

BLA 125603

Autologous Cultured Chondrocytes on Porcine Collagen Membrane (MACI)

Vericel Corporation

Biologic Constituent Reviewers:	Malcolm Moos, M.D., Ph.D. J. Terrig Thomas, PhD.
Device Constituent Reviewer:	Carolyn Yong, Ph.D.

CMC Review

1. **BLA#:** STN 125603
2. **REVIEW DATE:** December 12, 2016
3. **PRIMARY REVIEW TEAM:**
Medical Officer: Michael Yao
Pharm/Tox: Allen Wensky
Product Quality Team: John Thomas, Malcolm Moos, Carolyn Yong, Hyesuk Kong, Joseph Nielsen, Latoya Oliver-Powell
Facilities: Pankaj (Pete) Amin
Statistics: Stan Lin
Labeling: Loan Nguyen
RPM: Jean Gildner
4. **COMMUNICATIONS WITH APPLICANT:**

Communication/Document	Date
Filing Letter issued to Applicant	3/4/2016
Telecon with Applicant	3/9/2016
Day 74 Review Issues sent to Applicant	3/17/2016
IR sent to Applicant	3/23/2016
Telecon to discuss day 74 review issues	4/11/2016
Pre-License Inspection	5/9/2016 to 5/13/2016
IR sent to Applicant	5/26/2016
Response to IR sent 5/26/2016	6/3/2016
BLA amendment submitted by Applicant	6/16/2016
Telecon with Applicant	6/17/2016
IR sent to Applicant	6/20/2016
Mid-Cycle Telecon with Applicant	6/23/2016
BLA Amendment submitted by Applicant	6/27/2016
IR sent to Applicant	6/29/2016
Telecon with Applicant	6/29/2016
IR sent to Applicant	7/14/2016
IR sent to Applicant	7/20/2016
Mid-cycle meeting minutes sent to sponsor	7/21/2016
Response to IR sent on 7/20/2016	7/29/2016
Telecon with Applicant	8/19/2016
Response to IR sent 6/20/2016	8/25/2016
IR sent to Applicant	9/15/2016
BLA Amendment submitted by Applicant	9/21/2016
IR sent to Applicant	9/22/2016
Late cycle meeting with Applicant	9/30/2016
BLA amendment submitted by Applicant	10/11/2016
IR sent to Applicant	10/13/2016
BLA amendment submitted by Applicant	10/19/2016

Communication/Document	Date
Late cycle meeting minutes sent to Applicant	10/24/2016
IR sent to Applicant	10/27/2016
IR sent to Applicant	11/2/2016
BLA amendment submitted by Applicant	11/14/2016

5. SUBMISSIONS REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 1235603	1/04/2016	Yes
(b) (4)	12/04/2015	Yes

6. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: MACI
- b. Non-Proprietary Name: Autologous Cultured Chondrocytes on Porcine Collagen Membrane
- c. CAS name: N/A
- d. Common name: N/A
- e. INN Name: N/A
- f. Compendial Name: N/A
- g. OBP systematic name: N/A
- h. Other Names:
 - 1) United States Adopted Name (USAN): Not applicable to combination products
 - 2) European Medicines Agency (EMA) international non-proprietary name: Autologous cultured chondrocytes
- i. UNII codes G81HCH560, Porcine (b) (4) Collagen
D5P3K3V822, Autologous Cultured Chondrocytes
- j. NDC labeler code (01) 0 0698661 03001 8

7. PHARMACOLOGICAL CATEGORY: Autologous cellularized scaffold product**8. DOSAGE FORM:** Cellular sheet**9. STRENGTH/POTENCY:** 3 cm x 5 cm cellular sheet consisting of autologous cultured chondrocytes on a resorbable porcine Type I/III collagen membrane, at a density of at least 500,000 cells per cm²**10. ROUTE OF ADMINISTRATION:** Implantation**11. INSPECTIONAL ACTIVITIES:** PLI May 9-13, 2016**12. CONSULTS REQUESTED:**

Hyesuk Kong, Ph.D. (CBER/OCBQ/DBSQ/LMIVTS) – Sterility, Mycolasma, and Endotoxin analytical method validations

Joseph Nielsen, Ph.D., (CDRH/ODE/DSD/PRSB1) - Device Constituent

Latoya Oliver-Powell (CDRH/OC/DMQ/ASDB) - Quality Systems

13. PRECEDENTS**14. ADMINISTRATIVE****A. Signature Block**

Name and Title	Signature and Date
Reviewed by:	
Malcolm Moos, M.D., Ph.D. Cellular and Tissue Therapy Branch DCGT/OTAT/CBER	
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Concurred by:	
Steven Oh, Ph.D. Branch Chief, Cell Therapies Branch DCGT/OTAT/CBER	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewers Summary Recommendation

Recommendation:

The biologics license application (BLA) describes the control of materials, process, and specifications of the biologic constituent. The supporting Master File for the device constituent provides sufficient information to ensure its control and quality. The information as a whole is adequate to support licensure. This BLA is approvable from a product quality perspective.

Product and review overview:

MACI (Autologous Cultured Chondrocytes on Porcine Collagen Membrane), originally developed by Genzyme Corporation and acquired by Vericel in 2014, is intended for the repair of focal lesions in the articular cartilage of the knee. It is a combination product consisting of expanded autologous chondrocytes (biologic constituent; first Drug Substance) seeded onto a processed, (b) (4) porcine collagen membrane (device constituent; second Drug Substance). The expanded autologous chondrocytes and collagen membrane are combined (b) (4). During surgical implantation, it is secured in place with an appropriate fibrin glue.

(b) (4)

The device constituent, ACI-Maix Collagen membrane, of the combination product is a Type I/III collagen scaffold purified from porcine (b) (4) connective tissue. The finished and (b) (4) device is manufactured and supplied by a third party, Matricel GmbH, to the applicant. Matricel submitted a Type 5 Master File for the ACI-Maix Collagen membrane to CBER to support this BLA application. The manufacturing process consists of steps and use of reagents not uncommon to those used in the manufacture of similar FDA-cleared products. Therefore, it was concluded that toxicity risks can be adequately mitigated with the use of lot release specifications, biocompatibility testing, and execution of purchasing controls. The manufacturer conducted a comprehensive characterization of the collagen membrane; however, additional lot release specifications, i.e., (b) (4) will be implemented as Post-Marketing Commitments (PMCs).

The manufacture of the expanded autologous chondrocytes (biologic constituent; first Drug Substance) consists of a biopsy from a non-weight-bearing area of the patient's knee, transport of the biopsy to the manufacturing facility followed by (b) (4) depending on cell numbers obtained to generate the biologic constituent. Optional (b) (4) steps may be included to (b) (4), depending on the anticipated time to membrane seeding. The expanded autologous chondrocytes (first Drug Substance) are then seeded onto the ACI-Maix Collagen membrane (device constituent; second Drug Substance) manufactured by Matricel. The assembled construct is (b) (4) to yield the MACI Drug Product which is subsequently packaged for shipment. Review of the production and process controls for MACI involved both direct observation of the aseptic process during the pre-licensing inspection (PLI) of Vericel's manufacturing facility in Cambridge, MA and review of information submitted to the BLA.

