



DBSQ/OCBQ ANALYTICAL METHOD REVIEW MEMO

To The file: STN 125758/0

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Applicant Orchard Therapeutics (Europe) Ltd. (Orchard)

Subject Biologics License Application (BLA): Review of endotoxin, sterility, and mycoplasma analytical methods used for atidarsagene autotemcel (LENMELDY)

Recommendation: Approval

Executive Summary

The endotoxin, sterility, and mycoplasma analytical methods used for testing and release of (b) (4) LENMELDY drug product and the associated analytic method qualifications or validations were reviewed. The assays were adequately described and shown to be suitable for their intended purpose.

Conclusion

The analytical methods and their qualifications or validations reviewed for (b) (4) LENMELDY drug product were found to be adequate for their intended use. Orchard's postmarketing commitment received on March 12, 2024 (Amendment #58) commits to perform a comparability study as part of the LENMELDY drug product (b) (4)-based mycoplasma assay as required by 21 CFR 610.9. (b) (4) mycoplasma testing will be performed by (b) (4), while the (b) (4) prepared by (b) (4) will be tested by AGC Biologics S.p.A. Bresso site in Milan, Italy using the (b) (4)-based mycoplasma assay. The final validation study report will be submitted as a "Postmarketing Commitment - Final Study Report" by October 31, 2024.

Documents Reviewed

Information in sections of the original submission that describe control of (b) (4) Drug Product (DP) (3.2.S.4 and 3.2.P.5, respectively), including descriptions of (b) (4) DP specifications, analytical procedures of (b) (4) DP, and validation or qualification of these analytical

procedures were reviewed. In addition, responses to CBER's Information Requests (IRs) received on September 12, 2023 (Amendment #3), November 2, 2023 (Amendment #11), November 14, 2023 (Amendment #12), November 22, 2023 (Amendment #13), December 8, 2023 (Amendment #18), December 18, 2023 (Amendment #22), December 21, 2023 (Amendment #23), January 12, 2024 (Amendment #28), and February 15, 2024 (Amendment #41) were also reviewed as mentioned below.

1. Endotoxin Method ((b) (4) DP)

Introduction

Endotoxin testing for (b) (4) DP is performed at AGC Biologics S.p.A. (AGC) Bresso site in Milan, Italy. Specifications of (b) (4) for DP must be met for release of LENMELDY. The specification limit for the (b) (4) that is equivalent to (b) (4).

Method

The (b) (4) bacterial endotoxin test ((b) (4) -BET) is a (b) (4)

(b) (4)

(b) (4)

The methods are described in more detail below together with the tests performed to determine the suitability of the test methods for their intended use.

The original qualification reports for endotoxin lacked sufficient information to complete the review. Therefore, an IR was sent requesting data and clarification to fulfill these deficiencies. Responses were received on September 12, 2023 (Amendment #3) and December 8, 2023 (Amendment #18) which were found acceptable and explained below.

(b) (4)

(b) (4)

(b) (4) BET QUALIFICATION FOR DP

(b) (4)

Conclusion

The method suitability tests were performed and compliant with (b) (4) and the test results indicate there is acceptable product interference from (b) (4) DP test samples, thus indicating the (b) (4)-BET (b) (4) test methods are appropriate under the actual conditions of use.

2. Sterility Method ((b) (4) DP)

Introduction

Sterility testing for (b) (4) DP is performed at AGC Biologics S.p.A. (AGC) Bresso site in Milan, Italy. Specifications of (b) (4) 'Negative' for DP must be met for release of LENMELDY.

