

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****M E M O R A N D U M**

Food and Drug Administration  
Office of Device Evaluation  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Memo Date: Original March 11, 2016, Amended September 1, 2016 with final review

To: Record

From: Joe Nielsen, Ph.D., Biologist, CDRH/ODE/DSD/PRSB1

Sponsor: Vericel Corporation

Device Name: Matrix applied characterized autologous cultured chondrocytes

<b>Digital Signature Concurrence Table</b>	
Reviewer Sign-Off	
Branch Chief Sign-Off	
Division Sign-Off	

**Summary and Recommendation**

The consultant reviewed Master File (b) (4) for the ACI-Maix Collagen Membrane component of the Vericel Matrix combination product. The deficiencies identified in the original consult review were communicated to the Master File Holder on March 17, 2016 and June 20, 2016. The Master File Holder amended Master File (b) (4) with additional information responses on July 29, 2016 and August 25, 2016. The consultant concludes the Master File Holder has adequately addressed all deficiencies generated by this consultant, and recommends the Master File be found sufficient to conclude the ACI-Maix Collagen Membrane component is biocompatible and adequately characterized. See end of consult for review of Master file Holder responses.

**Indications for Use**

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

**Device Description**

Product consists of autologous cultured chondrocytes on a resorbable Type I/III collagen membrane, at a density of 500,000 to 1,000,000 cells per cm<sup>2</sup>.

**Review****Inspection of Device component manufacturer**

The consultant was asked for CDRH's perspective on whether the collagen matrix manufacturer should be inspected as the device component manufacturer. The consultant discussed this question with DSD Division management, and was advised that CDRH, would require a pre-approval inspection of the final device manufacturer, but may not request an inspection of a sub-component supplier without a specific reason to do so. This manufacture has a cleared collegian medical device (K123697). However, CDRH's Office

of Compliance confirmed this German manufacturer has never been inspected by FDA. This information was communicated to CBER. In addition, the consultant notes the master file contains elements of their Quality Systems program. The review team decided to consult CDRH's Office of Compliance to review the Quality Systems elements in the master file.

### **Master file review**

#### **1: Regional**

#### **2: Common Technical Document Summaries**

#### **3: Quality (3.2.S.1-7, 3.2.A, 3.2.R)**

#### **1 Regional**

The ACI-Maix Collagen Membrane (ACI-Maix Membrane, MAIX, AciMaix) is a device manufactured by Matricel GmbH solely for use by Vericel Corporation as a device component of their proposed combination product, the Vericel Matrix. Dated 12/2/2015


Device Master File (b) (4) Letter of Authorization

Name: ACI-Maix Membrane or ACI-Maix Collagen Membrane Matricel GmbH hereby authorizes Vericel Corporation to incorporate by reference information regarding the ACI-Maix Membrane in Device Master File (MF) (b) (4) into the Biological License Application (BLA) filed by Vericel Corporation for MAGI. We also authorize the FDA to review the aforementioned specific information in MF (b) (4) when considering the MACI BLA filed by Vericel Corporation. Matricel GmbH states that MF (b) (4) is current and Matricel GmbH will comply with the statements made within it. Matricel GmbH will notify FDA through an amendment to MF (b) (4) of any addition, change, or deletion of information in the MF. Matricel GmbH will also notify in writing Vericel Corporation that an addition, change, or deletion of information has been made to the MF.

Matricel GmbH  
Kaiserstrasse 100  
52134 Herzogenrath  
Nordrhein-Westfalen  
Germany  
FEI: 3007113424

US Agent:

(b) (4)



**Consultant comment:** The sponsor has provided an appropriate letter of authorization

allowing review of master file (b) (4).

## **2 Common Technical Document Summaries**

### **Table of contents**

- 3.2.S ACI-Maix Membrane – all individual 3.2.S sections are provided
- 3.2.A.1 Facilities and Equipment – includes a description of the facility, cleaning and cross-contamination controls, and a description of Quality Systems applicable to medical devices.
- 3.2.A.2 Adventitious Agents
- 3.2.A.3 Novel Excipients – not applicable
- 3.2.R Executed Batch Record for a representative lot
- 3.2.R.1 Biocompatibility – Evidence of biocompatibility derived from a series of studies


## **3 Quality (3.2.S.1-3.2.S.7)**

### **3.2.S.1 General Information**

**3.2.S.1.1 NOMENCLATURE** (ACI-MAIX MEMBRANE, MATRICEL) ACI-Maix Membrane or ACI-Maix Collagen Membrane


#### **3.2.S.1.2 Structure**

(b) (4)



