



BLA 125603

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

October 24, 2016

Dear Ms. Aguilera:

Attached is a copy of the memorandum summarizing your September 30, 2016, Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Jean Gildner at (240) 402-8296.

Sincerely,

Celia M. Witten, Ph.D., M. D.
Director
Office of Cellular, Tissue, and Gene Therapies
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: September 30, 2016 1300-1430
Meeting Location: Bldg. 71 Room 1206

Application Number: BLA 125603
Product Name: MACI – autologous cultured chondrocyte on porcine collagen membrane
Proposed Indications: the repair of symptomatic, full-thickness cartilage defects (single or multiple defects of the knee with or without bone involvement in adults.
Applicant Name: Vericel Corporation

Meeting Chair: John Thomas, Ph.D
Meeting Recorder: Jean Gildner

FDA ATTENDEES

Meghna Alimchandani, M.D., Pharmacovigilance Branch Chief, Division of Epidemiology/Office of Biostatistics and Epidemiology
Pete Amin, Ph.D., Manufacturing Review Branch 2
Steven Bauer, Ph.D., Cellular and Tissue Therapy Branch Chief
Kimberly Benton, Ph.D., Deputy Director, Division of Cell and Gene Therapies
Qiao Bobo, Ph.D., RAC, Branch Chief, Manufacturing Review Branch 2
Wilson Bryan, M.D., Director, Division of Clinical Evaluation and Pharmacology/Toxicology
Karen Campbell, M.S., Regulatory Coordinator, Division of Biological Standards and Quality Control
Jean Gildner, MSHS, MT (ASCP), CQA (ASQ), Regulatory Project Manager
Azada Hafiz, Office of Program and Strategic Programs
Ilan Irony, M.D., General Medicine Branch Chief
James Kenney, D.Sc., Chief, Laboratory of Microbiology, *In-vivo* Testing and Standards
Hyesuk Kong, Ph. D., Laboratory of Microbiology, *In-vivo* Testing and Standards
Shiowjen Lee, Ph.D., Statistics Team Lead, Division of Biostatistics
Stan Lin, Ph.D., Statistical Reviewer, Division of Biostatistics
Malcom Moos, M.D., Ph.D., CMC Reviewer
Loan Nguyen, Pharm.D, Regulatory Review Officer, Division of Case Management, Office of Compliance and Biologics Quality
Laurie Norwood, Deputy Director, Division of Manufacturing and Product Quality
Steven Oh, Ph.D., Chief, Cell Therapies Branch, Division of Cell and Gene Therapies
Raj Puri, M.D., Ph.D., Director, Division of Cell and Gene Therapies
Patrick Riggins, Ph.D., Branch Chief, Regulatory Management Staff
Bruce Schneider, M.D., General Medicine Team Lead
Stephanie Simek, Ph.D., Deputy Director, Office of Cellular, Tissue, and Gene Therapies
Ramani Sista, Ph.D., Regulatory Project Manager
Theodore Stevens, M.S., RAC, Associate Director for Information Management

Lisa Stockbridge, Ph. D., Supervisor, Advertising and Promotional Labeling Branch
John Thomas, Ph.D., Reviewer, Division of Cell and Gene Therapies
Michael Yao, M.D., Clinical Reviewer
Carolyn Yong, Ph.D., Devices and Combination Product Team Lead

EASTERN RESEARCH GROUP (ERG) ATTENDEES

Christopher Sese

APPLICANT ATTENDEES

In-Person

Margarita Aguilera, Senior Regulatory Consultant
David Recker, Chief Medical Officer
Ann Remmers, Senior Clinical Scientist
Barbara Matthews, Clinical Consultant
John Ilgenfritz, Principal Statistical Consultant

Cambridge, MA (on the phone)

Helena Correia, Interim Head of Regulatory Affairs
Ross Tubo, Chief Scientific Officer
Peter Bak, Global Medical Affairs
Liz Bicchieri, Director Pharmacovigilance
John Duguid, Director Process Development
Dan Orlando, Chief Operating Officer
Cynthia Entstrasser, Senior Director Quality
Leah Stidsen, Senior Quality System Engineer
Alex Ernesti, Senior Director Operations
Adrian Lowe, Senior Director Facilities Engineering
Kate Paiva, Sr. Manager Validation
John Moynihan, Associate Director Quality Control
Sam Prinzi, Manager Quality Control

Ann Arbor, MI (on the phone)

Caryn Cramer, Senior Director Corporate Communication
Fang Dong, Director Clinical Programming

BACKGROUND

BLA 125603/SECONDARY TRACKING NUMBER was submitted on January 4, 2016 for MACI – autologous cultured chondrocyte on porcine collagen membrane.

Proposed indication: the repair of symptomatic, full-thickness cartilage defects (single or multiple defects of the knee with or without bone involvement in adults.

PDUFA goal date: January 4, 2017

In preparation for this meeting, FDA issued the Late-cycle Meeting Materials on September 16, 2016.

DISCUSSION

1. Introduction Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

Summary of Discussion: Introduction of participants completed. Vericel proceeded with a power point presentation to aid in the discussion of issues.

2. Discussion of Substantive Review Issues

- Each issue will be introduced by FDA and followed by a discussion.

CMC:

1. (b) (4) sterility testing re-validation
 - a. Please provide an update on progress and confirm that the report will be submitted by October 1st, 2016, as planned

Summary of Discussion: Scheduled to be submitted October 1, 2016 via email with a formal amendment to follow October 3, 2016.