Method

The (b) (4) test is used in accordance with (b) (4). Test samples are (b) (4)

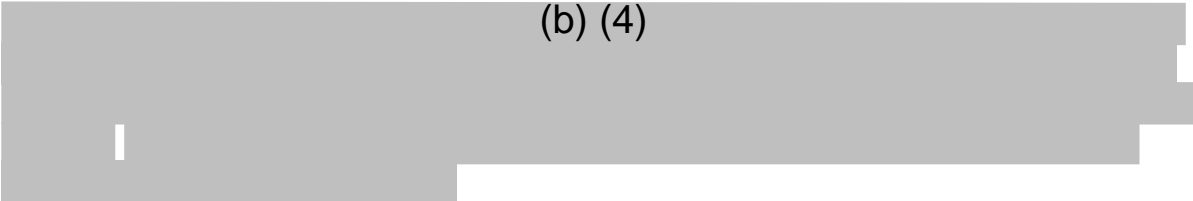
The (b) (4) sterility test system complies with the (b) (4) method of (b) (4), in that a test sample is (b) (4)

The methods are described in more detail below together with the tests performed to determine the suitability of the test methods for their intended use.

The original validation reports for sterility lacked sufficient information to complete the review. Therefore, IRs were sent requesting data and clarification to fulfill these deficiencies. Responses were received on September 12, 2023 (Amendment #3), November 2, 2023 (Amendment #11), November 22, 2023 (Amendment #13), December 18, 2023 (Amendment #22), January 12, 2024 (Amendment #28), February 15, 2024 (Amendment #41), and February 29, 2024 (Amendment #52), which were found acceptable and explained below.

(b) (4)

(b) (4)


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STERILITY TEST VALIDATION FOR DP

(b) (4)

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

(b) (4)

Conclusion

The method suitability tests were performed and compliant with (b) (4), and the test results indicate there is no product inhibition of microorganism growth. The (b) (4) test method was demonstrated to provide assurance equal to or greater than the (b) (4) method, thus indicating the (b) (4) and (b) (4) sterility test methods are appropriate under the actual conditions of use.

3. Mycoplasma Method ((b) (4) DP)

Introduction


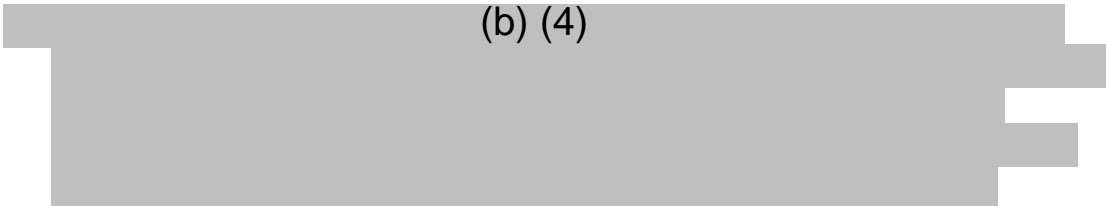
Mycoplasma testing for (b) (4) is performed at (b) (4) DP at AGC Biologics S.p.A. (AGC) Bresso site in Milan, Italy. Specifications of (b) (4) 'Not detectable' for DP must be met for release of LENMELDY.

Method

The tests for mycoplasma are performed in accordance with (b) (4)

(b) (4)



(b) (4)



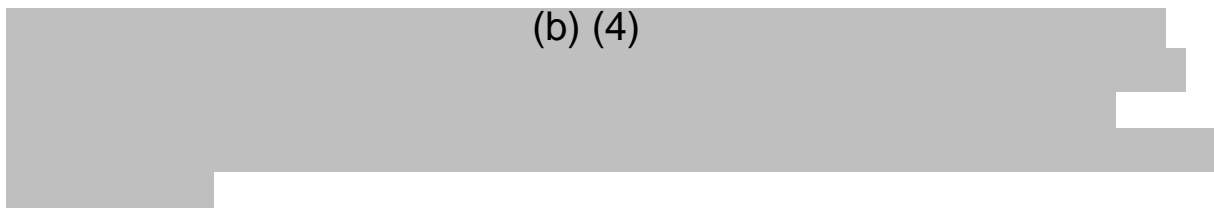
These methods are described in more detail below together with the tests performed to determine the suitability of the test methods for their intended use.