The overall process flow is diagrammed below:

(b) (4)

II. List of Post-market Commitments (PMCs) agreed by the Applicant

1. 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) 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.
2. 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.
 3. 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.

III. Review of Common Technical Document-Quality Module 1



A. Environmental Assessment or Claim Of Categorical Exclusion

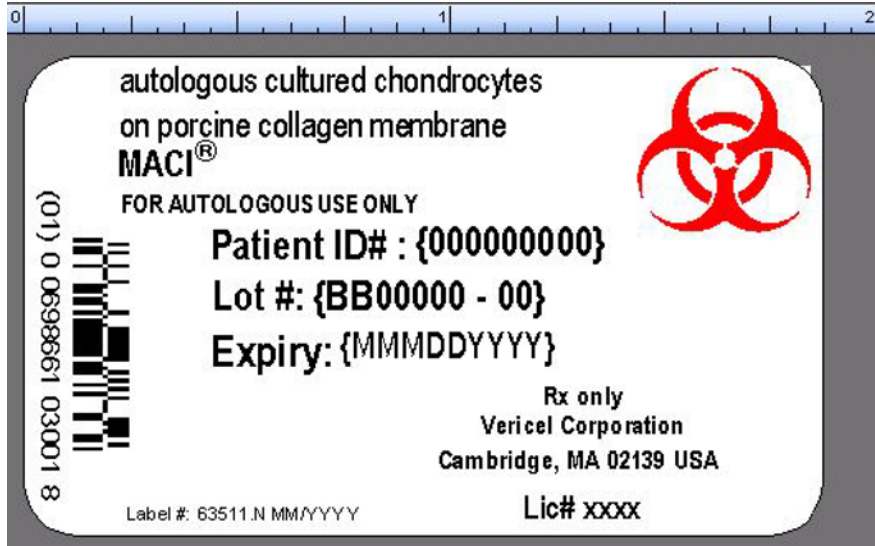
Categorical exclusion is requested. The impact for production and use of this product is (b) (4) at the same facility and presents no additional concerns.

V. Primary Container Labeling Review

Following discussions with the applicant, CBER's Advertising and Promotional Labeling Branch (APLB) found the package and container labels to be acceptable.

MACI Outer Bag Label

autologous cultured chondrocytes on porcine collagen membrane			
		(01) 0 0698661 03001 8	
MACI[®]			
FOR AUTOLOGOUS USE ONLY			
NOT EVALUATED FOR INFECTIOUS SUBSTANCES			
No preservatives. Do not use in patients with known allergies to gentamicin, other aminoglycosides, or products of porcine or bovine origin.			
Patient ID #: {Patient ID}			
{Patient Name}			
{Hospital Name}			
Lot #: {LOT # - Ext}			
Expiration: {MMMDDYYYY}			
Store at Room Temperature. DO NOT FREEZE			
This package contains one 3 x 5 cm MACI implant, consisting of autologous cultured chondrocytes on a resorbable Type I/III collagen membrane at a density of at least 500,000 cells per cm ²			
See package insert for full prescribing information and instructions for administration			
Rx Only			
Vericel Corporation			
64 Sidney Street, Cambridge, MA 02139 USA			
Lic. #: XXXX			
Label #: 64504.N - MM/YYYY			

MACI Dish LabelA photograph of a MACI dish label. The label is white with black text and a red biohazard symbol. It includes fields for Patient ID#, Lot #, and Expiry date, all with placeholder text in curly braces. The label also mentions 'autologous cultured chondrocytes on porcine collagen membrane' and 'FOR AUTOLOGOUS USE ONLY'. A barcode is visible on the left side, and the Vericel Corporation logo is on the right. The label number and license number are at the bottom.

autologous cultured chondrocytes
on porcine collagen membrane
MACI®
FOR AUTOLOGOUS USE ONLY

Patient ID# : {000000000}
Lot #: {BB00000 - 00}
Expiry: {MMMDDYYYY}

Rx only
Vericel Corporation
Cambridge, MA 02139 USA
Lic# xxxx

Label #: 63511.N MM/YYYY

(01) 0 0698661 03001 8

VI. Review of Common Technical Document-Quality Module 3.2**BLA/Review Organizational Note:**

This review has been organized into four main sections consisting of the separate review of the information for each Drug Substance followed by the review of Drug Product and the review of the quality system of the combination product. Reviewer comments are boxed.

- The first Drug Substance consists of the autologous culture expanded chondrocytes. The information for this biologic constituent is located in STN 125603.
- The second Drug Substance consists of the ACI-Maix Collagen membrane. Information for this device constituent is located in STM 125603 and (b) (4).
- The Drug Product is the packaged MACI product. The information for this combination product is located in STN 125603.
- The Quality Systems information for the MACI combination product is located in Module 1.11 of STN 125603.

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DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT**3.2.S DRUG SUBSTANCES****3.1 DRUG SUBSTANCE [Autologous Cultured Chondrocytes]****3.2.S.1 General Information****3.2.S.1.1 Nomenclature**

Not applicable to the Drug Substance. Autologous cultured chondrocytes are the biologic Drug Substance which is continuously manufactured to yield a mature construct consists of biologic and device constituents (Drug Product).

3.2.S.1.2 Structure

The biologic drug substance (DS) is a suspension of autologous expanded chondrocytes (b) (4) gentamicin and (b) (4) fetal bovine serum (FBS).

3.2.S.1.3 General Properties

The cells are (b) (4) and demonstrate typical chondrocyte morphology. They are processed aseptically and tested for sterility.

3.2.S.2 Manufacture**3.2.S.2.1 Manufacturer(s)**

Vericel Corporation
64 Sidney St
Cambridge, MA 02139
USA
FEI: 3002836337

3.2.S.2.2 Description of Manufacturing Process and Process Controls**3.2.S.2.2.1 Batch and Scale Definition**

Product produced from one patient biopsy of approximately (b) (4) constitutes a batch.

3.2.S.2.2.2 Cell Culture and Harvest**Manufacturing process overview**

(b) (4)

S.2 DRUG SUBSTANCE [ACI-Maix Collagen Membrane]

The review of the ACI-Maix Collagen Membrane device constituent of the MACI biologic-device combination product primarily consists of review of the information provided by the manufacturer of ACI-Maix Collagen Membrane in Master File [REDACTED] (hereafter referred to as 'MF'). Supporting information provided by the applicant in the STN 125603 submission is identified and reviewed where applicable. Dr. Joseph Nielsen (CDRH/ODE/DSD/PRSB1) provided consultative input to the review of the ACI-Maix Collagen Membrane. Please refer to the separate review memorandum of the CDRH review consultant of the subject MF for additional detailed information regarding the MF information reviewed, review issues and comments not included in this review memorandum.

