of ACI-Maix collagen membrane within expiry at the time of testing;
    - c. Provide in Annual Reports to the BLA, summary data for (b) (4) quantitation for all lots of ACI-Maix collagen membrane manufactured after BLA approval, until the acceptance criteria for (b) (4) have been established, based upon the evaluation of a total of (b) (4) released lots;
    - d. Provide updated acceptance criteria for (b) (4) testing after analysis of a total of (b) (4) released manufactured lots;
    - e. Add (b) (4) testing to future validation studies for the ACI-Maix collagen membrane.
  3. To perform the following to complete the implementation of (b) (4) testing as an ACI-Maix collagen membrane quality inspection item:
    - a. Develop a quantitative method and provide appropriate validation of the method by March 31, 2017;
    - b. Provide an initial release specification for (b) (4) by March 31, 2017 based on assessment of statistical tolerance intervals constructed from results of at least (b) (4) samples from (b) (4) lots of ACI-Maix collagen membrane within expiry at the time of testing;
    - c. Provide in Annual Reports to the BLA, summary data for (b) (4) testing on all lots of ACI-Maix collagen membrane manufactured after BLA approval, until the (b) (4) test acceptance criteria have been updated upon evaluation of an additional (b) (4) released lots after BLA approval;
    - d. Provide updated acceptance criteria for (b) (4) testing after analysis of an additional (b) (4) released lots after BLA approval;
    - e. Add (b) (4) testing to future validation studies for the ACI-Maix collagen membrane.
  4. To complete updates to all standard operating procedure (SOP) documentation requiring revision due to obsoleted procedures and to implement the revised SOPs by February 28, 2017.

We request that you submit information concerning nonclinical and chemistry, manufacturing, and control postmarketing commitments and final reports to your BLA 125603. Please refer to the sequential number for each commitment.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Status Update**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing commitment not subject to the reporting requirements of 21 CFR 601.70, you may report the status to FDA as a **Postmarketing Commitment – Status Update**. The status report for each commitment should include:

- the sequential number for each study as shown in this letter;
- the submission number associated with this letter;
- describe what has been accomplished to fulfill the non-section 506B PMC; and,
- summarize any data collected or issues with fulfilling the non-section 506B PMC.

When you have fulfilled your commitment, submit your final report as **Postmarketing Commitment – Final Study Report** or **Supplement contains Postmarketing Commitment – Final Study Report**.

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

## **POST-APPROVAL FEEDBACK MEETING**

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

## **PDUFA V APPLICANT INTERVIEW**

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V (“the Program”). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the

Program. For this purpose, first cycle actions include: approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review committee. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review committee will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely yours,

Wilson W. Bryan, MD  
Director  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research