The original qualification and validation reports for mycoplasma lacked sufficient information to complete the review. Therefore, IRs were sent requesting data and clarification to fulfill these deficiencies. Responses were received on September 12, 2023 (Amendment #3), November 14, 2023 (Amendment #12), and December 21, 2023 (Amendment #23), which were found acceptable and explained below. Additionally, a teleconference was held between the FDA and Orchard on November 30, 2023, to discuss expectations of the comparability study required as part of the DP mycoplasma test validation.

(b) (4)

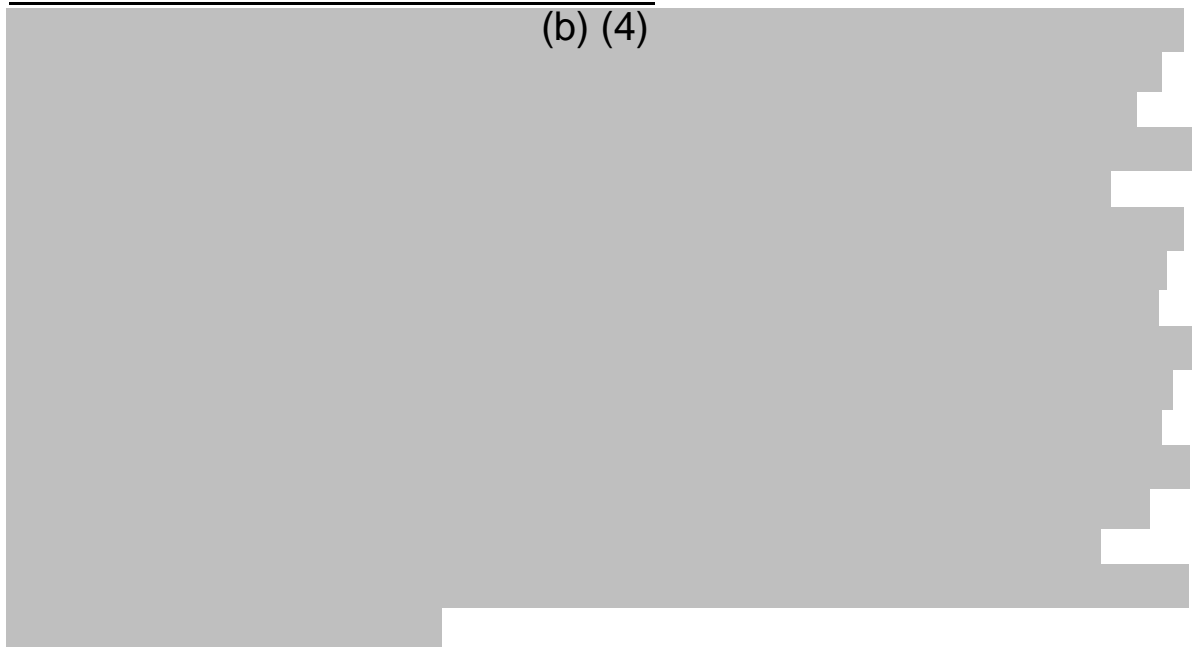


(b) (4)

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MYCOPLASMA TEST VALIDATION FOR DP

(b) (4)

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(b) (4)

Conclusion

The method suitability tests were performed and compliant with (b) (4), and the test results indicate there is no product interference from the test sample, thus indicating the (b) (4) and (b) (4) mycoplasma test methods are appropriate under the actual conditions of use. Orchard's post marketing commitment received on March 12, 2024 (Amendment #58) commits to perform a comparability study as part of the LENMELDY drug product (b) (4)-based mycoplasma assay as required by 21 CFR 610.9. (b) (4) mycoplasma testing will be performed by (b) (4), while the (b) (4) prepared by (b) (4) will be tested by AGC Biologics

S.p.A. Bresso site in Milan, Italy using the (b) (4)-based mycoplasma assay. The final validation study report will be submitted as a "Post marketing Commitment - Final Study Report" by October 31, 2024.