

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Abdominal & Surgical Devices Branch

Date: November 20, 2016

To: Carolyn Yong on behalf of Stephen Oh, Regulatory Business Process
OMPT/CBER/OCTGT/DCGT/CTB
Manager/OPRO
Steven.Oh@fda.hhs.gov

Office of combination products at combination@fda.gov

RPM: Carolyn Yong

Through: Ronald Swann, Chief, Abdominal & Surgical Devices Branch, DMQ, OC,
CDRH

From: Latoya Oliver-Powell, CSO, Abdominal & Surgical Devices Branch, DMQ,
OC, CDRH

Applicant: Vericel Corporation
64 Sidney Street
Cambridge, Massachusetts 02139

FEI: 3012560827

Application # BLA MF [REDACTED]

Consult # ICC1600265

Product Name: Trade Name – MACI (device:
ACI-MAIX Collagen Membrane)

Pre-Approval Inspection: Yes

Documentation Review: Response to IR received on June 23, 2016

Final Recommendation: Approve

The Office of Compliance at CDRH received a consult request from CBER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of BLA MF (b) (4).

PRODUCT DESCRIPTION

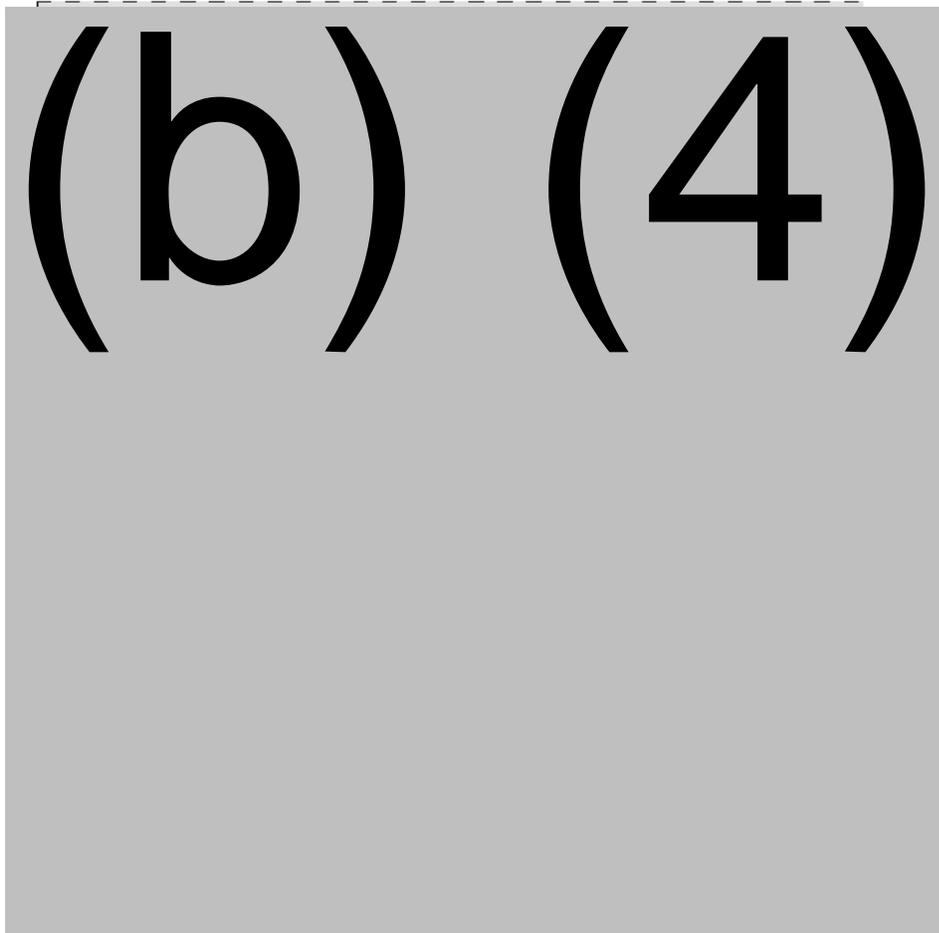
The MACI implant utilizes autologous chondrocytes which are extracted from a cartilage tissue biopsy of healthy cartilage from the patient's own knee. To complete the MACI implant the chondrocytes are expanded and seeded onto a bio-resorbable Type I / III collagen membrane (b) (4) cells per square centimeter. During a mini-open technique, damaged and / or diseased cartilage tissue is debrided from the defect area and the MACI implant is cut and shaped to fit and adhered in place using an off-the-shelf sealant.

