



From: Kouassi Ayikoe, DBSQC/OCBQ
Ritu Agarwal, DBSQC/OCBQ
Tao Pan, DBSQC/OCBQ
Hsiaoling Wang, DBSQC/OCBQ
Alfred Del Grosso, DBSQC/OCBQ
Lokesh Bhattacharyya, DBSQC/OCBQ

To: File: 125428/0

Through: William M. McCormick, Director DBSQC, OCBQ

Subject: Review Memo for the Response to Complete Response Letter – Heplisav [Hepatitis B Vaccine (Recombinant), Adjuvanted]; STN: 125428

Recommendation: CR Letter—Deficiencies

Summary of Review

A new BLA submitted by Dynavax Technologies Corporation for Heplisav [Hepatitis B Vaccine (Recombinant)], STN: 125428. The analytical methods and their validations were reviewed and found to have significant deficiencies, which were summarized as questions 12 – 25 and 41 in the Complete Response (CR) Letter, dated 22 February 2013. The sponsor has provided responses to the deficiencies listed in the CR Letter as Amendment 42, received on 15 March 2016. In addition, two new assays were included in the submission. This memo constitutes the final review memo for the procedures and method validations for the lot-release tests listed below.

Drug Substance

(b) (4)

Adjuvant

(b) (4)

(b) (4)



Drug Product

- 1018 ISS Adjuvant Content by (b) (4)
- HBsAg Concentration by (b) (4)
- Extractable Volume (b) (4)
- Adjuvant Identity by (b) (4)
- Adjuvant Integrity by (b) (4)

All procedures listed above, except the assay for adjuvant (b) (4) are found to be approvable. There are several deficiencies in the latter method and its validation, which are included in the CR Letter issued to the sponsor on 10 November 2016.

Background of Submission

A new BLA is submitted by Dynavax Technologies Corporation for Heplisav [Hepatitis B Vaccine (Recombinant), Adjuvanted], STN: 125428. The submission received a Complete Response (CR) Letter. In the CR letter issued on 22 February 2013, various deficiencies were cited. The deficiency items 12 – 25 and 41 are related to the analytical methods for the quality control lot release tests for the Drug Substance, Adjuvant, and the Drug Product, and their method validations. On 15 March 2016, the sponsor provided a full response to the deficiencies listed in the CR Letter as Amendment 42.

This memo constitutes the review memo of the information provided by the sponsor in Amendment 42 and subsequent amendments, which were submitted in response of our information requests (IR).

Submitted Information and Documents:

This is an electronic submission. Information submitted and reviewed includes:

- FDA Complete Response Letter (CRL) to Dynavax dated 22 February 2013
- CBER response to Dynavax type C meeting dated 17 October 2014
- 125428/0: 3.2.P.5.2 Analytical Procedures (referred to in Amendment 58)
 - Method Description for QC110: Determination of 1018 ISS Adjuvant (b) (4)
- 125428/0: 3.2.P.5.3 Validation of Analytical Procedures (referred to in Amendment 58)

- VAL- Q234B-R: Validation Report: Identity, Purity and (b) (4) of 1018 ISS in Heparisav Drug Product by (b) (4)
- 125428/0.42: 1.2 Cover Letter Dated 15 March, 2016
- 125428/0.42: 1.2 FDA Complete Response Letter, Dated 22 February, 2013
- 125428/0.42: 1.11.1 Quality Information Amendment , Response to FDA Complete Response letter, received 16 March 2016
 - Response to CRL Question # 12: (b) (4) (drug substance)
 - Response to CRL Question # 13: (b) (4) (drug substance)
 - Response to CRL Question # 15: (b) (4) (adjuvant)
 - Response to CRL Question # 16: (b) (4) (adjuvant)
 - Response to CRL Question # 17: (b) (4) (adjuvant)
 - Response to CRL Question # 18: (b) (4) (adjuvant)
 - Response to CRL Question # 19: (b) (4) (adjuvant)
 - Response to CRL Question # 20: (b) (4) (adjuvant)
 - Response to CRL Question # 21: (b) (4) (adjuvant)
 - Response to CRL Question # 22: (b) (4) (adjuvant)
 - Response to CRL Question # 23: 1018 ISS Adjuvant Content by (b) (4) Assay (drug product)
 - Response to CRL Question # 24: HBsAg Concentration by (b) (4) Assay (drug product)
 - Response to CRL Question # 24: Extractable Volume (b) (4) (drug product)
 - Response to CRL Question # 41: (b) (4) (drug substance)
 - Response to CRL Question # 51: (b) (4) (adjuvant)
- 125428/0.42: 3.2.S.4.1 Control of Drug Substance: Specifications
- 125428/0.42: 3.2.S.4.2 Analytical Procedures
 - Method Description for SOP QTM-000039: (b) (4) Determination of 1018 ISS Adjuvant by (b) (4)
 - Method Description for SOP QTM-000053: (b) (4) of 1018 ISS Adjuvant by (b) (4)
 - Method Description for SOP QTM-000377: Identity, Assay, Purity, and Impurity Profile of (b) (4)

