



CBER REGULATORY REVIEW MEMORANDUM

Date 8 November, 2019

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Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biological License Application (BLA) Submission Tracking Number
125685/0

Subject BLA: Review of Endotoxin Method Qualification; and (b) (4) Sterility and
(b) (4) Mycoplasma Test Method
Validations for Postnatal Thymus Derived Tissue (RETHYMIC)

Through James L. Kenney, D.Sc., Chief, LMIVTS
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Applicant Enzyvant Therapeutics GmbH (Enzyvant)

Product Postnatal Thymus Derived Tissue (RETHYMIC)

Biological License Application Submission Tracking Number (STN) 125685/0

Submission Received by CBER 05 April, 2019

Review Completed 8 November, 2019

Material Reviewed

Method qualification for endotoxin test, method validations for (b) (4) sterility test and (b) (4) using (b) (4) mycoplasma test performed on RETHYMIC, and information request responses received 15 May, 26 June, 30 August, 17 September, 04 and 15 October of 2019 were reviewed.

Executive Summary

After a thorough review of this BLA, this reviewer finds the endotoxin test method was qualified in accordance with (b) (4) and the product matrix for RETHYMIC drug product

was demonstrated to be suitable for the intended test method. Enzyvant's (b) (4) sterility test method and the (b) (4)-based mycoplasma test method performed on thymus organ media used in RETHYMIC's tissue culture were validated in accordance with (b) (4), respectively, by demonstrating the tested product matrix is suitable for these intended test methods. Enzyvant demonstrated these test methods provide assurance of tested matrix safety and purity that is equal to or greater than the assurance of the current compendial methods.

Background

On 05 April, 2019, Enzyvant submitted this BLA for RETHYMIC, allogeneic processed postnatal thymus-derived tissue for immune reconstitution in pediatric patients with congenital athymia, including patients with complete DiGeorge anomaly (cDGA), CHARGE syndrome associated with athymia, and forkhead box protein N1 (FOXP1) deficiency. RETHYMIC received both Breakthrough Therapy Designation (BTD) and Regenerative Medicine Advanced Therapy (RMAT) Designation on 13 April, 2017. It is manufactured from tissue obtained from unrelated donors under the age of 9 months undergoing cardiac surgery. It is administered in a single surgical procedure during at a dose of (b) (4) to 22,000 mm² of processed thymus tissue / m² recipient body surface area and implanted into the quadriceps muscle of the patient. The manufacturing of RETHYMIC drug substance includes collection of thymus tissue, slicing and culture for up to 21 days in thymus organ media (TOM). For drug product, the tissue is transferred to final container with (b) (4) media before it is transported to operation room for transplant. Since microbiological testing (i.e., sterility, mycoplasma and endotoxin) cannot be performed on the tissue directly, it is performed on (b) (4) TOM (b) (4) culture dishes regular intervals. (b) (4) media from drug product is not tested because of the number of manual aseptic manipulations during product administration. This sampling plan was deemed acceptable by the product office.

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 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. In addition, DBSQC has subject matter expertise in mycoplasma method validation, and other alternate microbiological test methods. Therefore, this review will focus on the validation of the (b) (4) system for sterility and (b) (4) using (b) (4) for mycoplasma testing (b) (4) media used in RETHYMIC's tissue culture, to determine if the product matrix is suitable for testing using the intended methods and if these methods provide respective sterility and mycoplasma assurance equal to or greater than the compendial methods. In addition, the qualification of bacterial endotoxin test method will be reviewed to ensure the matrix is suitable for the intended test method.

Review

(b) (4) Sterility Test Validation for RETHYMIC (b) (4) TOM

(b) (4) Microbial Detection complies with direct inoculation method of (b) (4)

[Redacted]

Because of limited availability of (b) (4) TOM, Enzyvant performed a feasibility study on (b) (4) TOM to determine (b) (4) has an impact on microbial growth. The test was performed using (b) (4)

[Redacted]

(b) (4)

[Redacted]

Limit of Detection (LOD)

The LOD was assessed by (b) (4)

[Redacted]

(b) (4)

(b) (4)

Specificity

Specificity is the ability of the method to recover a variety of microorganisms. It was assessed during LOD study mentioned above where the results demonstrated the (b) (4) system can detect a variety of microorganisms at (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 using different lots of media which was assessed during LOD study.

Ruggedness is the degree of test result reproducibility obtained by analysis of the same samples under variety of normal test conditions which was assessed during the LOD study.

The tests performed using different analysts and different lots of media under LOD results demonstrated acceptable robustness and ruggedness of (b) (4) System.

(b) (4) -BET Method Qualification for DP
(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Since endotoxin specification of RETHYMIC is directly dependent on the weight of the patient, the specification for each lot is calculated prior to the implant and CBER finds this acceptable.

(b) (4) Mycoplasma Test Validation for RETHYMIC (b) (4) TOM

The mycoplasma test is performed in accordance with (b) (4)

(b) (4)

LOD

The LOD was assessed by demonstrating the (b) (4)

(b) (4)

Specificity

Specificity is the ability of the method to detect only mycoplasma and no other mycoplasma-related microorganisms. Specificity was assessed during the LOD study where (b) (4)

Intermediate Precision

Intermediate precision was validated while evaluating assay LOD, as the tests were performed by different analysts on different days using different reagent lots. The LOD results support the intermediate precision of the assay.

Robustness

Robustness is the ability of the method to remain unaffected by small but delicate variations in methodology and provides assurance of its reliability during normal usage. The robustness was assessed during LOD where deliberate variations such (b) (4) of samples was assessed and found acceptable in accordance with (b) (4) robustness requirement.

Comparability Study

A comparability study between (b) (4) and the (b) (4) mycoplasma methods using (b) (4) TOM lot mentioned (b) (4)

Conclusion

After a thorough review of this BLA, this reviewer finds the endotoxin test method was qualified in accordance with (b) (4) and the product matrix for RETHYMIC drug product was demonstrated to be suitable for the intended test method. Enzyvant's (b) (4) sterility test method and the (b) (4)-based mycoplasma test method performed on (b) (4) media used in RETHYMIC's tissue culture were validated in accordance with (b) (4), respectively, by demonstrating the tested product is suitable for the intended test methods. Enzyvant demonstrated the test methods provide assurance of tested matrix safety and purity that is equal to, or better than, the assurance of the current (b) (4) method. Therefore, this reviewer finds the methods acceptable for their intended purpose and recommends their approval.