



From: Lokesh Bhattacharyya, DBSQ/OCBQ **APPROVED**
By Lokesh Bhattacharyya at 4:16 pm, Jul 10, 2017

To: File: 125428/0

Through: William M. McCormick, Director DBSQ, OCBQ **APPROVED**
By William M McCormick at 8:14 am, Jul 11, 2017

Product: Heplisav

Sponsor: Dynavax

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

Recommendation: Approval

Summary of Review

A new BLA submitted by Dynavax Technologies Corporation for Heplisav [Hepatitis B Vaccine (Recombinant)], STN: 125428. While all other quality control lot release tests for the drug substance, adjuvant and the drug product were adequately described and validated, and found approvable, deficiencies were identified in the validation of the assay method for Adjuvant (b) (4) for the drug product, which are included in the CR Letter issued to the sponsor on 10 November 2016. This memo provides review of the information provided by the sponsor in response to the CR Letter. The submitted information addressed our concerns adequately. The test method for Adjuvant (b) (4) in the drug product is found to be adequate as a quality control lot release test.

Background of Submission

A new BLA is submitted by Dynavax Technologies Corporation for Heplisav [Hepatitis B Vaccine (Recombinant), Adjuvanted], STN: 125428 in 2012. The submission received a Complete Response (CR) Letter, issued on 22 February 2013. The analytical methods and their validations were reviewed and found to have significant deficiencies, which were summarized as questions in the Complete Response (CR) Letter. On 15 March 2016, the sponsor provided a full response to the deficiencies listed in the CR Letter as Amendment 42. The analytical methods and their validations were reviewed and found to be approvable for all assays except one. The approvable assays include:

Drug substance: (b) (4)

Adjuvant: (b) (4)

Drug Product: 1018 ISS Adjuvant Content by (b) (4), HBsAg Concentration by (b) (4) Assay, Extractable Volume (b) (4) method.

However, the method validation for the assay for Adjuvant (b) (4) in Heplisav drug product (DP) was found to have significant deficiencies and was deemed not approvable. The deficiencies were summarized in Complete Response (CR) Letters issued on 22 February 2013 and 10 November 2016. The information provided by Dynavax in response to the CR Letter, dated 22 February 2013, were reviewed previously (Ayikoe et al., 28 November 2016 entitled: Review Memo for the Response to Complete Response Letter – Heplisav [Hepatitis B Vaccine (Recombinant), Adjuvanted]; STN: 125428). While all other quality control lot release tests for the drug substance, adjuvant and the drug product were adequately described and validated, and found approvable, deficiencies were identified in the validation of the assay method for Adjuvant (b) (4) for the drug product. This memo constitutes the review the information provided by the sponsor on the validation of the assay method for Adjuvant (b) (4) in response to the second CR Letter (dated 10 November 2016).

Submitted Information and Documents:

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

- Ayikoe et al., Review Memo for the Response to Complete Response Letter – Heplisav [Hepatitis B Vaccine (Recombinant), Adjuvanted]; STN: 125428, dated 28 November 2016.
- FDA Complete Response Letter (CRL) to Dynavax dated 10 November 2016.
- 125428/72: Type A Briefing Package Questions, received on 14 December 2016
- Response to Type A Briefing Package Questions, sent on 9 January 2017
- 125428/74: 1.11.1 Quality Information Amendment, received on 8 February 2017
 - Response to 10 November 2016 CRL, Question 49
- 125428/74: 3.2.P.5.3 Validation of Analytical Procedures
 - AD-2011-05 v3: Analytical Development Report – Robustness Test for the Heplisav 1018 ISS (b) (4) Test Method, Part 1 of 2, dated 18 Dec 2014
 - AD-2011-06 v1: Analytical Development Report – Robustness Test for the Heplisav 1018 ISS (b) (4) Test Method, Part 2 of 2, dated 16 Dec 2014
- 125428/84: 1.11.1 Quality Information Amendment, received on 9 May 2017
 - Response to 27 February 2017 Information Request

- 125428/89: 1.11.1 Quality Information Amendment, received on 26 May 2017
 - Response (2) to 10 November 2016 CRL, Question 49

Determination of 1018 Adjuvant (b) (4) in Drug Product

Method

(b) (4)

Type A Meeting

A review of the validation of the method identified a few deficiencies, which were summarized in the CR letter issued on 10 November 2016 as deficiency # 49. In response, Dynavax requested a Type A meeting to obtain clarification on some of the deficiencies identified by CBER and submitted a briefing package on 14 December 2017 (Amendment 72). In the Type A telecon meeting, held on 10 January 2017, Dynavax clarified that the method is intended only to provide (b) (4) in the drug product. It is not intended to provide (b) (4) of the adjuvant in the DP. The data on the impurities included in the submitted validation report is not relevant for the validation of this assay and should not be part of the review. Thus, CBER should ignore the deficiencies related to the impurities. CBER clarified that there are two generally accepted approaches to validate an assay for (b) (4)

Based on the data on impurities and absence of adequate validation data on (b) (4) in the validation report, CBER thought that Dynavax has taken the former approach. However, CBER would accept if Dynavax chooses to take the second approach. However, in that case, the method should be fully validated for (b) (4). CBER pointed out two major deficiencies for validation of the method for (b) (4).

