



CBER REGULATORY REVIEW MEMORANDUM

Date 23 November, 2016

From Hyesuk Kong, Ph. D.
Laboratory of Microbiology, *In-Vivo* Testing and Standards (LMIVTS)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biologics License Application: Submission Tracking Number # 125603/0

Subject BLA: Review of (b) (4) Sterility and (b) (4)
Mycoplasma Test Method Validations; and Bacterial Endotoxins Test Method
Qualification for Matrix Applied Characterized Autologous Cultured Chondrocytes

Through James L. Kenney, D.Sc., Chief, LMIVTS/DBSQC/OCBQ/CBER/FDA
William M. McCormick, Ph.D. Director, DBSQC/OCBQ/CBER/FDA

Applicant Vericel Corporation (Vericel)

Product Matrix Applied Characterized Autologous Cultured Chondrocytes (MACI)

Biologics License Application (BLA) Submission Tracking Number (STN) 125603/0

Submission Received by CBER 4 January, 2016

Review Completed 23 November, 2016

Material Reviewed

Method validations for: 1) (b) (4) sterility test and 2) (b) (4) using (b) (4) for the detection of mycoplasma performed on the drug product (DP); and method qualification for (b) (4)-bacterial endotoxin test ((b) (4)-BET) performed on the DP. In addition, the responses to CBER's Information Request (IRs) received 16 June, 11 October, and 18 October of 2016 were also reviewed.

Executive Summary

After a thorough review of this BLA, and the responses to CBER's IRs (Amendments 125603/0/9, 125603/0/19, and 125603/0/20), this reviewer finds Vericel's (b) (4) sterility test and (b) (4) Mycoplasma test methods were validated in accordance with (b) (4) and (b) (4), respectively, by demonstrating the tested product matrixes are suitable for these intended test methods. Also, (b) (4)-BET method was qualified in accordance with (b) (4) by demonstrating the MACI matrix is suitable for the intended test method. In addition, Vericel demonstrated the (b) (4) sterility and (b) (4) mycoplasma test methods provide assurance of the safety and purity of their Vericel's DP equal to or better than the assurance of the current compendial methods.

Background

On 4 January, 2016, Vericel submitted a BLA for MACI™ (matrix applied characterized autologous cultured chondrocytes) for the indication of repair of symptomatic, full-thickness cartilage defect(s) of the knee, with or without bone involvement (b) (4) in adults.

MACI is an autologous implant consisting of characterized cultured chondrocytes (biological component) seeded onto a resorbable Type I/III (ACI-Maix™) collagen membrane (device component). The autologous cultured chondrocytes and final MACI product are manufactured by Vericel, Cambridge, MA, while the ACI-Maix membrane is manufactured and supplied by Matricel GmbH, Germany (b) (4) exclusively for Vericel. The cultured chondrocytes in this MACI product is (b) (4).

MACI is implanted with the cell-side down. The implantation is performed using sterile surgical techniques and requires both the preparation of the defect bed and the application of fibrin sealant to the base and rim of the defect in order to secure the implant. Each implant 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 cm² to be trimmed by the surgeon to the size and shape of the defect. During the manufacturing processing, Gentamicin (an antibiotic) is used in the chondrocyte cell expansion media for during the formulation of the drug substance to lower the risk of contamination. The (b) (4) and MACI DP are tested for sterility and the presence of mycoplasma and bacterial endotoxin. Since the product is too short lived to adequately test for contamination prior to administration to patients, (b) (4).

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission: the confirmatory testing of submitted product samples; review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on the validation of the (b) (4) system for sterility and (b) (4) using (b) (4) for mycoplasma testing of Vericel's DP, to determine if this product matrix is suitable for testing using the intended method and if these methods provide sterility or mycoplasma assurance equal to or greater than the compendial methods; in addition, the qualification of (b) (4)-BET method performed on the DP to ensure the DP matrix is suitable for the intended test method.

Review

(b) (4) Sterility Test Validation

Vericel was requested to revalidate their (b) (4) sterility test method for limit of detection (LOD), (b) (4) and its LOD study did not meet CBER's current validation standards for an

alternate test method. However, CBER found the validation parameters of specificity, repeatability, ruggedness and equivalence acceptable in their (b) (4).

Vericel validated their (b) (4) sterility (b) (4) method, to ensure the (b) (4) is capable of detecting a wide variety of microbial organisms. The (b) (4) validation was performed using (b) (4) media type (b) (4) at (b) (4) for (b) (4) incubation.

Limit of Detection (LOD):

The LOD was assessed by demonstrating the lowest number of microorganism recovered from the sample matrix, as the test specification is (b) (4). Vericel performed their (b) (4) sterility LOD study using (b) (4) in accordance with (b) (4). The test was performed on (b) (4) DP lots ((b) (4)) using (b) (4) and (b) (4) environmental microorganisms ((b) (4)) known from the MACI product manufacturing environment (Table 1).

Table 1: Microorganisms used in the (b) (4) Re-Validation Study

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Overall, Vericel demonstrated the (b) (4) method was better than or equivalent to (b) (4) test method in detecting the tested microorganism in the MACI's DP.

A few testing and manufacturing deviations were noted in the test results, these were reviewed and found to have no impact on their LOD validation results.

(b) (4) -BET Method Qualification for Drug Product

Vericel qualified their (b) (4) -BET method on (b) (4) of MACI DP to demonstrate their DP matrix is suitable for the intended test method in accordance with (b) (4).

(b) (4)

(b) (4)

This reviewer finds their proposed BET release specification of (b) (4) for MACI DP acceptable.

Thus, CBER finds MACI DP is suitable for testing using the intended test method.

(b) (4) Mycoplasma Test Validation

(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Comparability Study

Vericel performed a comparability study between (b) (4) and the compendial (b) (4) method using (b) (4) as a reference (b) (4) in (b) (4) MACI samples to evaluate equivalency via parallel testing. (b) (4)

Based on the results of this study, Vericel concluded the (b) (4) method is better than the compendial (b) (4) method.

The (b) (4) method using (b) (4) assay with (b) (4) sample preparation and (b) (4) kits was validated in accordance with guidance provided under (b) (4) and (b) (4).

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds Vericel's MACI DP's matrix is suitable for testing using their sterility, mycoplasma, and bacterial endotoxin test methods and the validation and qualification were performed in accordance with (b) (4) and (b) (4), respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.