3.2.S.1 General Information

The ACI-Maix Collagen Membrane is manufactured by Matricel GmbH solely for use by Vericel Corporation as a device constituent of the MACI biologic-device combination product. 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.

3.2.S.1.1 Nomenclature

Trade Name	ACI-Maix Membrane
Collagen	Porcine Type I and Type III
Form	Sheet
Company Name, Trivial Names used to identify the device constituent in the BLA application and supporting MF	Matricel GmbH, ACI-Maix Membrane, MAIX, AciMaix

3.2.S.1.2 Structure

The ACI-Maix Collagen Membrane is purified from porcine [REDACTED] connective tissue. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

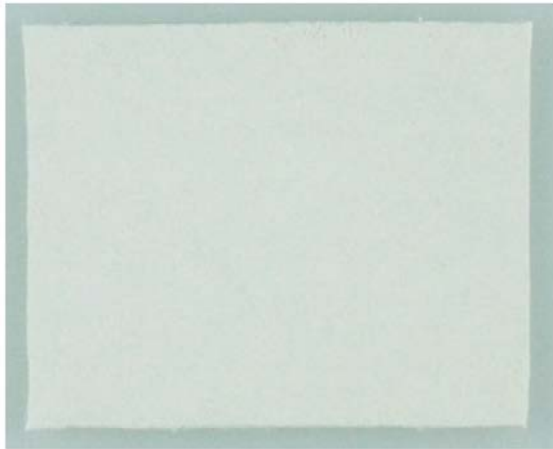
is reviewed in [Section 3.2.S.3.1](#) of this review.

3.2.S.1.3 General Properties

ACI-Maix Collagen Membrane is composed of a purified collagen fibrous network produced from porcine [REDACTED] using controlled manufacturing processes. 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 that 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. 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.

ACI-Maix Collagen Membrane:

“Smooth” Surface



“Rough” Surface



3.2.S.2 Manufacture

3.2.S.2.1 Manufacturers

The design, manufacturing, and packaging processes for ACI-Maix Membrane are carried out at the Matricel facility, except for the activities performed by the subcontractors used for [REDACTED]:

Name	Activity
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

The ACI-Maix Collagen Membrane product is based on Matricel's Covering Membrane (CM) platform technology. ACI-Maix manufacturing starts with the (b) (4) (porcine) tissue purification process according to the CM technology resulting in CM Bulk Material.

Thereafter, manufacturing proceeds with ACI-Maix manufacturing process. An overview of the manufacturing process is presented in the figure below (with more detailed descriptions following).

P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The following description of the Drug Product is reproduced from the BLA submission:

“The MACI drug product is a combination of autologous cultured chondrocyte cells attached to a purified, resorbable porcine-derived, collagen type I/III membrane (ACI-Maix™) at a density of 5×10^5 to 1×10^6 cells/cm² and confirmed positive for expression of chondrocyte-specific marker genes.

The final product is 14.5 cm² in size (3 cm by 5 cm with a small orientation notch cut from one edge). The drug product is packaged in 1 or 2 single-dose containers each consisting of a custom-designed bottom dish, Luer lock lid, and 5-point holding ring designed for easy access of the implant and maintenance of proper orientation during shipment. MACI drug product is shipped in an isotonic medium (excipient) and does not require any thawing, reconstitution, dilution, resuspension, or rinsing steps prior to use. Prior to implanting the drug product, it is sized and cut to fit the exact shape and size of the cartilage defect by the treating physician using a template of the defect.”

The final product components and amounts administered to patients are listed in Table 1 below.

Table 1: Drug Product (Final) Components

Component	Source	Amount Administered	Function
Autologous cultured chondrocyte cells	Biologic Component	5×10^5 to 1×10^6 cells/cm ² of membrane used	Active ingredient for generation of cartilage matrix within defect
ACI-Maix porcine-derived collagen type I/III membrane	Device Component	Cut to fit the shape and size of the patient's cartilage defect	Device component to ensure correct localization of chondrocyte cells within the defect
(b) (4)	(b) (4)	(b) (4)	(b) (4)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

There are two Drug Substances, expanded autologous chondrocytes, reviewed in [Section S.1](#), and porcine collagen type I/III membrane (ACI-Maix), reviewed separately in [Section S.2](#).

3.2.P.2.1.2 Excipients

(b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The transport medium used for Process 1 was (b) (4).

Following the acquisition by Genzyme, Vericel changed the transportation medium to (b) (4).

3.2.P.2.2.2 Overages

Not applicable; the final product is a single collagen membrane with attached cells that is trimmed to fit the patient's lesion(s) by the surgeon.

3.2.P.2.2.3 Physicochemical and Biological Properties

The product consists of expanded autologous chondrocytes attached to a porcine collagen Type I/III membrane. It meets release specifications for minimum cell number, identity, potency. Cells recovered from the membrane displayed chondrocyte-like properties by several in vitro assays, including (b) (4).

3.2.P.2.3 Manufacturing Process Development

As for the Drug Substance, the Drug Product changed during development, primarily between the initial commercial process and that used for the Summit trial (Process 2). These changes are summarized in Table 1 from the Pharmaceutical Development section (3.2.P.2.2.1, beginning on p. 8 of this section of the submission). Note that the site of manufacture for process 2 is indicated erroneously as Cambridge; this material was manufactured in (b) (4).

5 pages have been determined to be not releasable: (b)(4)

3.2.P.2.4 Container Closure System

This was reviewed separately by DMPQ.

3.2.P.2.5 Microbiological Attributes

These were reviewed separately by DBSQC.

3.2.P.2.6 Compatibility

No dosage or delivery devices are used with MACI; it is not reconstituted. Compatibility with container closure components was reviewed separately by DMPQ.

3.2.P.3 Manufacture**3.2.P.3.1 Manufacturer(s)**

Vericel Corporation
64 Sidney St
Cambridge, MA 02139
USA
FEI: 3002836337

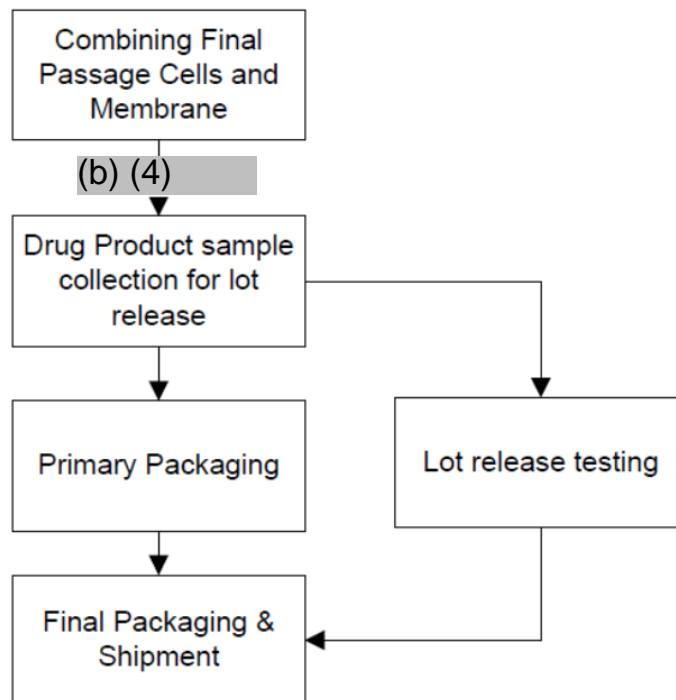
3.2.P.3.2 Batch Formula**Net Formulation for 1 Drug Product Unit¹**