- Dynavax provided data for specificity and precision of the assay for (b) (4) but did not provide data demonstrating linearity and accuracy of the assay.
- The results show that an impurity, (b) (4). This was not addressed in the validation report. At the minimum, Dynavax needs to show that (b) (4) is not generated due to as a product-related impurity in the formulation and does not change in the drug product with time. In addition, there should also be a clear

recognition that the specification, even though it is stated as (b) (4), it also includes (b) (4) impurity.

Dynavax pointed out that the amount of (b) (4) and will not affect the results. CBER agreed tentatively subject to review of the data provided by Dynavax.

In the Type A meeting on 10 Jan 2017, CBER and Dynavax agreed that additional data on the product-related impurity (b) (4) would be provided to demonstrate that (b) (4) is (b) (4), 1018, and does not change with time in the DP. CBER and Dynavax also agreed that an orthogonal method that has undergone a limited validation for specificity, accuracy, linearity and intra-assay precision, should be used to obtain the additional data on (b) (4).

In addition, CBER and Dynavax agreed that the sponsor would perform additional validation study to demonstrate linearity and accuracy of the 1018 Adjuvant (b) (4).

Dynavax provided response as Quality Information Amendments 74, 84 and 89.

Review of the Response submitted in Amendment 74

- 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).

Review of the Response

In response, Dynavax conducted two studies. In the first study, (b) (4)

(b) (4)

In a second experiment, (b) (4)

(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?

Review of the Response

Dynavax informed that Dynavax, Berkeley is the originating laboratory and Dynavax GmbH located in Dusseldorf, Germany is the receiving laboratory. Previously reported validation data, except reproducibility, were generated at the Dynavax, Berkeley site. However, the additional validation data for (b) (4) (linearity and accuracy), which Dynavax submitted as Amendment 84, were obtained at the Dusseldorf laboratory. The results are acceptable (see Review of the Response submitted in Amendment 84 later for details). The results combined with the results of reproducibility study that Dynavax submitted in Amendment 42 and previously reviewed to be adequate (Ayikoe et al., Review Memo for the Response to Complete Response Letter – HepHisav [Hepatitis B Vaccine (Recombinant), Adjuvanted]; STN: 125428, 28 November 2016) demonstrate adequate co-validation of the assay by both laboratories, and either may perform this assay for lot release.

- c. You have determined linearity by adding a 1018 ISS (b) (4) (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.

Review of the Response

Dynavax indicated that the drug product is diluted (b) (4) for the assay and provided a table comparing compositions of the drug product test article after dilution and the linearity samples. The table shows that the compositions are comparable.

- d. You have assessed LOQ and LOD for the (b) (4) only by adding it (b) (4) (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). 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.

Review of the Response

To address IR # d.i., the sponsor explained that the addition of the drug product to (b) (4) of the drug product, which is same as the dilution of the drug product necessary for this assay. Since the drug product is diluted (b) (4) for the assay, the composition of the solution after addition of the drug product to (b) (4) was comparable to that of samples used in the assay, except that it did not contain the (b) (4), of the adjuvant.

In response to IR # d.ii., Dynavax referred to the Type A meeting held on 10 January 2017 and indicated that, as per the agreement with CBER in the meeting, Dynavax would submit validation of the assay for the (b) (4), of the adjuvant (1018/AGU) only. Validation of the assay for impurities is not necessary. CBER agreed.

- 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.

Review of the Responses

In response to IR # e. and f., Dynavax referred to the Type A meeting held on 10 January 2017 and indicated that, as per the agreement with CBER in the meeting, Dynavax would submit validation of the assay for linearity and accuracy for the (b) (4), of the adjuvant (1018/AGU) only. Validation of the assay for impurities is not necessary. CBER agreed.

- 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.

Review of the Response

Dynavax indicated that the validation data other than those for Reproducibility were obtained at the Berkley site. However, no release testing will be performed at this site. All release testing will be performed at the Dusseldorf, Germany site. The validation data requested by CBER (linearity and accuracy of (b) (4)) would be generated at the Dusseldorf, Germany site, which would address CBER IR. The data were submitted on 26 May 2017. The results are acceptable (see Review of the Response submitted in Amendment 84 later for details). The results combined with the results of reproducibility study that Dynavax submitted in Amendment 42 and previously reviewed to be adequate (Ayikoe et al., Review Memo for the Response to Complete Response Letter – Heplisav [Hepatitis B Vaccine (Recombinant), Adjuvanted]; STN: 125428, 28 November 2016) demonstrate adequate co-validation of the assay by both laboratories, and either may perform this assay for lot release.

