



CBER REGULATORY REVIEW MEMORANDUM

Date 24 May, 2016

From Simleen Kaur
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 # 125597/0

Subject BLA: Review of Bioburden and Absence of Specified Microorganisms Method Qualifications for Cholera Vaccine, Live, Oral (Vaxchora TM)

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

Applicant PaxVax Bermuda Ltd. (PaxVax)

Product Cholera Vaccine, Live, Oral (Vaxchora TM)

Biologics License Application (BLA) Submission Tracking Number (STN) 125597/0

Submission Received by CBER 16 October, 2015

Review Completed 24 May, 2016

Material Reviewed

Method qualifications for: 1) bioburden and 2) absence of specified microorganisms performed on the (b) (4) drug product (DP) and buffer. In addition, the responses to CBER's Information Requests (IRs) received 8 January, 12 February, 4, 12 and 23 May of 2016 were reviewed.

Executive Summary

After a thorough review of this BLA, this reviewer finds PaxVax Bermuda Ltd. (PaxVax's) bioburden and absence of specified microorganisms tests were qualified in accordance with (b) (4) respectively.

Background

On 16 October, 2015, PaxVax submitted this BLA requesting priority review based on the Guidance for Industry - Expedited Programs for Serious Conditions - Drugs and Biologics. Vaxchora™ is indicated for active immunization against disease caused by *V. cholera* serogroup O1 in adults 18 years of age or older. It is supplied as a co-package of a single dose, multilayer foil sachet containing vaccine powder for reconstitution and a separate single dose, multilayer foil sachet containing buffer powder. The reconstitution procedure requires dissolution of the buffer in 100 mL of bottled water, followed by addition of the vaccine powder and mixing. The reconstituted vaccine is administered orally. The recommended dosage strength of the vaccine is 4×10^8 to 2×10^9 CFU/dose of recombinant live attenuated *V. cholerae* vaccine strain CVD 103 HgR.

Manufacturing of Drug Substance and Drug Product

The manufacturing of Vaxchora™ bulk drug substance (BDS) is performed (b) (4)

For manufacturing of DP, lyophilized and milled (b) (4)

The BDS is then blended with the dried lactose, filled into labeled multilayer foil sachets (packets) and tested for potency, bioburden and absence of specified microorganisms before released.

Manufacturing of Buffer

The buffer is manufactured by (b) (4)

(sodium bicarbonate/sodium carbonate), dried lactose and ascorbic acid are blended together, packaged and also transferred to PaxVax. Upon receipt, the bulk buffer is inspected, filled into sachets, labeled and tested for bioburden and absence of specified microorganisms before released.

The Division of Biological Standards and Quality Control (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, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are

released according to licensed test methods and product specifications. Therefore, this memo covers the review of PaxVax's bioburden and absence of specified microorganisms test qualification reports to ensure Vaxchora™ product matrix is suitable for these intended test methods.

Review

(b) (4) Drug Product (DP)

Bioburden Test Qualification for (b) (4) DP

The bioburden test method qualification was performed on (b) (4) three lots of DP (i.e., (b) (4) to demonstrate the matrixes do not inhibit bacterial and fungal growth. The test was performed according to (b) (4)

This process was then (b) (4) for each of the remaining indicator microorganisms. A (b) (4)

The recovery of CFUs in the presence of samples did not differ by more than a factor of (b) (4) from the microorganism's representative PC CFU count and the NCs had no growth. Based on these results, the bioburden test method for the (b) (4) DP was performed in accordance with (b) (4) and the test results indicate their matrixes are suitable for the intended test method.

The bioburden results performed on the (b) (4)

. Upon CBERs request, PaxVax added an alert limit of (b) (4) to better track and trend the manufacturing process for improved quality oversight.