- Method Description for SOP DUS-QC-0109-05: Concentration determination by (b) (4) for 1018bISS from Heplisav™ Drug product
- Method Description for DUS-SOP-QC-110-08: Analytical Method for Determination of Identity of 1018 ISS Adjuvant in HEPLISAV by (b) (4)
- 125428/0.42: 3.2.S.4.3 Validation of Analytical Procedures
 - Method Validation Report VAL-A119-06-R v1: Determination of (b) (4) Concentration in HBsAg Drug Substance by the (b) (4)
 - Method Validation Report MF/VAL/AV/047/RPT: Quality Control Test Method for Determination of (b) (4)
 - Method Validation Report VAL-100717: Quality Control Test Method for Determination of (b) (4)
 - Method Validation Report VAL-100621: Validation of (b) (4) Method QTM-000377
- 125428/0.42: 3.2.P.5.1 Control of Drug Product: Specifications
- 125428/0.42: 3.2.P.5.3. Validation of Analytical Procedures
 - Method Validation Report VAL-Q139C-R: Determination of (b) (4) Concentration in 1018 ISS-HBsAg Drug Product by (b) (4)
 - Method Validation Report VL097: Determination of HBsAg Protein Concentration in HEPLISAV Drug Product by (b) (4)
 - Method Validation Report VL093: Determination of Identity of 1018 ISS Adjuvant in HEPLISAV by (b) (4)
 - Method Validation Report VAL 100722: Validation of (b) (4) Method QTM-000377
- 125428/0.48: 1.11.1 Quality Information Amendment , Response to FDA Request sent on 27 April 2016, (b) (4) Method and Validation, received on 16 May 2016
- 125428/0.55: 1.11.1 Quality Information Amendment , Response to FDA Request sent on 18 July 2016, received on 28 July 2016
- 125428/0.58: 1.11.1 Quality Information Amendment , Response to FDA Request sent on 27 April 2016, received 17 August 2016
 - 3.2.P.5.1 Specification
- 125428/0.62: 1.11.1 Quality Information Amendment , Response to FDA Request sent on 02 September 2016, received on 16 September 2016
- 125428/0.71: 1.11.1 Quality Information Amendment , Response to FDA Request sent on 02 September 2016, received on 31 October 2016

Review Narrative

Question 12.(b) (4) Content by (b) (4) Assay [Drug Substance]

The following comments were included in the CR Letter.

(b) (4)

Question 23. 1018 ISS Adjuvant Content by (b) (4) Assay [Drug Product]

Please address the following comments:

- a. How is the extinction coefficient cited in Section 3.2.1 (p. 3) of the SOP QC109-02 determined?

Review of the response: (b) (4)

The response is satisfactory.

- b. Provide description of Sample 1 and Sample 2 used for System Suitability study in the method validation report, Document No. VAL-Q139C-R.

Review of the response: The sponsor clarified that Samples 1 and 2 are independent dilutions of Heplisav DP lot (b) (4) (designated system suitability sample for the validation study). The response is satisfactory.