Ingredient	Amount	Function	Reference Standard
Autologous chondrocyte cells	(b) (4)	Active Ingredient	In-house
ACI-Maix membrane	14.5 cm ² per unit	Cell delivery device component	Supplier and In-house
(b) (4)	(b) (4)	(b) (4)	In-house Section 3.2.P.4.1

¹ Dose is patient specific based on the size of the defect(s). Net formula for a two membrane order is 2x each component.

3.2.P.3.3 Description of Manufacturing Process and Process Controls

Figure 1: General Overview of Biological Drug Product Manufacturing Process



(b) (4)




Figure 6: Image of Gross Batch Formulation and Net Formulation and Sample Removed for Release Testing

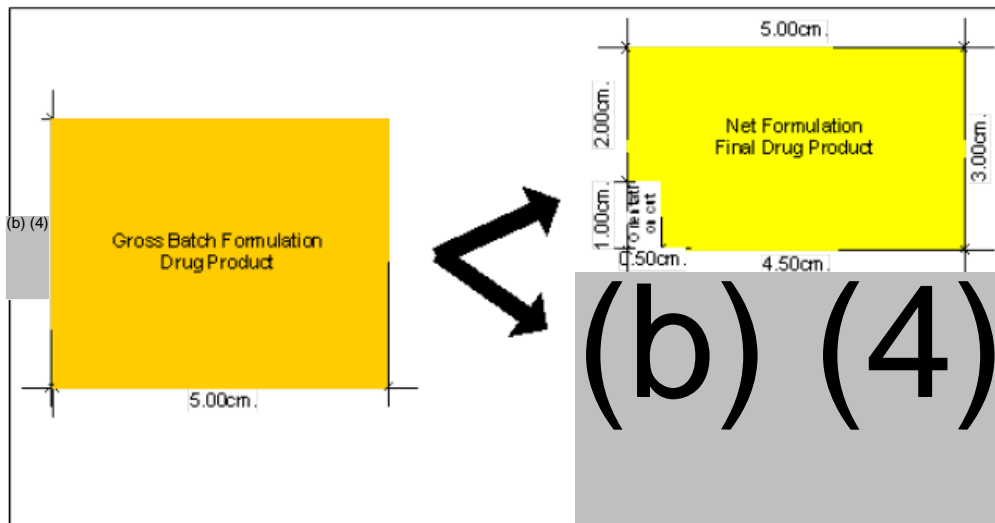
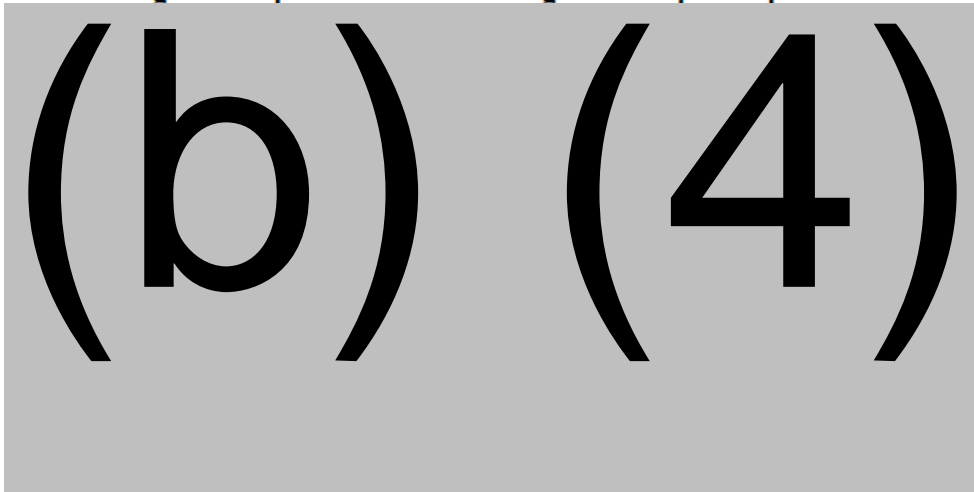


Figure 7: Image of Template Used For Cutting Test Sample Strip



The primary packaging (sterile product dish), lid, and x-ring are removed from packaging and inspected for defects and particles. The product membrane is transferred to the dish, cell side up. The x-ring is replaced to keep the membrane submerged and in place during shipping. (b) (4) are then removed for final container material sterility testing. The dish is sealed with a sterile polycarbonate helical lock cover, labelled, and placed into a (b) (4) secondary pouch, which is then sealed.

3.2.P.3.4 Controls of Critical Steps and Intermediates

These are summarized in Table 1 from 3.2.P.3.4.2, p. 2 of the submission.

Table 1: Process Operating Parameters for Drug Product

Phase	Process Element	Criteria / Target / Range	Rationale/Justification/Supporting Information
Membrane Loading & Incubation	Membrane size for loading (L x W)	(b) (4)	Specification requirement for membrane to be held by loading ring to stay submerged
	Volume of cell suspension for loading	(b) (4)	Volume qualified in 10-088-TR (Section 3.2.S.2.6)
	Number of cells loaded onto membrane	(b) (4) membrane (5×10^5 to $1 \times 10^6/\text{cm}^2$)	Range used for clinical pivotal study (MACI00206) Range qualified in 10-088-TR (Section 3.2.S.2.6)
	Days for membrane incubation	(b) (4)	Validated Range in GTR-654-03-01 (Section 3.2.S.2.5)
(b) (4) & Sample Collection	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)
Primary Packaging	Volume of transport media used in primary container	(b) (4)	(b) (4) used in clinical pivotal trial DP transport (MACI00206) - Volume in dish used during container closure GTR-573-03-01 (Section 3.2.P.2.4) and stability 11-055-TR (Section 3.2.P.8.3)
Product Shipping	Transport Temperature	(b) (4)	11-050-TR and 12-089-TR (Section 3.2.P.8.3) support range

3.2.P.3.5 Process Validation and/or Evaluation

Validations were done with material from (b) (4) different donors and (b) (4) different lots of FBS; (b) (4) membranes were prepared from each cell strain. Each was tested for conformance to the release specification delineated in section 3.2.P.5.1. The summary data from these validations is reproduced from the submission below:

Table 1: Drug Product Process Validation Data Room (b) (4)

(b) (4)

Table 2: Supportive Drug Product Process Validation Data (b) (4)

(b) (4)

It is apparent that all acceptance criteria were met.