#### **3.2.S.1.3 General properties**

ACI-Maix Collagen Membrane is composed of a purified collagen fibrous network produced from porcine (b) (4) using controlled manufacturing processes. It is a CE marked medical device in Europe (Notified Body 0481, CE-marked as of January 22, 2003), for use in Collagen Covered Autologous Chondrocyte Implantation (CACI) procedures. Starting materials for the ACI-Maix Collagen Membrane are obtained from European Union certified slaughterhouses under strict veterinary authority controls from animals declared fit for human consumption. ACI-Maix Collagen Membrane is (b) (4)



The ACI-Maix Collagen Membrane has one smooth surface and one rough surface. The smooth surface of the membrane has a dense, compact fibrous structure (Figure 1). This dense structure imparts the mechanical integrity to the membrane. The other surface of the membrane has a rough appearance and consists of fibers arranged in a loose, open-fibrous structure (Figure 2). During production of MACI, the open-fibrous surface of the

membrane is seeded with chondrocytes. During surgical implantation of MACI, the open-fibrous cell seeded surface of the membrane is positioned adjacent to the debrided cartilage defect. The ACI-Maix Collagen Membrane is bioresorbed via normal metabolic pathways for proteins.

**Consultant comment:** Product characterization is reviewed below.

Figure 1 ACI-Maix Collagen Membrane Smooth Surface



Figure 2 ACI-Maix Collagen Membrane Rough Surface



### 3.2.S.2 Manufacture

#### 3.2.S.2.1

**Table 1                      Manufacturers**

<b>Name</b>	<b>Activity</b>
Matricel GmbH Kaiserstraße 100 52134 Herzogenrath Germany	Manufacturer of ACI-Maix Membrane

(b) (4)	(b) (4)
(b) (4)	(b) (4)

**3.2.S.2.2 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS (ACI-MAIX MEMBRANE, MATRICEL)**

(b) (4)



(b) (4)

(b) (4)

**3.2.S.2.3.1.8 Specification for Animal Tissue:** The specification for the animal tissue is provided in Table 2 (Matricel Document (b) (4) “(b) (4) tissues Specification”).

3.2.S.2.3.1.9 Incoming Inspection and Quarantine procedure: At arrival in the Matricel facility, the porcine tissues are subject to incoming inspection according to (b) (4), including evaluation against the specifications (Table 2). (b) (4)

3.2.S.2.3.1.10 Certificate for Animal Material and the Health Attestation: Certificates are provided for (b) (4) slaughterhouses.

3.2.S.2.3.1.11 Procedure for Control of Documents and Data: A copy of the procedure for control of documents and data is provided in Matricel Document SOP (b) (4) .

3.2.S.2.3.1.12 Procedure for Facility Cleaning: A copy of the procedure for Matricel facility cleaning is provided in SOP (b) (4) and in Instruction QS-WI-0984-B (original document in German language with English translation).

3.2.S.2.3.2 Control of Materials - Other Components: Materials used in the processing of the tissue undergo incoming inspections at Matricel upon arrival and are further described in detail in Table 3. Certificates of Analysis (CoA) for the materials are provided.

**Consultant comment:** Regulatory submissions should describe the following to ensure the safety of animal derived tissue products:

- a. the animal species;
- b. the age of animal;
- c. the specific tissue(s) used;
- d. the animals' country of origin and residence (with more specific geographic information location when appropriate) and when such information is available;
- e. the methods for monitoring the health of herd and the health of specific animals from which tissues are collected (e.g., vaccinations with live modified viruses that can co-purify in the desired tissue, active surveillance for human pathogens);
- f. the United States Department of Agriculture (USDA) status of the abattoir;
- g. the methods of ensuring compliance with USDA Animal and Plant Health Inspection Service (APHIS) importation and USDA Food Safety and Inspection Service (FSIS) inspection requirements;
- h. the methods and conditions for transporting animal tissue (e.g., tissue refrigeration and quarantine); and
- i. the procedures for maintaining records on the above cited issues should be presented in regulatory submissions.
- j. test methods and release criteria permitting animal tissues to be further processed and/or combined with other animal tissue(s) or device components for manufacture;
- k. quarantine procedures for tissues until they have met/failed release criteria;
- l. test methods and acceptance criteria for assessing in-process and final product bioburden or sterility;



(b) (4)

(b) (4)

**Interactive deficiencies (requested June 20, 2016)**

- 1. Please provide the following additional information to ensure the safety of the animal tissue derived collagen product:**
  - a. The master file states the slaughterhouses have been inspected by the USDA. Please identify the methods used to ensure compliance with USDA inspection requirements.**
  - b. Please identify quarantine procedures for tissues until they have met/failed release criteria.**
  - c. Please provide certification the manufacturing facility has not processed animal tissues that came from countries with bovine spongiform encephalopathy or transmissible spongiform encephalopathy risk.**

**Response (072916 and 082516):**

**Response to 1a:**

**072916:** In MF Section 3.2.S.2.3.1.1 it is stated that the slaughterhouses have not been inspected by the USDA. Could you please clarify whether the word not is missing in your question? Assuming that the word not is indeed missing in your question, Matricel will provide an overview of the requirements that the slaughterhouses currently do comply with. Expected timeline: Will be amended to the MF by end of August.

