



CBER REGULATORY REVIEW MEMORANDUM

Date 24 June, 2021

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Food and Drug Administration (FDA)

To Biological License application (BLA) Submission Tracking Number 125734/0

Subject BLA: Review of (b) (4) and Bacterial Endotoxin Test
Method Qualifications for Donislecel

Through Maryna Eichelberger, Ph.D., Director, DBSQC
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Applicant CellTrans

Product Purified Allogeneic Islets of Langerhans for Transplant (Donislecel)

Biological License Application Submission Tracking Number (STN) 125734/0

Submission Received by CBER 19 May, 2020

Review Completed 24 June, 2021

Material Reviewed

Method validation for a (b) (4) sterility test method and a qualification for a bacterial endotoxin test method. In addition, information request (IR) response received 16 December of 2020 was also reviewed.

Executive Summary

After a thorough review of this BLA, this reviewer finds the (b) (4) sterility test method was validated in accordance with (b) (4) and the bacterial endotoxin test method was qualified in accordance with (b) (4). Both test methods were demonstrated to be suitable under the actual conditions of use.

Background

On 19 May, 2020, CellTrans resubmitted this BLA for Donislecel, an allogeneic pancreatic islet cellular therapy indicated for the treatment of brittle Type 1 diabetes (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy. The original submission was submitted on 31 May, 2017 and withdrawn on 14 July, 2017. Please see STN 125651/0 for additional information.

Donislecel is a suspension of viable allogeneic islets of Langerhans (i.e., hormone-secreting cells) including β -, α -, pancreatic peptide-, δ - and ϵ -cells derived from the pancreas of a deceased donor. The manufacturing process for Donislecel is continuous starting from the qualification of incoming donor pancreas and ending with islet cell harvest and suspension. The final drug product (DP) consists of an infusion bag containing up to a maximum of 1×10^6 equivalent islet number (EIN) cells from a single donor, formulated in buffered transplant medium supplemented with HEPES buffer and human serum albumin. The route of administration is intraportal infusion into the hepatic portal vein using a catheter. The recommended minimum dose is 5,000 EIN/ kg patient body weight for initial transplant and 4,000 EIN/kg patient body weight for subsequent transplants. The maximum dose should not exceed 10 cc per transplant or 1×10^6 EIN. Additional transplants may be required to achieve an adequate clinical response.

The DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and suitable under the actual conditions of use. 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, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released per their product's licensed test method specifications. Therefore, this review will focus on the validation of the (b) (4) sterility test and the qualification of bacterial endotoxin test methods to ensure they are suitable for their intended use.

Review

(b) (4) Sterility Test Validation

The (b) (4) sterility test system complies with the (b) (4) method of (b) (4) in that a (b) (4)

(b) (4)

CellTrans performed a detailed validation study for their (b) (4) sterility system for Donislecel that covered limit of detection (LOD), specificity, robustness and ruggedness in accordance with (b) (4) as well as a comparability study with the (b) (4) sterility method. Repeatability results were determined from LOD and ruggedness experiments. Throughout the validation, tests for each microorganism were performed in (b) (4)

The (b) (4) validation was performed using (b) (4)

(b) (4)

(b) (4)

Limit of Detection (LOD):

The LOD was assessed by (b) (4)

(b) (4)

(b) (4)

Robustness and Ruggedness

Robustness is the ability of the method to remain unaffected by small, but deliberate variations in method parameters and provides an indication of method reliability.

Robustness was determined by (b) (4)

Ruggedness is the degree of test results reproducibility obtained by analysis of the same samples under a variety of normal test conditions, which was assessed during the LOD study to address analyst variability and reproducibility between (b) (4) different analysts. The tests performed using (b) (4) (b) (4) during the LOD test demonstrated acceptable robustness and ruggedness of the (b) (4) sterility test method.

Specificity:

Specificity is the ability of the method to (b) (4)

Method Suitability Assay:

CellTrans performed a method suitability test (bacteriostatic and fungistatic qualification) using (b) (4) lots (b) (4) of Donislecel to demonstrate the product does not inhibit bacterial and fungal growth. The test was performed using (b) (4)

(b) (4)

(b) (4)

(b) (4)

Comparability Study:

CellTrans performed a comparability study between (b) (4) and the (b) (4) method. (b) (4) lots of human islets (b) (4) (b) (4) were tested using the (b) (4) microorganisms, media and incubation conditions listed in Table 2 below:

Table 2: Microorganism, Media and Incubation Conditions used in Comparability Study

Microorganism	(b) (4) Media	(b) (4) Media	(b) (4)
(b) (4)			

(b) (4)

After review of the information submitted in this BLA, this reviewer recommends the approval of (b) (4) Sterility Test method, as the method was validated in accordance with (b) (4) and was found to be suitable for its intended use.

Endosafe® (b) (4) -BET Method Qualification
(b) (4)

[REDACTED]

Information Request and Review

The following question was sent in an IR to the sponsor on November 23, 2020 and response was received on December 16, 2020.

1. Please provide a complete bacterial endotoxin qualification report for Donislecel drug product showing the matrix is suitable for testing using the (b) (4) method. Please include maximum (b) (4), all tested (b) (4) positive product control percent recoveries, lot numbers with their respective potencies, final selected (b) (4) and endotoxin test results.

Review of the Response

CellTrans qualified their (b) (4) -BET by testing (b) (4) lots (b) (4) of Human Islet final DP to demonstrate their method is suitable under the actual conditions of use in accordance with (b) (4). The (b) (4) was calculated to be (b) (4) by (b) (4).

[REDACTED]

A suitability test for interfering factors was performed on Human Islet final DP samples (b) (4).

[REDACTED]

After review of the information submitted in this BLA and the response to the IR, this reviewer finds CellTrans' (b) (4) -BET test method was qualified and performed in accordance with (b) (4) demonstrating it is suitable under the actual conditions of use.

Conclusion

After a thorough review of this BLA, this reviewer finds bacterial endotoxin test method was qualified in accordance with (b) (4) and the (b) (4) sterility test method was validated in accordance with (b) (4) by demonstrating these methods are suitable under the actual conditions of use and the (b) (4) sterility test method was demonstrated to be equivalent to or better than the (b) (4) sterility test method.