- c. How do the concentrations of (b) (4) used in the specificity study compare to those in the formulated product?

Review of the response: The sponsor explained that (b) (4)

. Such design for specificity study is acceptable.

- d. What are the (b) (4) of the diluents (a) (b) (4), 1018 ISS, in the specificity study? Did the diluents contribute to (b) (4) of the analyte, when the analytes are diluted with them?

Review of the response: (b) (4)

[REDACTED]

. The results show that the method is specific for the 1018 ISS content determination for the intended DP samples.

- e. We do not agree that accuracy of an assay can be inferred automatically once linearity, precision and specificity are established. Provide data to show accuracy over the range of the assay (b) (4). At the minimum accuracy should be evaluated at three concentration levels, the target concentration, and the lowest and the highest concentrations of the assay range.

In addition, FDA provided further clarification in the response to Dynavax type C meeting (dated Oct. 17, 2014) as following:

The method proposed in the BLA involves measurement of (b) (4) in the drug product and determination of concentration using extinction coefficient. The proposed experimental plan is not clear. We suggest that the accuracy of the method is demonstrated from spike-recovery studies from the product matrix. For example, (b) (4)

Review of the response: (b) (4)

The response is satisfactory.

Conclusion:

The issues under CR Letter comment #23 have been addressed adequately, and the 1018 ISS Adjuvant Content by (b) (4) Assay has been validated adequately for the Drug Product.

Question 24. HBsAg Concentration by (b) (4) Assay [Drug Product]

The following comments were included in the CR Letter.

- a. Please identify which of the results included in Table 2 of the validation report (Document # VAL-DE A090-4-R) were performed at the Dynavax Berkeley laboratory and which ones were performed at the Dynavax Europe laboratory.

Review of the Response: The sponsor provided clarification for Table 2 of the original validation report VAL-DE A090-4-R, and identified the locations where different system suitability samples were tested. Furthermore, the sponsor indicated in the response to the CR letter that the method was re-validated at one location (Method Validation Report, VL097). The reviewer found the response to be adequate.

- b. Section 7.2 (specificity) of the validation report (Document # VAL-DE A090-4-R) states, “Dynavax Berkeley qualification report QUAL-Q116C-R demonstrates that
- (b) (4)
- ” Please explain what (b) (4)
- ” means. Provide the qualification
- report QUAL-Q116C-R.

Review of the Response: The sponsor indicated that 1018 ISS (b) (4)

Question 24b has been adequately addressed in the response.

- c. Provide results showing specificity, intermediate precision and reproducibility (inter-laboratory precision) using (b) (4) concentrations over the assay range, (b) (4).

Review of the Response: In response to Question 24c, the method was re-validated for its specificity and intermediate precision (Method Validation Report, VL097). The sponsor argued since the method would only be used in one location, the validation of reproducibility is unnecessary, which the reviewer concurs.

The specificity of the method was demonstrated by examining the

(b) (4)

Based on the data provided, it was concluded that the concerns raised in CR letter question 24c have been adequately addressed; the specificity and intermediate precision of the method have been validated within drug product matrix over the assay range.

- d. How are the Expected Concentrations reported in section 7.3.2 of the validation report (Document # VAL-DE A090-4-R) determined? Have you used the same assay method or a different method?

Review of the Response: In the response to Question 24d, the sponsor clarified that the Expected Concentrations of test samples in the previous validation report (VAL-DE A090-4-R) was determined by the same assay method. However, the sponsor referred to the

response to Question 24e for a new validation approach for the evaluation of the accuracy of the method. The response is adequate.

- e. We do not agree that accuracy of an assay can be inferred automatically once linearity, precision and specificity are established. Provide data to show accuracy over the range of the assay. At the minimum accuracy should be evaluated at three concentration levels, the target concentration, and the lowest and the highest concentrations of the assay range.

Review of the Response: In the response to Question 24e, the sponsor re-validated the accuracy of the method through a series of spike-recovery studies (Validation Report: VAL-A119-06-R v1):

(b) (4)

(b) (4)

□

□

Conclusion:

The issues under CR Letter comment #24, have been addressed adequately, and the HBsAg Concentration by (b) (4) Assay has been validated adequately for the Drug Product.