An Aseptic Process Validation is described (section 3.2.P.3.5.2), which the applicant commits to performing [REDACTED]. Data from three runs is provided (GTR-753-05-01, section 3.2.S.5). For details, refer to DMPQ review.

Drug Product Transport Validation is described in section 3.2.P.3.5.2. (b) (4)

[REDACTED] and high static (b) (4) and dynamic (b) (4) temperature challenges. Temperature within the dishes was maintained tightly (22-28 °C) through the high temperature challenges. During the cold challenge, the dish temperature ranged as low as 9 °C. This is well within the acceptable limits based on the stability data.

3.2.P.4 Control of Excipients**3.2.P.4.1 Specifications**

The single excipient site is (b) (4)

(b) (4) It is a well-established defined medium containing (b) (4).

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

Not applicable. (b) (4) is a chemically defined medium adequately controlled by vendor Certificates of Analysis.

3.2.P.4.4 Justification of Specifications

This medium has been used for transport of (b) (4) for many years and has consistently maintained stability of these very similar products. It was also used in all clinical studies in this application.

3.2.P.4.5 Excipients of Human or Animal Origin

None.

3.2.P.4.6 Novel Excipient

None.

3.2.P.5 Control of Drug Product**3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)****MACI Release Specifications**

Test Performed	Acceptance Criteria	Reference Standard
Visual Inspection	Intact Membrane No detectable particulates	In house test
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	In house test (based on (b) (4) ; sample cut from final product)
Identity	(b) (4) (Positive for chondrocyte cells)	In house test ((b) (4) to sample cut from final product)
Potency	(b) (4)	In house test (sample cut from final product)
Sterility Final Product**	Negative	(b) (4) conducted on final conditioned medium)
Endotoxin	(b) (4)	(b) (4)
<i>Mycoplasma</i>	Negative	(b) (4)

** Final data will not be available prior to administration of product

Justification of these specifications is covered in the next section.


3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Note: Microbiological safety was reviewed separately by DBSQC.

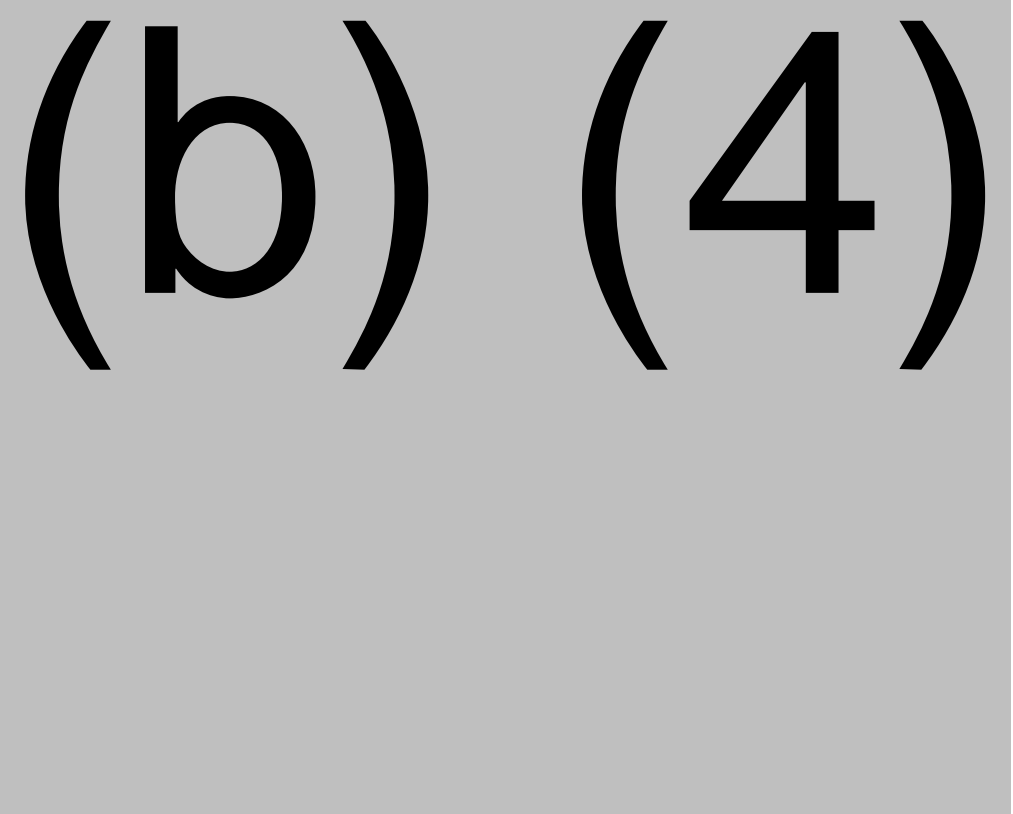
Visual inspection

This is done to assess particulates or possible physical damage to the product. Inspection is done against both a white and black background 30-60 cm from the evaluator's eye.

(b) (4)



(b) (4)



3.2.P.5.3.4 Identity

(b) (4)

(b) (4)

The assay was validated as a (b) (4) using over (b) (4) samples. The validation acceptance criteria and performance are summarized in the table below:

Table 3: Identity Validation Summary

Evaluation	Criteria	Results
Accuracy	(b) (4)	(4)

(b) (4)

These performance characteristics are excellent, consistent with current best practices for [REDACTED]. The development reports confirm that the assay is robust even to a significant degree of [REDACTED].

Potency

The potency assay, termed the ^{(b) (4)}, is also based on (b) (4)

[REDACTED]

(b) (4)

As for the identity assay, these performance characteristics too are excellent, and consistent with current best practices.

It should be noted that initially, no specification was established for the lower limit of [REDACTED] expression (which would correspond to an upper limit for the [REDACTED]). Thus, the specification of [REDACTED]. It was recommended that a lower limit for [REDACTED] (upper limit for [REDACTED]) be established.

This issue was discussed with the applicant, and an amendment was submitted to the BLA that addressed this concern by setting an acceptance limit for the assay as requested.

Sterility, Endotoxin, Mycoplasma

Microbiological safety testing was reviewed by DBSQC. Some concerns regarding the sterility testing validation (choice of test strains, incubation temperatures) were discussed and communicated to the applicant, and resolved by the submission of additional validation data in an amendment to the BLA; see DBSQC review for details.

3.2.P.5.4 Batch Analyses

Release specifications for (b) (4) lots, (b) (4) membranes from each, are tabulated; all values are well within the acceptance criteria.

3.2.P.5.5 Characterization of Impurities

The identity assay evaluates (b) (4)

(b) (4) assay is used to determine (b) (4).

Microbiological safety testing was reviewed by DBSQC to assesses microbial contaminants and endotoxin (see the DBSQC review for details).

