



DBSQ/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file: STN 125737/0

From:

Reviewer	Date finalized	Stamp	Supervisor	Stamp
Tao Pan, Ph.D. (lead reviewer)			Tao Pan, Ph.D. Acting Chief, LACBRP	
Hyesuk Kong, Ph.D.			James L. Kenney, D.Sc., Chief, LMIVTS	
Noel Baichoo, Ph.D.			Muhammad Shahabuddin, Ph.D. Chief, LBVI	

Through: Maryna Eichelberger, Ph.D., Division Director, CBER/OCBQ/DBSQ

Applicant: VBI Vaccines Inc.

Subject: Review of Analytical Methods used for the Lot release of PREHEVBRIO (Hepatitis B Vaccine [recombinant]) Drug Substance (DS) and Drug Product (DP)

Recommendation: Approval

Summary:

The following analytical methods used for lot release of PREHEVBRIO (Hepatitis B Vaccine [recombinant]) and the associated method validations or qualifications, were reviewed:

1. Physical description for (b) (4) DP (Tao Pan)
2. (b) (4) for DS (Tao Pan)
3. (b) (4) for DS (Tao Pan)
4. (b) (4) DP (Tao Pan)
5. (b) (4) method for DS (Tao Pan)
6. (b) (4) for DS (Tao Pan)
7. Aluminum content by (b) (4) for DP (Tao Pan)
8. Volume of injection for DP (Tao Pan)
9. Identity of (b) (4) DP (Noel Baichoo)

10. (b) (4) DS (Noel Baichoo)
11. (b) (4) DS (Noel Baichoo)
12. Potency (in vivo) of DP (Noel Baichoo)
13. (b) (4) of Hepatitis B surface antigen to adjuvant in DP (Noel Baichoo)
14. Sterility Test for (b) (4) DP (Hyesuk Kong)
15. Endotoxin of (b) (4) DP (Hyesuk Kong)

Conclusion: The analytical methods and their validations and/or qualifications reviewed for the PREHEVBRIO (Hepatitis B Vaccine [recombinant]) drug substance and drug product were found to be adequate for their intended use.

Documents Reviewed

Information in sections of the BLA (STN125737) submissions that describe control of DS and DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validation of these analytical procedures were reviewed. Additional information in amendments specified by each reviewer were also reviewed.

Background

On 30 November, 2020, VBI submitted this BLA for PREHEVBRIO indicated for the prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older. PREHEVBRIO is presented as a sterile single-dose suspension of 1.0 mL for intramuscular injection.

PREHEVBRIO is a recombinant, hepatitis B vaccine, produced in Chinese Hamster Ovary (CHO) cells genetically modified to produce the three envelope proteins of the hepatitis B virus: the small (S), middle (pre-S2), and large (pre-S1) hepatitis B surface antigens (HBsAg). (b) (4) aluminum hydroxide [Al(OH₃)] at 0.5 mg/mL as an adjuvant to generate the formulated bulk drug product and filled into single dose vials at a concentration of 10 µg/mL HBsAg.

DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriately described, validated and suitable for the intended purposes.

The following analytical methods used for DS and DP release were reviewed:

1. Physical Description for (b) (4) DP (Tao Pan)

Release testing for physical description of (b) (4) DP is performed by SciVac in Rehovot, Israel.

(b) (4)



(b) (4)

1.2. *Physical Description for DP*

Method

The HBsAg drug product (DP) appears turbid when mixed, and forms a clear colorless upper solution and white precipitate upon settling, which is determined by visual inspection. The physical inspection of HBsAg DP is based on a visual evaluation of the vial content to identify particulates or damage to the vial. The method involves (b) (4)

and the vaccine solution should be turbid when mixed. The method was sufficiently described with details on the execution and the generation of reportable result.

Method Validation

The analytical method for the physical inspection of HBsAg DP is a simple method, and it is acceptable not to validate it.

Conclusion

Based on information provided, the physical inspection method for HBsAg DP is adequately described and suitable for its intended use.

2. (b) (4) for DS (Tao Pan)

(b) (4) DS is performed by SciVac in Rehovot, Israel.

Method

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

(b) (4)

7. Aluminum Content (b) (4) for DP (Tao Pan)

Release testing for aluminum content of DP are performed at (b) (4)

Method

The aluminum (Al) content of HBsAg DP is determined (b) (4)

The description of the analytical method provided in the submission is sufficient with details on the execution of the method, system suitability criteria, and the generation of reportable result.

Method Validation

(b) (4)

(b) (4)

(b) (4)

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(b) (4)



Conclusion

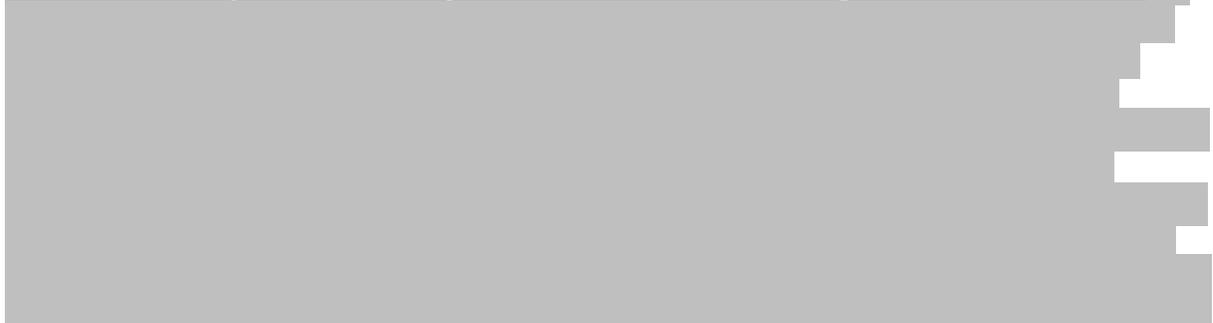
Based on the information provided in original BLA and Amendment 0.15, the method has been validated for its intended purpose: the determination of aluminum content in HBsAg DP.