2. Revisions to (b) (4) test for ACI-Maix
 - a. Please provide an update on progress and confirm that the revisions will be submitted by September 30th, 2016, as planned.

Summary of Discussion: Revision to (b) (4) test for ACI-Maix was submitted as a BLA amendment on September 21, 2016, and is currently under review by FDA.

3. Proposed (b) (4) testing for ACI-Maix
 - a. Please provide a definitive timeline for revisions to the proposal and their implementation

Summary of Discussion: Proposed (b) (4) testing for ACI-Maix was submitted as a BLA amendment on September 21, 2016, and is currently under review by FDA.

4. Documentation of the in-progress Design History File for the device constituent of the MACI combination product
 - a. Please provide a definitive timeline for submission of further responses and when the Design History File will be completed

Summary of Discussion: Documentation of the in-progress Design History File for the device constituent of the MACI combination product was submitted as a BLA amendment on September 21, 2016 and is currently under review by FDA.

5. (b) (4) Testing of ACI-Maix
 - a. Please provide a definitive timeline for implementation

Summary of Discussion: Submitted update to Master File on August 25, 2016. The estimated completion of the method development, validation and initial acceptance criteria is June 2017. This was acknowledged by the FDA.

3. Information Requests

CMC:

1. Information Request sent September 15, 2016

- a. Maximum number of lots processed per shift and per day

Summary of Discussion: FDA asked applicant to please provide the maximum number of patient biopsy/cells that may be processed per shift and per day in the (b) (4). Vericel stated there was no defined or validated maximum number of biopsies/cells that may be processed per shift per day. FDA stated that the estimated maximum of (b) (4) per day did not appear to be feasible and requested that Vericel conduct a risk assessment, including a media fill simulation to validate manufacturing utilizing all of the Biosafety Cabinets at maximum staffing.

- b. Maximum number of lots that may be incubated in the same incubator
- c. Precautions to prevent cross contamination and mix-up

Summary of Discussion: Vericel described the procedure to prevent cross contamination. Each patient lot will be (b) (4)

FDA agreed that the segregation procedure was acceptable.

- d. Dynamic environmental (viable particulate) monitoring program

Summary of Discussion: Dynamic environmental monitoring was inadvertently not included in the BLA. This will be provided. FDA will review and communicate with Vericel if necessary.

- e. Sensitivity of test used for container closure validations

Summary of Discussion: Vericel will provide the closure container studies when completed by March 31, 2017. FDA found this to be acceptable.

- f. Frequency of HEPA filter integrity testing for the vacuum unit

Summary of Discussion: Vericel is currently not testing the filter integrity of the HEPA vacuum units but plan to complete this by January 2017. FDA found this to be acceptable.

Please provide a definitive timeline for your response to the above Information Request.

2. A separate information request was sent to Matricel on September 15, 2016 regarding their manufacturing facility. Please note that a satisfactory review of the Matricel MF is necessary prior to the approval of this BLA.

Additional issues: FDA asked Vericel to comment on why the SOP concerning Purchasing Controls (SOP MP1-005), submitted in response to the Information Request sent September 22, 2016, is marked “under revision”. Vericel stated that the planned revisions would not include any major substantive changes, and would involve changes to administrative information in transitioning from Genzyme to Vericel systems. FDA requested a timeline for the submission of the final SOP versions.

4. Risk Management Actions (e.g., REMS)

1. Review of the submitted data does not suggest a safety concern that would necessitate either a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint. Should the product be licensed, routine pharmacovigilance is recommended to monitor the risks associated with MACI.
2. Vericel will follow-up all expedited cases of spontaneous adverse event reports and has submitted healthcare provider training materials to be implemented voluntarily, should this product be approved.

Summary of Discussion: Vericel acknowledged the FDA’s comments.

5. Postmarketing Requirements/Postmarketing Commitments

1. PREA PMR for a deferred pediatric study to evaluate safety and efficacy of MACI in subjects aged 10 to 17 years with knee cartilage defects due to trauma (b) (4) [REDACTED].

Summary of Discussion: Vericel acknowledged the FDA’s comments.

6. Major Labeling Issues

1. We are discussing internally the value of including in labeling summary descriptive results of KOOS pain scores and KOOS SRA scores over 5 years for MACI and microfracture groups (from SUMMIT Extension). In particular, we are discussing the value of information on durability of effect to physicians and patients. In addition, we are discussing internally about the exclusion of the results of the responder analyses from labeling. We will communicate our conclusions to Vericel, along with justifications for our positions.

Summary of Discussion: Vericel presented an overview of the MACI00809 study (SUMMIT Extension). FDA acknowledged the limitations of including data from the SUMMIT extension

study, but thought that the data could still be valuable, even if only descriptive. FDA will continue to discuss this issue internally.

7. Review Plans

1. The completion of the CMC review is pending the receipt of responses to the outstanding information requests noted above.
2. We anticipate beginning labelling discussions by mid-October.

Summary of Discussion: FDA will contact Vericel in October to initiate labeling discussions.

8. Wrap-up and Action Items

1. Vericel asked when they can expect comments on the HCP training materials. The FDA stated that the review is ongoing and they anticipated providing comments in a few weeks.
2. FDA to provide meeting minutes in 14 days.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.