



Our STN: BL 125603/0

**BLA FILING REVIEW  
ISSUES IDENTIFIED**

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

**March 17, 2016**

Dear Ms. Aguilera:

Please refer to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, and to our filing letter dated March 4, 2016. While conducting our filing review we identified the following potential review issues:

**PRODUCT INFORMATION**

The following comments refer to the cross-referenced (b) (4) .

1. Purified collagen may contain (b) (4) even when derived from relatively acellular tissue such as (b) (4) membranes. (b) (4) , which could affect the safety profile of the device component. In addition, (b) (4) evaluation is considered important to demonstrate product manufacturing consistency and for evaluating the (b) (4) . Therefore, please include (b) (4) testing as a covering membrane (CM) bulk material quality inspection item and provide a specification and discussion for the release specification with supportive data. Alternatively, please provide a (b) (4) assessment of the ACI-Maix Membrane from representative lots with sufficient process validation data to the Master File.
2. The Master File includes a (b) (4) genotoxicity assay. However, no (b) (4) genotoxicity assay is capable of (b) (4) genotoxic mechanisms. A (b) (4) genotoxicity assays should be conducted as recommended in (b) (4) and per FDA's recognition of this standard. The genetic toxicity test battery for medical devices should include at least (b) (4) assays including (b) (4) . As you have previously conducted the (b) (4) , please conduct an additional (b) (4) genotoxicity studies to provide a comprehensive evaluation of the genotoxicity of the ACI-Maix Membrane.

Please note that you as the BLA holder should be made aware of any changes made to the device constituent (Matricel ACI-Maix Collagen Membrane) of your combination product, and ensure that any such changes are properly reported to both the BLA and the Master File (MF). We recommend that you discuss with the MF holder a mechanism, such as a quality agreement, by which you will be informed of any changes relevant to the device constituent. You may wish to consider recommendations on Quality Agreements in the Draft Guidance for Industry: Contract Manufacturing Arrangements for Drugs: Quality Agreements (March 2013), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm353925.pdf>. The guidance also provides information on the obligations of the BLA holder and contract manufacturers.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

If you have any questions, please contact the Regulatory Project Manager, Ron Chamrin, at (240) 402-8269.

Sincerely yours,

Raj K. Puri, MD, PhD  
Director, Division of Cellular and Gene Therapies  
Office of Cellular, Tissue, and Gene Therapies  
Center for Biologics Evaluation and Research