The firm provided the chart below to provide an overview of the CM Bulk Material and ACI-Maix membrane manufacturing process.

CM Bulk Material and ACI-Maix Membrane Manufacturing Process

Flow:

Figure 1 (provided by firm)



(b) (4)

Room and Facility Classifications:

Process	ISO/EU GMP Classification
(b) (4)	

Intended Use: MACI is indicated for the repair of symptomatic, full-thickness cartilage defects (single or multiple) of the knee, with or without bone involvement (b) (4) in adults.

REGULATORY HISTORY

The product is manufactured at Matricel GMBH located at KAISERSTRASSE 100, HERZOGENRATH, Germany. Matricel is supplier of the device constituent and is not involved in the manufacturing of the final combination product.

The following facility was identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

<p>Name: Matricel GMBH</p> <p>Address: Kaiserstrasse 100, Herzogenrath, Germany</p> <p>FEI number: None recorded</p> <p>Vericel Corporation</p> <p>Address: Kaiserstrasse 100, Herzogenrath, Germany</p> <p>FEI number: 3012560827</p>	<p>Matricel is a supplier of the device constituent and is not involved in the manufacturing of the final combination product.</p>	<p>No Inspectional History documented. According to CBER, no FDA inspection has been conducted.</p> <p>Responsibility: Matricel is a supplier of the device constituent and is not involved in the manufacture of the final combination product.</p> <p>Inspection Recommendation: CDRH Office of Compliance is not requiring a Pre-approval inspection for this supplier, as the major activities related to the manufacturing and development of the final combination product appear to take place at final combination product manufacturer, Vericel Corporation.</p> <p>CDRH Office of Compliance will defer to CBER as to whether an inspection should be conducted at Matricel prior to approval.</p> <p>Responsibility: Vericel is responsible for all manufacturing activities surrounding the finished combination product.</p> <p>Inspection Recommendation: CDRH Office of Compliance defers to CBER as to whether an inspection will be conducted prior to approval of this application.</p>

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DOCUMENTATION REVIEW (Abbreviated Review)

The documents provided by the firm are currently being reviewed; the application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

The following documentation deficiencies were identified in reference to 21 CFR Part 4 and 21 CFR 820 for the finished combination product, MACI, should be sent to the Applicant/Licensure of the Application.

1. A summary of the firm's management structure with executive responsibility who manage, perform, and assess work affecting quality of the product and related controls to ensure that the firm's quality policies are appropriately implemented and followed, and the product appropriately designed and manufactured in conformance with CGMP requirements, including quality system requirements met as per 21 CFR 820.20.
2. A summary of the firm's design control system under 21 CFR 820.30 must be included for the device constituent part and combination product. The design control information should include initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that

meets the proposed intended use of the final combination product, design changes, and design history file. For changes made to the device constituent part of the combination product, the impact of the design changes on the overall combination product performance should be considered and documented. All the design control activities must be documented in the Design History File (DHF) and subjected for design reviews. In addition, the location of DHF should be provided to the Agency for the facility inspection determination.

3. Summary of information pertaining to the Purchasing Control as per 21 CFR 820.50 to demonstrate controls and documentation for components, products, or services (example (b) (4) received at the sponsor's facility for use in the manufacture of the combination product. The summary should include the applicant's evaluation process of their suppliers that meet the manufacturing acceptance criteria of the combination product specifications. Notification of changes by the suppliers should be considered in the firm's Purchasing/Supplier agreement as changes to incoming specification can impact the safety and effectiveness of the final combination product.
4. Summary of information related to Corrective and Preventive Actions (CAPA) as per the requirement of 21 CFR 820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. The CAPA system must account for investigations into failures in the device constituent. CAPA activities for the analysis of sources of quality data to identify existing and potential cause of nonconformances, related investigations, and actions considered to correct and prevent recurrences of problems and non-conformances, including the verification or validation of the actions should be documented under the firm's CAPA System as described in 21 CFR 820.100.

DOCUMENTATION REVIEW (Comprehensive Review)

Management Control, 21 CFR 820.20

SOP (b) (4) states that the Executive Management is responsible for ensuring that the QM-system is established and implemented and requires that the firm's Executive Management have regular and defined management reviews of the QM-system to determine its effectiveness and assure that the principles and policies are communicated. This SOP also stated that it is the responsibility of the Executive Management to communicate the Quality Policy and Quality Objectives to the organization. The SOP further states that the firm's Quality Policy was established by the Executive Management. In formulating the quality policy, the Executive Management ensures that the policy is appropriate to the purpose of the company, and includes a commitment to comply with the requirements and continually improve the effectiveness of the quality management system. The Quality Policy is generated per QS-F0-0103 *Quality Policy*. According to the firm, the Quality Policy is posted in the company, and its role is explained and discussed at the general orientation training provided to all employees.

