

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file STN 125774

From:

Reviewer	Role	Date finalized	Stamp	Supervisor	Stamp
M. Nahid Parvin, Ph.D.	Lead Reviewer	04/12/2023		Muhammad Shahabuddin, Ph.D.	
Claire H. Wernly, Ph.D.	Reviewer	12/14/2022		James L. Kenney, D.Sc.	
Tao Pan, Ph.D.	Reviewer	12/06/2022		Kenneth Phillips, Ph.D.	

Through Maryna Eichelberger, Ph.D.
Division Director, DBSQC/OCBQ

Applicant: Krystal Biotech, Inc.

Subject: Review of Analytical Method used for lot release of VYJUVEK™ (beremagene geperpavec, B-VEC/KB103) (b) (4) and Drug Product (DP)

Recommendation: Approval

Executive Summary:

The following analytical methods used for lot release of VYJUVEK™ (beremagene geperpavec) and the associated analytical method validations or qualifications, were reviewed:

1. Herpes Simplex 1 (HSV-1) Plaque Titer Assay on DP (M. Nahid Parvin)
2. (b) (4) by (b) (4) on DP (M. Nahid Parvin)
3. (b) (4) by (b) (4) on DP (M. Nahid Parvin)
4. (b) (4) by (b) (4) on DP (M. Nahid Parvin)
5. (b) (4) by (b) (4) on DP (M. Nahid Parvin)
6. (b) (4) (Claire H. Wernly)
7. Sterility Test on DP (Claire H. Wernly)
8. Endotoxin test on DP (Claire H. Wernly)
9. (b) (4) (Claire H. Wernly)
10. Appearance of DP (b) (4) (Tao Pan)

11. (b) (4) Measurement of DP (b) (4) (Tao Pan)**Conclusion:**

The analytical methods and their validations and/or qualifications reviewed for the beremagene geperpavec (b) (4) drug product were found to be adequate for their intended use.

Documents Reviewed:

Information in sections of the original submission that describe control of (b) (4) and 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 of analytical procedures were reviewed. Additional information in amendments #125774/0.12, #125774/0.19, #125774/0.28, #125774/0.53 and #125774/0.55, received on October 4, October 28, November 14, 2022, March 17, and March 28, 2023, respectively, were also reviewed.

Background:

Krystal Biotech, Inc. submitted its first original BLA on June 02, 2022, STN 125744 for beremagene geperpavec (B-VEC, also called KB103) for the treatment of wounds for patients over 6 months of age with dystrophic epidermolysis bullosa (DEB) per Section 351(a) of the United States Public Health Service Act. B-VEC holds the following designations: fast track, orphan drug (DRU-2016-5588), rare pediatric disease (RPD-2016-95), and regenerative medicine advance therapy.

B-VEC is a replication-incompetent, non-integrating HSV-1-based vector engineered to express full-length, functional human collagen VII (COL7). The HSV-1 strain (b) (4) was used to produce B-VEC, as the (b) (4) strain is less virulent than other commonly used HSV-1 strains. The vector was generated by (b) (4)

DP is vialled (b) (4) with no additional formulation, supplied as a sterile suspension in single-dose vials. B-VEC DP is mixed with excipient gel prior to topical administration to DEB wounds. The storage temperature of DP is -15°C to -25°C and can be stored at 2° to 8°C for up to one month.

The following facilities perform the methods reviewed:

1. Krystal Biotech Inc., Pittsburgh, PA
2. (b) (4)
3. (b) (4)

DBSQC reviews BLA and their supplements to ensure the analytical methods are appropriately described, validated and suitable for intended purposes. The following analytical methods used for DS and DP release were reviewed:


1. Herpes Simplex 1 (HSV-1) Plaque Titer Assay on DP (M. Nahid Parvin)

Introduction




Krystal Biotech uses Herpes Simplex Virus-1 (HSV-1) Plaque Assay (b) (4) to determine the viral titer of DP. The assay is performed using (b) (4) cells. This is Krystal Biotech's proprietary genetically modified (b) (4) cell line used to manufacture and test the product. The assay was developed and validated in Krystal Biotech's Quality Control laboratory, Pittsburgh, PA. The DP specification for this assay is (b) (4).