**082516:** In MF Section 3.2.S.2.3.1.1 it is stated that the slaughterhouses have not been inspected by the USDA. Inspection of foreign slaughterhouses is performed by the Food Safety and Inspection Services (FSIS) branch of the USDA (<http://www.fsis.usda.gov/wps/portal/fsis/home>). Detailed information on the eligible countries, products and foreign establishments that are currently eligible to export to the US can be found in the International Affairs section (<http://www.fsis.usda.gov/wps/portal/fsis/topics/international-affairs/importingproducts/> eligible-countries-products-foreign-establishments). Currently, Germany is eligible for exporting raw as well as processed pork to the US. Countries that are eligible to export meat, poultry or and/or egg products have gone through the initial equivalence process that includes submission of documentation that supports government oversight of their food safety inspection system. After conclusion of document reviews, FSIS has performed an onsite audit, the rulemaking process has concluded, and the country has been listed as equivalent in the Code of Federal Regulations (9 CFR §327.2). As the method to ensure compliance with the USDA inspection requirements, Matricel will only harvest porcine tissues from slaughterhouses that are located in countries that are eligible to export raw pork to the US. Eligible countries will be monitored by subscribing to the FSIS email service that informs subscribers when new content is added to the FSIS website, more specifically on changes in the status of Eligible Foreign Establishments, Equivalence Process and Foreign Audit Reports.

**Consultant comment 1a:** The initial review noted the Master File stated that slaughterhouses have not been inspected by the USDA. The consultant confirmed the Master File Holder's interpretation of the error (omission of not) in deficiency 1a. The Master File Holder has amended the master file to state that inspection of the foreign slaughterhouses is performed by the Food Safety and Inspection Services (FSIS) branch of the USDA. In addition, the Master File Holder confirms Germany is on the list of countries eligible to import porcine products into the USA. Response adequate

**Response to 1b (072916):** Incoming inspection of the tissues is performed (b) (4) described in Figure 1 of MF Section 3.2.S.2.2. The harvesting process and transportation of the tissues is described in MF Section 3.2.S.2.3.1.2, Matricel Document QS-WI-0901-D. Upon arrival at the Matricel facility, (b) (4)

Matricel Document QS-TI-1046-B, provided in

this amendment, describes the incoming inspection requirements. Inspection items involve: (b) (4)

Section 3.2.S.2.3.1.2 has been updated to reflect this additional information. Response adequate

**Consultant comment 1b:** The Master File Holder has clarified the incoming tissue inspection procedures. The inspection includes (b) (4)

The consultant concludes the incoming product inspection is adequate, and (b) (4). Response adequate

**Response to 1c (072916):** A certification is provided as an attachment to Section 3.2.A.2.3 indicating that the Matricel manufacturing facility has never processed any tissues from animals with a bovine spongiform encephalopathy or transmissible spongiform encephalopathy risk.

**Consultant comment 1c:** The Master File Holder has provided the requested certification confirming the Matricel manufacturing facility, located in Herzogenrath, Germany, has not processed any animal tissue coming from countries with bovine spongiform encephalopathy or transmissible spongiform encephalopathy risk. Response adequate

**Conclusion:** The additional information provided in response to deficiency 1a-c along with the information included in the original Master provides adequate information to ensure the safety of the animal tissue derived collagen product, and is consistent with the recommendations in the 1998 Animal Derived Tissue Guidance.

2. (b) (4)

(b) (4)

(b) (4)

(b) (4)



(b) (4)		

4. The biocompatibility test reports are dated from 2002 to 2005. Please confirm the collagen membrane evaluated in these biocompatibility studies is representative of the current collagen mesh product using the same manufacturing processes with the same final identify and purity specifications.

**Response (072916):** It is confirmed that the collagen membrane evaluated in the biocompatibility studies dated from 2002 to 2005 is representative of the current collagen mesh product using the same manufacturing process with the same (b) (4) specifications. An overview of the significant changes since 2005 is provided in Table 1 in Section 3.2.S.2.6.2 submitted in the original MF. All changes that occurred were assessed as not having an adverse effect on the quality or safety of the product.

**Table 1 Change History for ACI-Maix Membrane**

	(b) (4)		