Question 26. Extractable Volume [Drug Product]

a. Please provide data to indicate that you consistently meet the required specification.

Review of the Response: The method involves (b) (4)

(b) (4) The proposed specification is not less than (b) (4). However, the sponsor has not provided any result in the original submission.

In Amendment 42, the sponsor provided lot-release test results from (b) (4) lots, all of which shows that the extractable volume is 0.7 mL, which met the proposed specification of (b) (4) mL. However, while reviewing the data, the sponsor found out that the in-house method is not consistent with the (b) (4) harmonized method for this test. The in-house method include the volume (b) (4) as the extractable volume, thereby overestimates the volume. An evaluation showed that the volume retained by the needle varied between (b) (4). Thus, the values are overestimated by the same amount. Retesting the same (b) (4) lots using the (b) (4) harmonized method show that the extractable volume ranges between (b) (4) all of which met the proposed specification.

The sponsor also presented results for the determination of (b) (4), which uses a (b) (4) method. The results from the same lots show that the (b) (4) of the liquid varies from lot to lot in the range (b) (4). The average (b) (4) value is used for the determination of extractable volume.

Conclusion:

The sponsor has adequately addressed the comment # 25 of the CR Letter.

Question 41. Assays for (b) (4) [Drug Substance]

On November 5, 2012, CBER requested that you include in the HBsAg Drug Substance Commercial Release Specification the following tests:

(b) (4)

At this time SOPs, method validation protocols and validation reports for these tests have not been received by CBER. Please provide this information.

(b) (4)

Conclusion: An adequate description of the method is provided and the method was satisfactorily validated.

Additional Test Methods







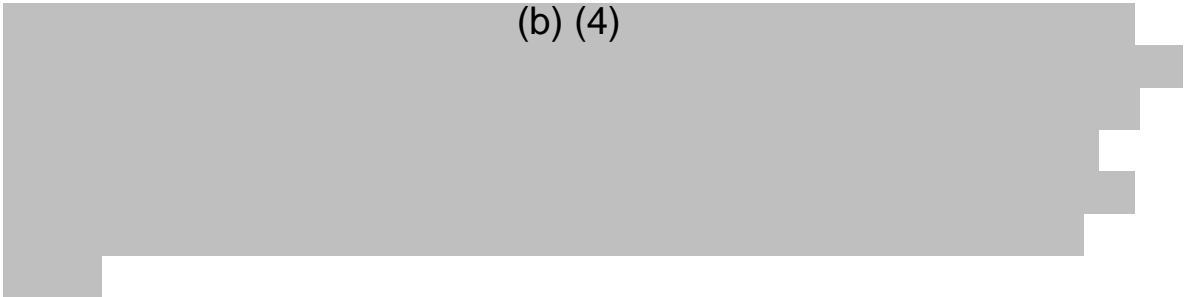
Adjuvant Identity by (b) (4) [Drug Product]

In Amendment 42, the sponsor submitted a new validated (b) (4) method for the identification of the adjuvant in the final container drug product. In this method, identity was established by comparing the (b) (4) of 1018 standard to the (b) (4) of the (b) (4) of the adjuvant in the test samples, run concurrently.

Method

(b) (4)

(b) (4)



Conclusion: The revised method and validation report provided sufficient information to allow approval of this test method as part of this application.







Determination of 1018 Adjuvant (b) (4) [Drug Product]

In Amendment 58 (17 August 2016), Dynavax agreed to include the (b) (4) assay for adjuvant (1018 ISS) in the HEPLISAV Drug Product by (b) (4) as a release test for the drug product. A method description of the procedure described in the SOP (SOP-QC-0110) and the method validation report (VAL-Q234B-R) were submitted as part of their original submission (125428/0) received on 26 April 2012 but was not reviewed at that time because

the purpose of this assay was not clear. The “Method description” provides adequate details of the procedure.