Measurement of residual gentamicin in (b) (4) lots determined an average of 9.2 µg per membrane (GTR-658-05-01), approximately 8700 fold below a typical therapeutic dose for patients with severely compromised renal function; for a patient with normal renal function, the figure is 26,000-52,000. Thus, no release specification for this potential impurity is needed (3.2.P.5.5.2.1, p. 2). A similar analysis was conducted for (b) (4)

(b) (4). As such, no release specification is needed.

Residual FBS was also measured (GTR-658-05-01) and found to be below the assay limit of detection of (b) (4). MACI is contraindicated in patients who are allergic to bovine products, so no release specification has been established.

The impurities profile is acceptable.

3.2.P.6 Reference Standards or Materials

Given the large variation from one lot to the next, due to the autologous nature of the product, reference standards are not applicable.

3.2.P.7 Container Closure System

See the DMPQ review for details.

3.2.P.8 Stability**3.2.P.8.1 Stability Summary and Conclusion**

Evaluations were done at (b) (4) for varying time points (0, 4, 6, (b) (4)) at low and high seeding density, using the final product release specifications and three donor lots with

(b) (4) membranes apiece (study 11-055-TR). At these temperatures, the final product remained within specification at each time point. Though there was some variability within the data set, no trend with storage time was apparent. The data support a (b) (4) day margin for error past the stated dating period of six days at both temperatures. Similar studies were done for stressed conditions: (b) (4). The identity assay results dropped with time at (b) (4), but remained with specification. (b) (4)

(b) (4)

Finally, stability to actual transport was assessed by assaying product lots in (b) (4), shipping them to Cambridge, and holding them at ambient temperature until six days after the actual packaging date to reflect the proposed dating period. No significant differences between the two time points were apparent, supporting a dating period of 6 days under the labeled storage conditions of “Store at room temperature. Do not freeze”. The supporting data are provided below.

3.2.P.8.2 Post-Approval Stability Commitment

The applicant committed to testing a minimum of (b) (4) per year using the same lot release criteria.

3.2.P.8.3 Stability Data

Table 7, summarizing the conclusions, is reproduced from section 3.2.P.8.3, p. 8 of the submission.

Table 7: Stability of Drug Product Post Shipping (Study 11-050-TR)

Lot Number ¹	(b) (4)		(b) (4)		Identity (b) (4)		Potency ²				Sterility No Growth	
	(b) (4)		(b) (4)				(b) (4)		(b) (4)			
	(b) (4)	(b) (4)	(b) (4)	(b) (4)	Day 0	Day 6	Day 0	Day 6	Day 0	Day 6	Day 0	Day 6
010411A-2 day, Max	(b) (4)	(b) (4)	(b) (4)	(b) (4)	5.23	7.11	21.07	21.45	-7.02	-6.59	Pass	Pass
010411A-2 day, Min	(b) (4)	(b) (4)	(b) (4)	(b) (4)	6.69	7.13	20.39	21.03	-5.31	-5.29	Pass	Pass
010411B-2 day, Max	(b) (4)	(b) (4)	(b) (4)	(b) (4)	6.11	5.73	22.67	21.48	-5.07	-5.38	Pass	Pass
010411B-2 day, Min	(b) (4)	(b) (4)	(b) (4)	(b) (4)	6.59	5.90	22.78	21.05	-5.12	-5.06	Pass	Pass
010411C-2 day, Max	(b) (4)	(b) (4)	(b) (4)	(b) (4)	6.63	7.46	20.38	22.07	-5.59	-5.96	Pass	Pass
010411C-2 day, Min	(b) (4)	(b) (4)	(b) (4)	(b) (4)	6.73	7.47	21.13	21.11	-5.29	-5.18	Pass	Pass

¹ Noting minimum and maximum loading density as “Min” and “Max.”

² Study 11-050-TR criteria was conducted with an acceptance criterion for (b) (4) and a potency specification /acceptance criterion of (b) (4). Values have been updated in this table to reflect current criterion in the submission as (b) (4) and potency as (b) (4). Potency (b) (4) data was extracted from the study report and included in table next to the original cycle time value.

Additional studies (13-037-TR, 13-037-TR) were performed using the proposed commercial process in the Cambridge facility with a total of (b) (4) lots, (b) (4) membranes per lot. MACI product was placed in final packaging and held between (b) (4) for (b) (4) days. All of the same specifications used in the previous studies were met.

3.2.A Appendices Table of Contents

3.2.A.1 Facilities and Equipment
Reviewed by DMPQ.

3.2.A.2 Adventitious Agents Safety Evaluation
Reviewed by DBSQC.

3.2.A.3 Novel Excipients
None.

3.2.R Regional Information (U.S.A.)

3.2.R.1 Executed Batch Records
Batch records for three lots are provided.


3.2.R.2 Method Validation Package
The method validations are given in Table 2 from this section, reproduced below:

MACI Drug Product Test Methods and Validations

Test	Acceptance Criteria	Testing Facility	Validation	
			Method	Report
Visual Inspection	Intact Membrane No detectable particulates	Vericel	Section 3.2.P.5.2	Visual method
(b) (4)	(b) (4)			GTR-508-04-01 GTR-542-04-01 Summarized in Section 3.2.P.5.3
(b) (4)	(b) (4)			GTR-529-04-01 GTR-547-04-01 Summarized in Section 3.2.P.5.3
Identity	(b) (4) (Positive for chondrocyte cells)			GTR-524-05-01 Summarized in Section 3.2.P.5.3
Potency	(b) (4)			GTR-524-05-01 Summarized in Section 3.2.P.5.3

Sterility Final Product	Negative			GTR-139-03-01 GTR-168-03-01 Summarized in Section 3.2.S.4.3
Endotoxin	(b) (4)			GTR-541-04-12 Summarized in Section 3.2.P.5.3
<i>Mycoplasma</i>	Negative			GTR-603-04-01 GTR-603-04-01-A Summarized in Section 3.2.P.5.3

(b) (4)



approval.

COMBINATION PRODUCTS CGMPs [21 CFR Part 4] –Quality System

1. General Information

1.1. Combination Product Category

Biologic-device combination (21 CFR Part 3 combination product)

1.2. Type of Combination Product

Single entity (two or more regulated constituent parts that are physically, chemically or otherwise combined and produced as a single entity)

1.3. Constituent Parts

Biologic: Autologous cultured chondrocytes

Device: ACI-Maix Collagen Membrane

1.4. Final Combination Product and Constituent Manufacturers

1.4.1. Final Combination Product Manufacturer

Vericel Corporation

64 Sidney Street

Cambridge, Massachusetts 02139

1.4.2. Constituent Manufacturers

1.4.2.1. Biologic

Vericel Corporation

Autologous cultured chondrocytes are manufactured on-site and combined with the device constituent part to produce the MACI biologic-device combination product.

1.4.2.2. Device

Matricel GmbH

Kaiserstrasse 100

D-52134 Herzogenrath, Germany

The ACI-Maix Collagen membrane is manufactured by Matricel solely for use by Vericel Corporation as a device constituent of the MACI biologic-device combination product.