The firm stated that Quality Policy provides a framework for establishing specific quality objectives, and provides direction for the continuous improvement effort. According to the firm, its quality policy is also communicated to customers, consumers and other interested parties. For this purpose, the Quality Policy is available as a public document and the Quality policy is displayed in public locations throughout Matricel. The Management Representative is the individual responsible for managing the control, reporting, communication, and maintaining the effectiveness of the QM-system. He has the authority and responsibility to:

- Ensure that the QM-system is implemented, maintained and continually improved

- Promote awareness of regulatory and customer requirements throughout the organization
- Report to the executive management on the efficiency and performance of the quality system

According to the firm, interrelation of all employees who manage, perform and verify work affecting quality is identified in the Organizational Chart as presented in the applicable section of the Quality Management Manual (QMM). The interrelation of employees in the company is also defined in operational procedures and other documents defining the roles and responsibilities. Executive Management ensures that the employees have sufficient independence and authority to perform these tasks, in particular, internal auditors and the employee responsible for monitoring experience from the post-production stage and reporting adverse events. The firm stated that all departments and functions in Matricel are responsible for implementing, maintaining the effectiveness, and improving the firm's Quality Management System.

The information provided by the firm appears to have adequately address the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm provided procedures for its design control activities. The procedures appear to provide explanation of its design, and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file activities.

The information provided by the firm appears to adequately address the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The firm provided a copy and an amendment to its Purchasing Control Procedure (MP1-005). The procedure documents how the firm evaluates, controls and maintains records for suppliers.

The information provided by the firm appears to adequately address the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

The firm has provided a copy of its Quality Manual QA1-010. The manual included a section regarding how the firm handles its CAPA's. According to the firm, its procedures are established and maintained for the implementation of corrective and preventive action. These procedures describe methods for taking action to eliminate causes of actual or potential nonconformities, and include requirements to correct/prevent the identified root cause, and evaluate effectiveness of the corrective and preventive action per QA3- 027. The firm stated that its procedures for handling customer complaints are described in CS1-039 and QA1-001. These procedures include ensuring that necessary investigations occur, and corrective action or preventive action is taken, based on customer complaints. Procedures addressing product nonconformities are described in QA3-002. The firm stated that the procedures include determining whether preventive and corrective actions should be taken based on the identified nonconformance. Additionally, the firm stated its CAPA and other improvement activities are identified through the use of management reviews, internal audits, process data, quality records, audit results, supplier notifications, trend analysis, and other appropriate data sources. According to the firm, the data are used to detect, analyze, and eliminate potential causes of nonconformity. These procedures are described in QA1-044, QA1-045, and QA3-027.

The information provided by the firm appears to adequately address the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