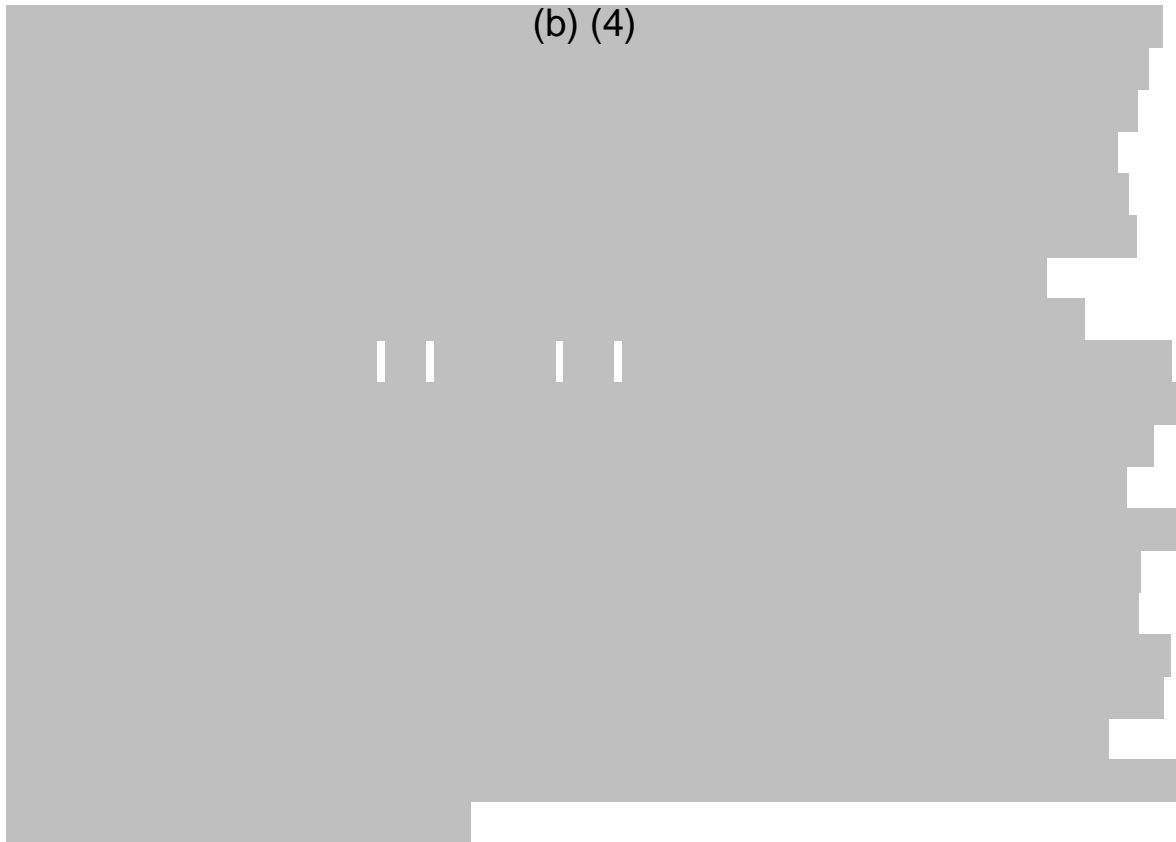
- h. In attachment N of your validation report, you have identified results for (b) (4) but not for the other impurities. Please identify which table corresponds to which impurity in this attachment.
- i. You indicated that you inferred accuracy based on the results of the linearity, precision and specificity (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), you may provide accuracy of the method for these two impurities (b) (4).
- j. You assessed accuracy of the method for (b) (4). 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.

Review of the Responses

In response to IR # h., i., and j., Dynavax referred to the Type A meeting held on 10 January 2017 and indicated that, as per the agreement with CBER in the meeting, Dynavax would submit validation of the assay for linearity and accuracy for the (b) (4), of the adjuvant (1018/AGU) only. Validation of the assay for impurities is not necessary. CBER agreed.

- k. You have not conducted robustness studies for your method. Please provide the data and the statistical evaluation of your results from adequate studies to demonstrate your method robustness.