1.5. Manufacturing Flow

1.5.1. Production and Process Controls

MACI Manufacturing Flow with QC Sample Points

Drug Substance

(b) (4)

MACI Manufacturing Flow with QC Sample Points
Drug Product

(b) (4)

Production and process controls were reviewed during the on-site PLI conducted by CBER and deemed acceptable.

1.5.2. Acceptance Activities

Vericel controls the manufacturing of the combination product and performs the acceptance activities for:

- a. receiving of the device constituent part and materials/components to be used in the combination product;
- b. in-process testing performed during the manufacturing/assembly;
- c. final release of the combination product

The information described above is covered by the drug and biologic cGMPs and was evaluated during the PLI inspection and Master File and BLA submission review. The information reviewed has been deemed adequate by the Facilities reviewer and Product Quality team.

2. Device Quality System Regulation Provisions Review [21 CFR Part 820]

Vericel is applying the drug CGMP-based streamlining approach established under 21 CFR 4.4(b)(1) and will therefore comply with the drug CGMPs and specified provisions from the Quality System (QS) regulation (and CGMP requirements for biological products, as applicable).

During the PLI, the necessary documentation did not exist to demonstrate the applicant's compliance with most of the specified provisions from the QS regulation. As a result, a PLI 483 observation was issued to the applicant noting the absence of documentation for the MACI combination product regarding management responsibility, design controls and corrective and preventive actions (CAPA). In the review that follows, the documentation submitted in response to the PLI 483 observation in amendments STN 125603/0014 and 0018, dated 9/21/2016 and 11/14/2016, respectively, Module 1.11, as well as through interactive review to address each of the applicable specified provisions from the Quality System (QS) regulation are reviewed accordingly. Latoya Oliver-Powell (CDRH/OC/DMQ/ASDB) provided consultative input in the evaluation of the applicant's compliance with applicable QS requirements for the approvability of BLA 125603.

Document QA1-010 Vericel Cambridge Quality Manual, Revision Q (dated 25JUL16) is the governing document that describes the quality system of the Vericel Cambridge facility as required by conformance to relevant regulations, standards, and guidance documents. It provides an overview with reference to specific SOPs to all customers, suppliers, and employees of the specific controls implemented at the Vericel Cambridge facility to ensure the quality of products and services.

2.1. Management Responsibility [21 CFR 820.20]

Document: QA1-010 Vericel Cambridge Quality Manual, Revision Q (dated 25JUL16)
The Vericel Cambridge Quality Manual

2.1.1. Quality Policy

"The Vericel Cambridge facility designs, manufactures, and distributes therapeutic products based on tissue culture technology. We provide for our

personnel and customers an environment of quality excellence with a commitment to comply with regulatory requirements and continually improve the effectiveness of the Quality Management System.”

2.1.2. Quality Plan

The site publishes a quality plan establishing key quality performance indicators (QPIs) that assist the site in monitoring the ongoing health of the Quality Management System. Quality plan documents are published each year as a technical report, and receive a closeout report recording the site’s performance against the established QPIs. These QPIs and additional metrics are also reviewed at intervals throughout the year as part of the Quality Management Review program per QA1-045.

2.1.3. Organizational Structure

Management will assign qualified employees to all functions which may affect quality. Quality system documents, supported by job descriptions, shall define the qualifications, responsibilities, and authority of these employees. Organizational charts and job descriptions are maintained per QA1-028.

The applicant has created a Quality Council designed to approve and communicate quality goals and objectives to the site, monitor performance, and maintain quality systems. It is co-chaired by the Site Operations and Site Quality Heads. Members of the Quality Council include, but are not limited to, department heads (or equivalent) covering Manufacturing, Supplier Management, Quality Operations, Quality Systems, Validation, Research and Development (R & D), Engineering, Facilities, and Regulatory Affairs.

2.1.4. Management Review

The applicant states that management shall review key performance indicators of the quality management system quarterly to ensure its continuing suitability, adequacy, and effectiveness per QA1-045. The review includes assessing opportunities for improvement and the need for changes to the QMS, including the quality policy and quality objectives. The review will include, but not be limited to, the following elements:

- Results of regulatory inspections and findings, audits, and commitments made to regulatory agencies
- Customer complaints, recalls, interdictions
- Conclusions of process performance and product quality monitoring
- Process control performance indicators (e.g. Deviation, CAPA, and change management)
- Effectiveness of process and product changes including those arising from corrective actions and preventive actions
- Follow-up actions from previous management reviews

- Provision, training, and/or realignment of resources
- Recommendations for improvement

Document: QA1-045 Quality Management Review, Revision A (dated 18JUN13)

The QA1-045 SOP defines the process for Quality Management Review (QMR) for which the overall objective is to monitor, evaluate, and continually improve the Quality Systems and related processes.

The information provided for quality policy, quality plan, and management review procedures supports top-level commitment to quality. It should be noted that in the response for the request for the SOP for Purchasing controls which also references the QA1-045 QMR document, Vericel indicated that this SOP is under revision as Vericel continues to transition from Genzyme/Sanofi systems and procedures. Therefore, the applicant has preliminarily addressed the requirements of 21 CFR 820.20. The applicant will complete revisions to the subject SOP and implement the procedures by February 28, 2017 (PMC).

2.2. Design Controls [21 CFR 820.30]

In response to 483 PLI Observation #3.b, the applicant has developed procedures to implement design controls.

Document: QA3-054 Design Control, Revision N (dated 29JUL16)

This SOP describes the process by which the design and development of new or modified medical device/combination products are controlled by Vericel during the development cycle to ensure that product specifications are properly established and that the design released to production meets those requirements. Five stages of design control are outlined in the table below.

Stage	Name of Stage	Description (Typically includes)
(b)		(4)

(b) (4)

The MACI product was not historically developed under a formal Design Control program. Therefore, some early-stage deliverables required by Design Stages 0 through 3 are not available and cannot be retroactively created. Vericel indicates that the MACI product is currently considered to be in Stage 4, “Product Launch”, under this newly implemented system.

2.2.1. Design History File

Document: QA-052 Design History File (DHF) (16-041-TR, Implemented 29JUL16)

Vericel has compiled a Design History File (DHF) for the MACI combination product. A DHF was not compiled throughout the development of MACI by Genzyme, from whom Vericel acquired the product in May of 2014. Therefore, Vericel created an initial MACI DHF retrospectively. The current DHF consists of 9 volumes of which a scanned copy was submitted in STN 125603/0014, received 9/21/2016. It should be noted that all appropriate reports, procedures, and documents are referenced by number and title in the DHF and many are available in the BLA submission, however copies of all referenced site documents (e.g., equipment qualification) are not included in the attached scanned copy. All documents are maintained onsite within document management systems according to Vericel site procedures.