8. Volume of Injection for DP (Tao Pan)

Release testing for volume of injection of DP is performed by SciVac in Rehovot, Israel.

Method

The volume of injection of HBsAg DP is measured based on the procedures described in ^{(b) (4)}



The analytical method is sufficiently described, with details on operation procedures, and the generation of reportable result.

Method Validation

(b) (4)



and it is acceptable not to validate it.

Conclusion

Based on information provided, the method for volume of injection for HBsAg DP is adequately described and suitable for its intended use.

9. Identity of (b) (4) DP (Noel Baichoo)

Release testing for identity of (b) (4) DP is performed by SciVac in Rehovot, Israel.

Method

(b) (4)



Identity of the DP is determined by (b) (4)



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(b) (4)

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Conclusion

The (b) (4) method to determine (b) (4) DP identity is adequately described and validation data demonstrate it is suitable for its intended purpose.

10. (b) (4) of DS (Noel Baichoo)

(b) (4)

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(b) (4)

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(b) (4)

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12. Potency (in vivo) of DP (Noel Baichoo)

The animal portion of potency release testing for DP is performed by an external contractor (b) (4). The serum testing part of the potency testing is performed by SciVac in Rehovot, Israel.

Method

(b) (4)

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Method validation

(b) (4)



(b) (4)



Conclusion

The in vivo method to determine potency in DP is adequately described and validation data demonstrate it is suitable for its intended purpose.

13. (b) (4) of Hepatitis B surface antigen to adjuvant in DP (Noel Baichoo)

Release testing for (b) (4) of DP is performed by SciVac in Rehovot.

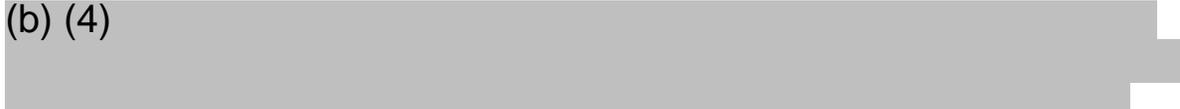
Method

(b) (4)



Method validation

(b) (4)



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(b) (4)



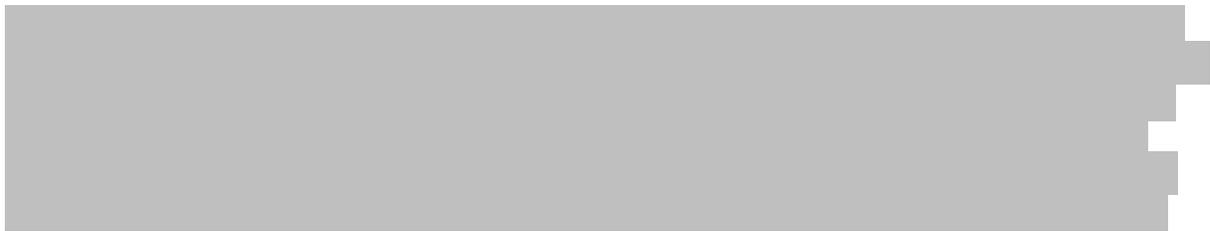
Conclusion

The (b) (4) method to determine (b) (4) in DP is adequately described and validation data demonstrate it is suitable for its intended purpose.

14. Sterility Test for (b) (4) DP (Hyesuk Kong)

Release testing of sterility for (b) (4) DP was performed by SciVac in Rehovot, Israel.

(b) (4)



(b) (4)



Sterility Test Qualification for DP

The (b) (4) PREHEVBRIO® DP was qualified using the (b) (4) method by performing B&F qualification studies at VBI's facility in Rehovot, Israel to demonstrate the PREHEVBRIO® DP does not inhibit bacterial and fungal growth.

(b) (4)



Information Request for Sterility and Review

The following IR was submitted to the Sponsor on 30 April 2021 and the response was received on 7 May 2021 in amendment 125737/0/7.

1. For sterility method validation by (b) (4) (b) (4) (b) (4) (b) (4) (section 3.2.P.5.3) for drug product (DP), sterility validation reports VLR-0001000 for (b) (4) VLR-0001663 for DP were submitted. The section of materials and reagents described in the validation reports included (b) (4), but specifics regarding the number of (b) (4) and its (b) (4) were not provided. Please provide details regarding the (b) (4) procedure in the suitability study.

Review of the Response

The reviewer found all requested information and the response was found acceptable.

Conclusion

After review of sterility method qualification results, this reviewer concludes this method was qualified in accordance with (b) (4) and the test results indicate there is no product inhibition on microorganism growth.

15. Endotoxin of (b) (4) DP (Hyesuk Kong)

Release testing of endotoxin for (b) (4) DP was performed by SciVac in Rehovot, Israel.

(b) (4)

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(b) (4) -BET Qualification for DP

VBI qualified their (b) (4)-BET method (validation protocol VLP-0001628) by testing (b) (4) lots (i.e., (b) (4)) of PREHEVBRIO DP at the VBI's facility in Rehovot, Israel, to demonstrate their method is suitable under the actual conditions of use in accordance with (b) (4) and reported these results in validation report 'VLR-0002538'. Since the manufacturing process for (b) (4) DP is the same except for a (b) (4) step only, the qualification study performed on the (b) (4) samples was found acceptable for the DP.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Conclusion

After review of (b) (4)-BET method qualification results, this reviewer concludes this method was qualified in accordance with (b) (4) and was demonstrated to be suitable under the actual conditions of use.