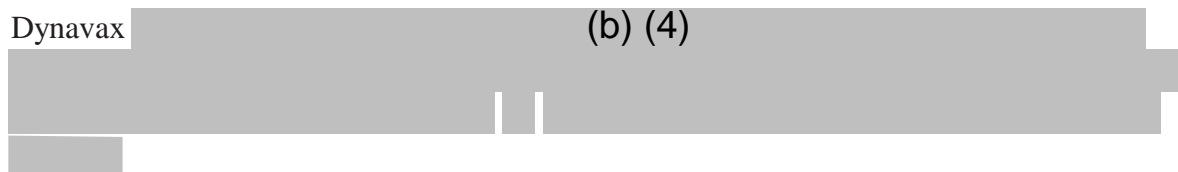
(b) (4)



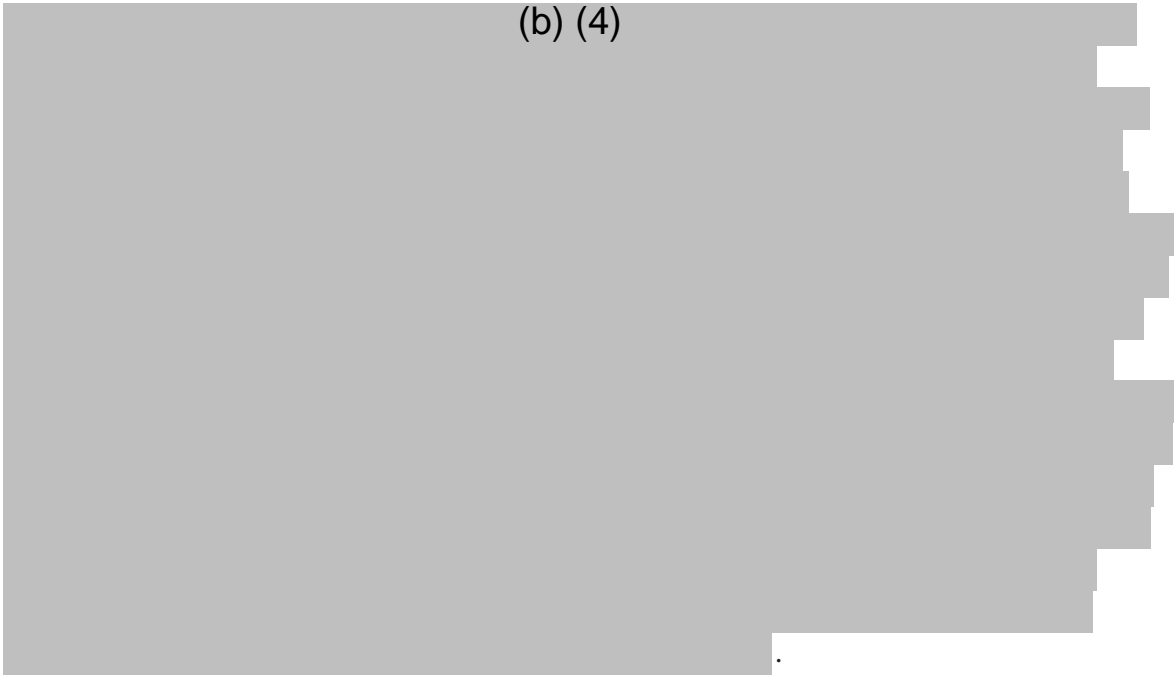
Review of the Response submitted in Amendment 84: Assessment of Linearity and Accuracy of (b) (4) in the Adjuvant (AGU/1018)

In the Type A meeting on 10 Jan 2017, CBER and Dynavax agreed on a validation approach for the (b) (4) method for determining (b) (4) in the drug product to address outstanding validation issues of the method. In this approach, Dynavax would provide data demonstrating linearity and accuracy of the method. Specificity and precision data presented before by the sponsor had been reviewed and found acceptable (Ayikoe et al., Review Memo for the Response to Complete Response Letter – Heplisav [Hepatitis B Vaccine (Recombinant), Adjuvanted]; STN: 125428, dated 28 November 2016).

Dynavax (b) (4)



(b) (4)



It may be worth noting here that the (b) (4) of the DP presented in the document entitled Response to 10 November 2016 CRL, Question 49 (Amendment 74) do not appear to be consistent with (b) (4). They appear to be consistent with much higher amounts of (b) (4) in the DP samples. Even though the (b) (4) shows a few impurity (b) (4) within the separation window, the largest impurity (b) (4) constitutes only (b) (4), as per the results provided by the sponsor in Amendment 74.

Review of the Response submitted in Amendment 89

In the Type A meeting on 10 Jan 2017, CBER and Dynavax agreed that additional data on the product-related impurity (b) (4) would be provided to demonstrate that (b) (4) is not a degradation product of 1018. CBER and Dynavax also agreed that an orthogonal method that has undergone a limited validation for specificity, accuracy, linearity and intra-assay precision, should be used to obtain the additional (b) (4) data.

Validation of the Orthogonal Method for the Determination of (b) (4) impurity

(b) (4)