- The applicant has compiled a comprehensive DHF which is organized to provide documentation in parallel with the requirements of 21 CFR 820.30. The DHF describes activities regarding design and development plan, design input, design output, design verification and design validation. Additionally, the DHF contains risk assessments.
- There are incomplete sections in the DHF as the product is currently in Stage 4 of the Design Stage. It is indicated that these sections will be completed either before completing of Design Stage 4, or afterwards during Design Stage 5, Post Marketing. This is acceptable.

2.2.2. Design Reviews

Document: QA3-051 Design Reviews (Implemented 29JUL16)

This document is intended to provide the minimum requirements for project teams on how to prepare, conduct and document formal design reviews during the development process.

The Design Reviews SOP supplements the Design Control procedure detailed in QA3-054 and adequately addressed 21 CFR 820.30(e). The DHF indicates that due to the legacy status of the MACI product documented Design Review at Stages 0 through 3 of MACI development are not available and cannot be retroactively created. A Design Review will be held and documented as a Design Stage 4 deliverable prior to product launch. This is acceptable.

2.2.3. Design Transfer and Change Control

Design Transfer and Change Control are described in Sections 7.1.9 and 7.8, respectively of SOP QA3-054 Design Control, Revision N (dated 29JUL16). Change control involves requirements either while a project is still open and has not been released to market (Pre-Market Document Version Control) or after a product has been released to market (Post-Market Change Control).


The Design Control SOPs and Design History File with accompanying attachments, together adequately address the requirements of 21 CFR 820.30.

2.3. Purchasing Controls [21 CFR 820.50]

The purchase of any materials, equipment, or services required to meet product and/or quality system requirements must be subject to purchasing controls.

2.3.1. Evaluation, Control and Records of Suppliers

(b) (4)



(b) (4)

Risk Category	User Requirements	Audit Schedule
1	(b) (4)	
2		
3		

Quality Control and Quality Compliance will maintain the list of approved suppliers and perform audits of these suppliers in accordance with the schedule.

2.3.2. Purchase and Receipt

Based on material use and demand, Materials Management will place orders with suppliers using the part numbers and associated approved material specifications. Upon receipt, all materials that require QC inspection are received as quarantine until the material can be inspected. Vericel Quality Control Raw Materials will inspect all quarantined materials against the material specifications and release the materials for use only if all requirements are met. Rejected materials will be returned to the supplier or discarded. Rejection of materials will initiate an investigation with the supplier and, where necessary, documented corrective actions.

2.3.3. Supplier Changes

In accordance with requirements of the signed Quality Technical Agreements, all suppliers of GxP materials are required to notify Vericel of any changes to the components, manufacture (both process and location),

specifications, and packaging of the material provided to Vericel. Appropriate Vericel subject matter experts perform an internal assessment of the change to determine any potential impact to the material and product, if qualification/validation is required, as well as any regulatory implications. Vericel will initiate the Supplier Change Notification procedure for any changes to components, manufacture, specifications, and packaging and will review the changes at the regularly scheduled Supplier Management Team meeting. Based on the nature of the change, actions could include deviations, change controls, initiation of Supplier Corrective Actions, and identification and qualification of new suppliers for the material or service. Supplier events and corrective actions are reviewed during Quarterly Management review.

2.3.4. ACI-Maix Membrane – MACI Device Constituent

ACI-Maix Membrane, the device constituent supplied by Matricel, is a Risk Category 1 Inspection Class IV material. As such, in place are a business assessment, confidentiality agreement, routine site audits (most recent October 04-05, 2016), a Quality Technical/Business Agreement, and material qualification requirements documented in a material specification.

Document: MP1-005 Purchasing Controls Vericel Cambridge, Revision A (for implementation on 30NOV16)

The following SOPs referenced within MP1-005 were provided on November 14, 2016 in STN 125603/0018:

SOP Number	SOP Title
MP1-001*	Procedure for Receipt and Distribution of Quality Control Inspected Materials
MP1-004	Return Goods Authorization Procedure
MP2-007	Performing a Business Assessment of a New GxP Supplier
MP2-008	Creating a Business Agreement
MR1-003*	Creating a Purchase Order
QA1-006	Material, Service or Vendor Request Procedure
QA1-042	Supplier Management Team
QA1-045*	Quality Management Review
QA1-054*	Supplier Change Notification
QA1-055	Approved Supplier List

QA1-071	Quality Technical Agreements (in final approval stages within documentation management system)
QA3-002	Guidelines for Deviations and Investigations in Trackwise
QC1-002	Quality Control Inspected Materials Program
QC1-055*	Supplier Corrective Action Request Procedure

* Previously provided in response to September 22 request

It should be noted that in the response for the request for SOP for Purchasing Controls MP1-005, which also references the QA1-045 QMR document, the applicant indicated that this SOP is under revision as Vericel continues to transition from Genzyme/Sanofi systems and procedures.

Document: Quality Service Agreement between Vericel Corporation and Matricel GmbH date of issue (October 20, 2015)

The Quality Agreement constitutes the technical agreement required under European Manufacturing Practice (GMP) legislation 2003/94/EC Article 12, and FDA GMP 21 CFR 210, 211 to cover the final packaged ACI-Masic membrane product manufactured by Matricel. The Quality Agreement is intended to fulfill the requirements of 21 CFR 820.50 Purchasing Controls.

The Purchasing Controls summary, relevant SOPs and Quality Service Agreement between the applicant and manufacturer of the device constituent, all provided by the applicant in STN 125603/ 0018, dated 11/14/2016, adequately address the requirements of 21 CFR 820.50.

2.4. Corrective and Preventive Action (CAPA) [21 CFR 820.100]

The applicant has provided a copy of its Quality Manual QA1-010. The manual included a section regarding how the firm handles its CAPAs. SOPs referenced within were provided for review in STN 125603/ 0018, dated 11/14/2016:

SOP Number	SOP Title
QA3-027	Guidelines for CAPA, Task and Effectiveness Review Records in Trackwise
CS1-039	Vericel Product Event Intake Procedure
QA1-001	Event Investigation Procedure
QA3-002	Guidelines for Deviations and Investigations in Trackwise
QA1-044	Periodic Product Review
QA1-045	Quality Management Review

According to the applicant, 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 applicant 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 applicant stated that the procedures include determining whether preventive and corrective actions should be taken based on the identified nonconformance. Additionally, the applicant 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 applicant, 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 supports that the applicant has established procedures and controls for implementing corrective and preventive action as required per 21 CFR 820.100.

2.5. Installation [21 CFR 820.170]

This requirement is not applicable to this combination product.

2.6. Servicing [21 CFR 820.200]

This requirement is not applicable to this combination product.

BLA 125603 is approvable from the perspective of the applicable Quality System Requirements based on the information amended to the application and reviewed on the PLI. The CDRH compliance consultant is in agreement with this determination. However, the applicant will commit to completing revisions to all documentation requiring such in the transition from Genzyme/Sanofi systems and procedures and to implement the procedures by February 28, 2017 (PMC).