Method

(b) (4)



Conclusion: The sponsor has provided adequate description of the method but the method validation has several deficiencies. The method cannot be approved for lot release due to significant deficiencies, which were included in the CR letter.

Deficiencies Included in the CR Letter

The following deficiencies were identified in the CR letter issued on 10 November 2016 as Deficiency # 49.

Regarding the (b) (4) assay for adjuvant (1018 ISS) in HEPLISAV Drug Product by (b) (4)

Following your communication on 19 August 2016 (Amendment 56) that you will include the (b) (4) assay for adjuvant (1018 ISS) in the Heplisav Drug Product by (b) (4) as a release test, we have reviewed your method SOP (DUS-SOP-QC-0110) and the method validation report (VAL-Q234B-R) and have the following request for information.

- a. Please provide appropriate data to show that the (b) (4) shows all impurities present in 1018 ISS (adjuvant) and that none of them are (b) (4).
- b. In your method validation report it is stated that the validation applies to Dynavax Berkeley and Dynavax Europe laboratories. Please identify your originating and receiving laboratories for this assay. In which laboratory(ies) were all of the validation characteristics, other than Reproducibility, evaluated?
- c. You have determined linearity by adding a 1018 ISS (b) (4) (section 7.3 of your validation report). Please explain how this mixture compared with the actual drug product by providing detailed compositions of both.
- d. You have assessed LOQ and LOD for the (b) (4) only by adding it to (b) (4) HBsAg (section 7.4 of your validation report).
 - i. Please explain how this mixture compared with the actual drug product by providing detailed compositions of both.
 - ii. As per your assay method (DUS-SOP-QC-0110) you do not measure (b) (4) impurity (b) (4). You measure (b) (4) impurities (b) (4). Please provide data for LOQ and LOD for (b) (4) or show by your data that LOQ and LOD for (b) (4) are essentially the same as those of (b) (4) in the drug product.

- e. Please provide data to demonstrate LOQ and LOD for other impurities present in 1018 ISS in the drug product.
- f. Regarding intermediate precision,
 - i. In attachment K of your validation report, you have identified results for (b) (4) but not for the other impurities. Please identify which table corresponds to which impurity in this attachment.
 - ii. Please provide overall RSD from three experiments for (b) (4) and that for each of the other impurities.
- g. Although not clearly stated, it appears from your report that all of the validation data, except those for Reproducibility, were obtained in one laboratory. However, you indicated that the validation applies to both of your laboratories, located at Berkeley and in Europe, implying that you plan to carry out this test at both laboratories to obtain data for lot release. Please provide comparability data from both laboratories with sufficient number of the drug product lots to indicate that the results from the two laboratories are comparable. We suggest that you assess at least 6 lots.
- h. In attachment N of your validation report, you have identified results for (b) (4) but not for the other impurities. Please identify which table corresponds to which impurity in this attachment.
- i. You indicated that you inferred accuracy based on the results of the linearity, precision and specificity (section 7.7 of your validation report) but have not shown any data or data analysis to indicate how you concluded accuracy of the method for the (b) (4) and different impurities, except (b) (4). We do not agree that accuracy can be inferred automatically from the results of the specificity, linearity and precision. Please provide details of your data/data analysis to show how you inferred accuracy of your method from the results of the specificity, linearity and precision. Alternatively, please provide data to demonstrate accuracy of the (b) (4) and of different impurities from spike-recovery studies or by comparing with results obtained using an orthogonal method. Since you decided to measure (b) (4) impurities (b) (4), you may provide accuracy of the method for these two impurities (b) (4).
- j. You assessed accuracy of the method for (b) (4) on the basis of (b) (4) percent. We do not agree with your approach because the percent measurement may be affected due to variation in the area of the (b) (4) and other impurities. Please provide data in which assessment of accuracy is based on (b) (4) of each impurity.

- k. You assessed accuracy of the method for (b) (4) on the basis of (b) (4) percent. We do not agree with your approach because the percent measurement may be affected due to variation in the area of the (b) (4) and other impurities. Please provide data in which assessment of accuracy is based on (b) (4) of each impurity.