

Mid-Cycle Communication Teleconference

July 21, 2016

Application type and number: BLA 125603

Product name: Autologous chondrocytes seeded on a porcine-derived collagen membrane

Proposed Indication: Repair of symptomatic, full-thickness cartilage defects (single or multiple) of the knee, with or without bone involvement (b) (4) in adults

Applicant: Vericel Corporation

Meeting date & time: June 29, 2016 at 1200 to 0100 PM

Committee Chair: John Terrig Thomas

RPM: Jean Gildner

FDA Attendees:

John Terrig Thomas, Chair

Jean Gildner, RPM

Patrick Riggins RPM

Malcom Moos, CMC (DCGT)

Carolyn Yong, CMC (DCGT)

Simleen Kaur, CMC (DBSQC)

James Kenney, CMC (DBSQC)

Hyesuk Kong, CMC (DBSQC)

William McCormick, CMC (DBSQC)

Bruce Schneider, Clinical (DCEPT)

Michael Yao, Clinical (DCEPT)

Meghna Alimchandani, Pharmacovigilance (DE)

Azada Hafiz, Operations Analyst (CDER)

Eastern Research Group (ERG) Attendee:

Christopher Sese, Independent Assessor

Vericel Attendees:

Margarita Aguilera, Senior Regulatory Consultant

David Recker, Chief Medical Officer

Ross Tubo, Chief Scientific Officer

Dan Orlando, Chief Operation Officer

Helena Correia, Interim Head of Regulatory Affairs

Ann Remmers, Senior Clinical Scientist

Lorien Armour, CMC Regulatory Consultant

Liz Bicchieri, Director Pharmacovigilance

Fang Dong, Associate Director Clinical Programming

John Duguid, Principal Scientist

Cynthia Entstrasser, Senior Director Quality

Caryn Cramer, Regulatory Submissions Consult

Joshua Hodgdon, Manager Compliance

Peter Bak, Global Medical Affairs

Matricel Attendees:

Leon Old Damink, Head of Regulatory Affairs and Quality Management,
Ingo Heschel, Managing Director

BACKGROUND

BLA 125603/00 was submitted on January 4, 2016 for MACI.

Proposed indication: Repair of symptomatic, full-thickness cartilage defects (single or multiple) of the knee, with or without bone involvement (b) (4) in adults

PDUFA goal date: January 3, 2017

In preparation for this meeting, FDA issued Mid-cycle Meeting Materials on June 27, 2016.

DISCUSSION

1. **Discussion of Substantive Review Issues**

a. Cellular Component:

i. (b) (4) sterility testing validation

Summary of Discussion: Dr. Kenney read an Information Request to the Applicant requesting the performance of a Limit of Detection study in accordance with (b) (4) using (b) (4) lots of MACI drug substance, the (b) (4) and at least (b) (4) known environmental microorganisms.

Results were requested to the FDA on or before October 1, 2016. Vericel agreed to send the FDA a list of their current environmental microorganisms from their Cambridge facility, which will be reviewed for selection to be included in their Limit of Detection study, and stated they would do their best to comply with the requested results date.

b. Membrane component

i. PLI Form 483 responses:

The Agency acknowledged receipt of the responses to the four Form 483 observations issued following the PLI from 03May2016 to 13May2016. Vericel was informed that observation 2, regarding container closure integrity and observation 4 regarding space and storage issues were under review, but would not be discussed further at this meeting.

Summary of Discussion:

Observation 1 - (b) (4) Test:

- Vericel committed to replacing the current (b) (4) test with a (b) (4) [REDACTED], such as (b) (4) [REDACTED]
 - Vericel requested a teleconference with the Agency to discuss acceptable studies of (b) (4) [REDACTED]; this was agreed upon.
 - In the meantime, Vericel will revise the acceptance criteria for the (b) (4) test by 30Sept2016 for (b) (4) [REDACTED] assessments, based on statistical analysis of historical and recent data.
 - No further validation work will be conducted on the current (b) (4) test

Observation 3 - Design Control and documentation:

Vericel stated that the Quality Manual will be available in July, and a new Design Control procedure will be created by late August. However, the execution of the Design Control program, including the establishment of a Design History File (DHF) was not anticipated to be available until November 18, 2016. Vericel was informed that submission of a major amendment late in the review cycle may require an extension of the current review clock. FDA suggested Vericel submit the Design Control program sooner, to allow time for review during the current review cycle. Vericel was reminded that the DHF should have been available during the PLI and in lieu of submitting the actual DHF, Vericel may send a pdf copy for review as it comes available.

ii. Genotoxicity and (b) (4) [REDACTED] testing

Summary of Discussion: Vericel stated that the genotoxicity testing is complete and is undergoing an internal review. (b) (4) [REDACTED] testing on (b) (4) [REDACTED] ACI-Maix lots will be completed by mid-August. The results of both will be submitted to the BLA and MF in August.

iii. (b) (4) [REDACTED] Lot Release Testing

Summary of Discussion: Vericel requested clarification of what is required by the Agency. FDA stated that the testing could be used as a lot release test or it could be done periodically to confirm manufacturing quality.

iv. (b) (4) [REDACTED] specifications - No discussion

v. (b) (4) [REDACTED] testing acceptance criteria

Summary of Discussion: Vericel is currently discussing with Matricel regarding the type of testing to be conducted. As noted above, Vericel requested a teleconference with the FDA to discuss the best path forward to which the FDA agreed.

vi. ACI-Maix (Matricel) manufacturing questions

Summary of Discussion: Marticel will respond to the 20Jun2016 IR by 30Jun2016 and amend the MF in several rounds with an expected completion date of end of August.

Pre-Clinical: No current outstanding issues

Clinical:

- a. No outstanding IRs
- b. Preliminary review committee thinking regarding risk management

Summary of Discussion: At this time, a Risk Evaluation and Mitigation Strategy (REMS) is not required. Vericel agreed to provide surgeon training materials (undertaken voluntarily by Vericel). FDA asked if Vericel planned on any additional tracking of adverse events or postmarketing registry type study. Vericel has no plans for a postmarketing registry study, but will have a list of patients who were treated with MACI and plans on routine monitoring of adverse events as per regulations and will obtain follow-up as needed.

- 2. **Major safety concerns identified to date:** No safety issues
- 3. **Outstanding IR:** Only those identified related to CMC issues
- 4. **New Information Requests:** FDA requested Applicant provide the surgeon training materials for review. Applicant agreed to provide this information.
- 5. **Proposed date(s) for the late-cycle meeting:** September 20, 2016