Method


(b) (4)



(b) (4)




(b) (4)




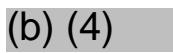
Conclusion

The validation data show that the analytical procedure to determine HSV infectious titer is suitable for its intended use. The protocol used to qualify reference standard is acceptable.

(b) (4)




(b) (4)









16 pages determined to be not releasable: (b)(4)

(b) (4)



(b) (4)

7. Sterility Test on DP (Claire H. Wernly)

Introduction

This test is performed on DP by (b) (4)



Method

(b) (4) performed sterility testing using the (b) (4) method. The (b) (4) sterility test used for non-filterable products is performed in accordance with (b) (4) and provides assurance of sterility for the matrix represented by the sample. (b) (4)

The method is described below, together with the tests that were performed to demonstrate suitability of the test method according to its indicated use.

Method Qualification

A qualification study was performed to demonstrate the method is suitable under the actual conditions of use in accordance with (b) (4). The test was performed using (b) (4)

(b) (4)

(b) (4)

(b) (4)

Information Request and Review:

An IR was sent to Krystal on 23 September 2022 with a response received on 04 October 2022 (Amendment #12). The request asked Krystal for additional data to supplement their sterility

test reports (i.e., Krystal075-164 and KB-DOCS-01830). The response to CBER's IR was reviewed as part of the DP sterility test qualification above.

Conclusion

The method suitability test was performed and compliant with (b) (4) and the test results indicate there is no product inhibition on microorganism growth, thus indicating the (b) (4) sterility test method is appropriate under the actual conditions of use.


8. Endotoxin test on DP (Claire H. Wernly)

Introduction

This test is performed on DP at Krystal Biotech, Inc. in Pittsburgh Pennsylvania.


Review of Method

(b) (4)



Review of Method Qualification

(b) (4)



Information Request and Review:

Two IRs were sent to Krystal on 23 September 2022 and 14 October 2022 with responses received on 04 October 2022 (Amendment #12) and 28 October 2022 (Amendment #19) respectively. The requests asked Krystal for clarification to their endotoxin test report (i.e., PRO-

0178F1.00) and revision of release specifications to better reflect their process capabilities. The responses to CBER's IRs were reviewed as part of the DP endotoxin test qualification above.

Conclusion

Krystal submitted bacterial endotoxin concentration results from DP lots, and all were within their revised release specification (i.e., (b) (4)). After review of the (b) (4) test, this reviewer concludes the test methods were performed and compliant with (b) (4) .

(b) (4)

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(b) (4)

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10. Appearance of DP (b) (4) (Tao Pan)

Introduction

(b) (4)

The appearance of (b) (4) B-VEC DP is determined by visual inspection; (b) (4) the release specification for B-VEC DP is “Opalescent yellow to colorless liquid, free from extrinsic visible particulates”. The release testing for appearance of (b) (4) DP (b) (4) is performed at Krystal Biotech's Quality Control laboratory.

Method and Method Verification

The appearance of (b) (4) B-VEC DP is determined to ensure they are within their respective specifications, to identify the presence of foreign matter or particulates, and/or to monitor changes in color, clarity, or particulate formulation (b) (4). A description of the method was provided: (b) (4)

The method is simple and straightforward; it is acceptable not to validate it. The batch records from three different B-VEC DP batches have shown that all three met the release specification for appearance, as described as “Opalescent yellow to colorless liquid, free from extrinsic visible particulates”. The method has been verified for the testing of B-VEC DP.

Conclusion

Based on information provided, the appearance method for B-VEC DP (b) (4) has been verified for its intended use of release testing of the B-VEC DP (b) (4)

(b) (4)