Microbiological Examination: Absence of Specified Microorganisms for (b) (4) DP




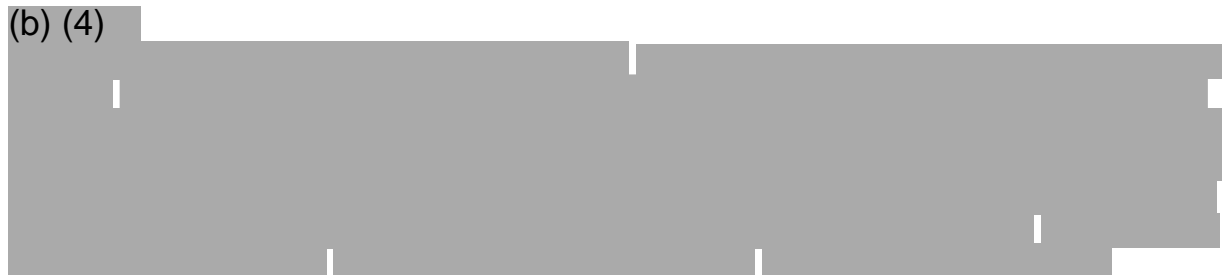
PaxVax qualified their microbiological quality tests for (b) (4) 'Tests for Specified Microorganisms' to show their product matrix is suitable for testing using the intended testing methods. The test was performed on (b) (4)

(b) (4)

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

(b) (4)

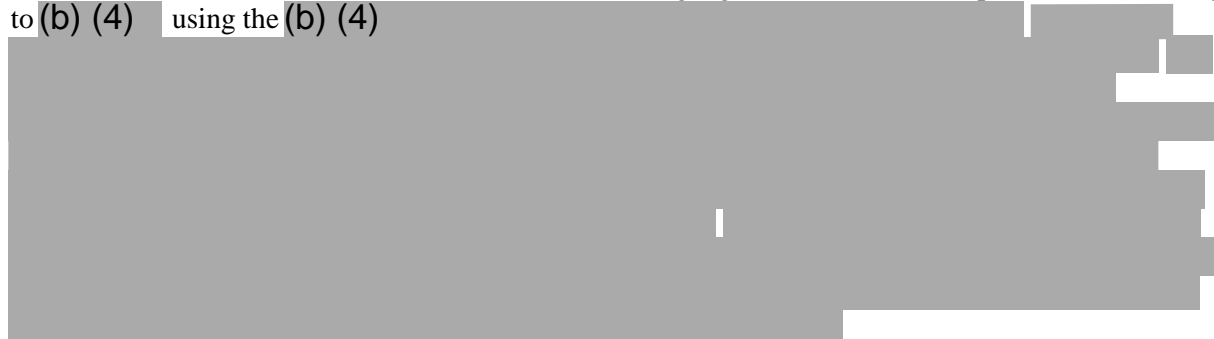
(b) (4)



Buffer

Bioburden Test Qualification for Buffer

The bioburden test method qualification was performed on one lot (i.e., (b) (4)) of buffer to demonstrate the matrix does not inhibit bacterial and fungal growth. The test was performed according to (b) (4) using the (b) (4)



The recovery of CFUs in the presence of samples did not differ by more than a factor of (b) (4) from the microorganism's representative PC CFU count and the NCs had no growth. Based on these results, the bioburden test method was performed in accordance with (b) (4) and the test results indicate the Buffer's matrix is suitable for the intended test method.

The bioburden results performed on the (b) (4)

Upon CBER's request, PaxVax added an alert limit of (b) (4) to better track and trend the manufacturing process for improved quality oversight.

Microbiological Examination: Absence of Specified Microorganisms for Buffer


PaxVax qualified their microbiological quality tests for (b) (4)

'Tests for Specified Microorganisms' to show the product matrix is suitable for testing using the intended testing methods. The test was performed on one lot (i.e., (b) (4)) of buffer for (b) (4)

(b) (4)

(b) (4)

(b) (4)



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(b) (4)



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(b) (4)



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Conclusion

After a thorough review of the information submitted in this BLA, this reviewer finds PaxVax's bioburden and specified microorganisms test methods were qualified in accordance to (b) (4) and (b) (4), respectively, by demonstrating the (b) (4), DP and buffer matrixes are suitable for these intended test methods.