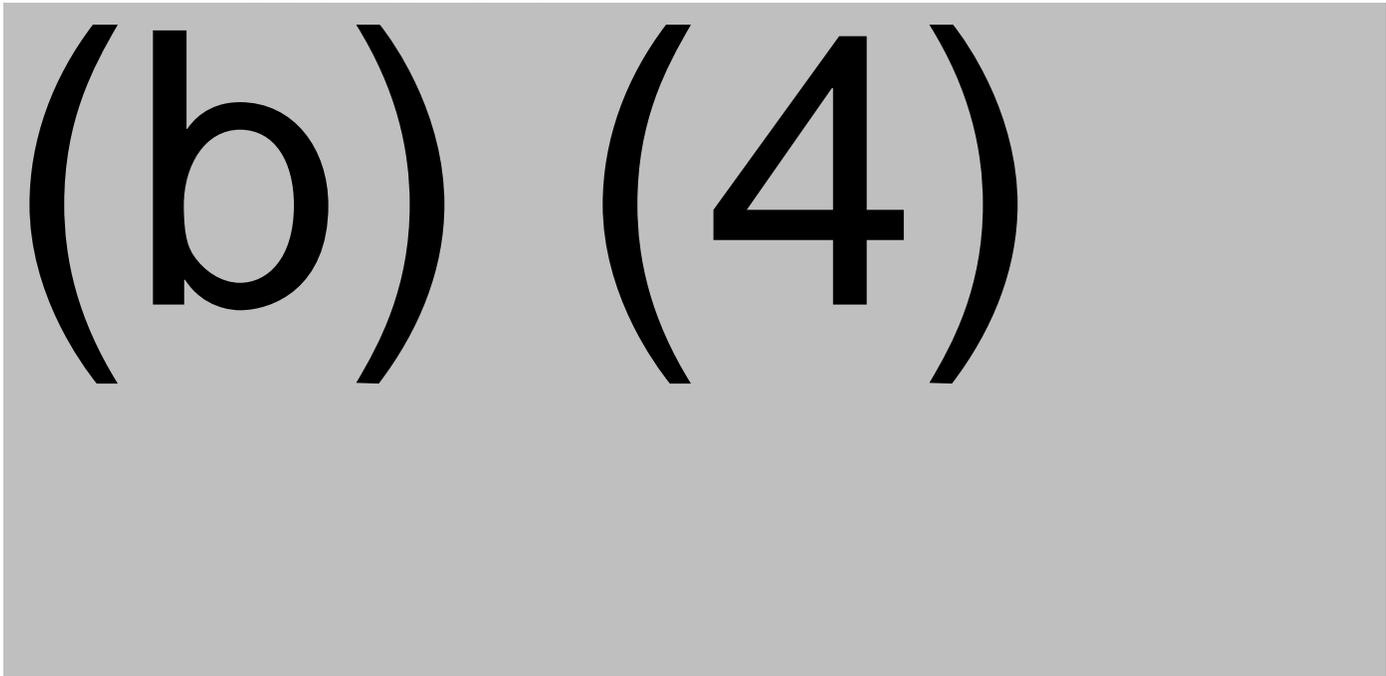
Production and Process Controls

This information was reviewed during the on-site pre-License inspection and deemed sufficient by CBER; therefore CDRH defers to CBER on this matter.

Production Flow

MACI Manufacturing Flow with QC Sample Points
Drug Product

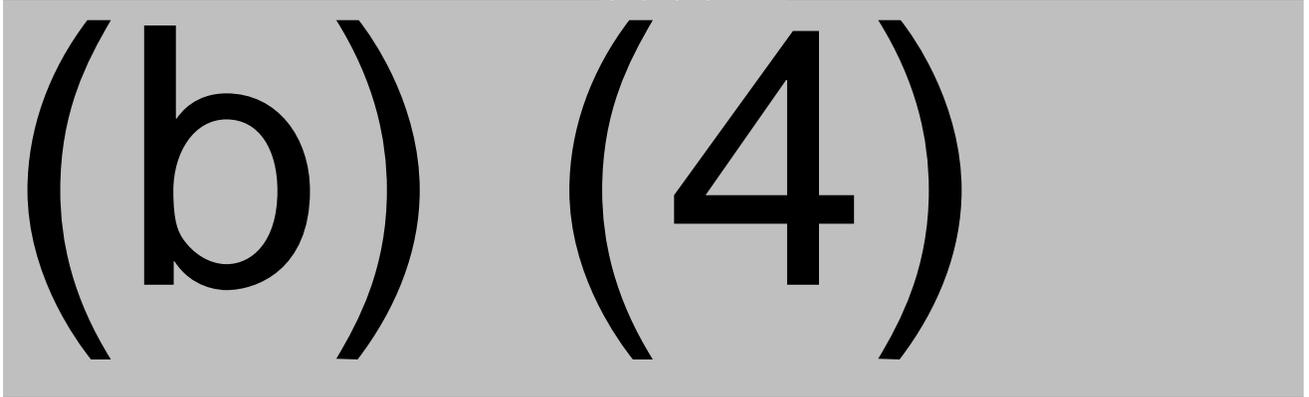
(b) (4)



MACI Manufacturing Flow with QC Sample Points

Drug Substance

(b) (4)



INSPECTOR
COPY

(b) (4)

Acceptance Activities

This information was covered by cGMPs and the MF/BLA review. Vericel (the sponsor) conducts all these activities. The information has been deemed adequate by CBER; therefore CDRH defers to CBER on this matter.

OVERALL RECOMMENDATION

The application for MACI combination product filed under BLA MF (b) (4), appears to be approvable from the perspective of the applicable Quality System Requirements, based on the information provided per the specificity of the consult request. Please note: CBER has conducted an on-site pre-License inspection. CDRH Office of Compliance will defer to CBER's findings, as it relates to the approval of this application.

Latoya Oliver-Powell

Prepared: LOliver-Powell: 10/20/16, 11/20/16

Revised: RSwann:

CTS No.: ICC1600265

BLA MF (b) (4)

Review Cycle Meeting Attendance:

Month/Day/Year

Month/Day/Year

Month/Day/Year

