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Subject: Final Review Memo for the New BLA Submission – Heplisav [Hepatitis B Vaccine (Recombinant)]; STN: 125428
To: File: 125428/0
Through: William M. McCormick, Director OCBQ/DBSQC HFM-680

Recommendation: CR Letter—Incomplete Submission

Summary of Review

A new BLA is submitted by Dynavax Technologies Corporation for Heplisav [Hepatitis B Vaccine (Recombinant)], STN: 125428. This memo is the final review memo and applies to the review of the test procedures and validation reports for the lot-release tests listed below.

Drug Substance

(b) (4) [Redacted]

Adjuvant

(b) (4) [Redacted]

Drug Product

- 1018 ISS Adjuvant Identity by (b) (4)
- 1018 ISS Adjuvant Content by (b) (4) Assay
- HBsAg Concentration by (b) (4) Assay
- pH (b) (4)
- Particulate Contamination: Sub-visible Particles/Particulate Matter (b) (4)
- Extractable Volume (b) (4)

In-process Tests

(b) (4) [Redacted]

Based on the review of the above test methods and their respective method validation reports several deficiencies were identified. These deficiencies were brought to the attention of Dynavax Technologies Corporation in an Information Request (IR) sent on August 16, 2012. As of the time of writing this memo, only a few of the questions/comments were addressed. The information provided by the sponsor up to this point does not permit complete review. Thus, it is recommended that the application is not approved at this time but a Complete Response (CR) letter is sent to the sponsor asking them to address the outstanding issues and comments, which are summarized at the end of this memo in "CR Letter" section.

Background of Submission

A new BLA is submitted by Dynavax Technologies Corporation for Heplisav [Hepatitis B Vaccine (Recombinant)], STN: 125428. The immunogenic component, hepatitis B surface antigen (HBsAg), subtype adw, is produced in the yeast strain *Hansenula polymorpha* using recombinant technology. HBsAg is a lipoprotein particle of approximately (b) (4) in diameter. The protein component consists of a polypeptide chain containing (b) (4) amino acids with a theoretical molecular weight of (b) (4). The 1018 ISS Adjuvant is a 22-mer phosphorothioate oligonucleotide with a molecular mass of (b) (4) which is produced by (b) (4). HBsAg Drug Substance is formulated with 1018 ISS Adjuvant to produce HEPLISAV Drug Product.

Submitted Information and Documents:

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

- Cover letter

Drug Substance

(b) (4) [Redacted]

(b) (4)

Drug Product

- 3.2.P.5.1: Specifications—Final Container
- 3.2.P.5.2: Analytical Procedures

- 3.2.P.5.2: SOP – Identity Determination of 1018 ISS in Heplisav by (b) (4) (Document number: QC 152-01)
- 3.2.P.5.2: SOP – (b) (4) Determination of 1018 ISS in Heplisav Drug Product by (b) (4) (Document number: QC 110-06)
- 3.2.P.5.3: Validation Report: Identity, Purity and (b) (4) of 1018 ISS in Heplisav Drug Product by (b) (4) (Document number: VAL-Q234B-R)
- SOP QC 109-02: Identity and Concentration determination by (b) (4) for ISS from Drug product
- 3.2.P.5.3: Method Validation Report—Determination of Oligonucleotide Concentration In 1018 ISS-HBsAg Drug Product by (b) (4) (Document number: VAL-Q139C-R)
- SOP A090-06: Determination of HBsAg Protein Concentration in Heplisav Drug Product by the (b) (4)
- 3.2.P.5.3: Method Validation Report—Determination of HBsAg Protein Concentration In Heplisav Drug Product by the (b) (4) (Document number: VAL-DE A090-4-R)
- Method Description for Extractable (b) (4) (Referenced document No: SOP PH04-10)

Review Narrative

Drug Substance

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Adjuvant

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

Drug Product

1. 1018 ISS Adjuvant Identity by (b) (4)

Method

A (b) (4) is used to confirm the identity of 1018 ISS Adjuvant in the Drug Product. The SOP, QC152-01: Identity Determination of 1018 ISS in Heplisav by (b) (4), is submitted. The method employs (b) (4)

Identity of 1018 ISS is tested by analyzing (b) (4)

confirms the identity of 1018 ISS Adjuvant in the Drug Product. The SOP method includes appropriate assay acceptance criteria for the identity test.

Method Validation

(b) (4)

Information Request

None.

Conclusion

The method is appropriate and it was validated adequately. There is no outstanding issue. The method can be approved for lot-release testing.

2. 1018 ISS Adjuvant Content by (b) (4) Assay

Method

The concentration of 1018 ISS Adjuvant in Heplisav drug product is determined by
(b) (4)

However, no data were provided in support of the extinction coefficient value. A detailed test procedure, SOP QC109-02: Identity and Concentration determination by (b) (4) for ISS from drug product, is submitted.

Method Validation

(b) (4)

(b) (4)

(b) (4)

Information Request and Review of Response

The following Information Request (IR) was sent to Dynavax Technologies Corporation on August 16, 2012. None of the IR questions have been addressed by the sponsor as of the time of writing this memo.

- a. How is the extinction coefficient cited in Section 3.2.1 (p. 3) of the SOP QC109-02 determined?
- b. Provide description of Sample 1 and Sample 2 used for System Suitability study in the method validation report, Document No. VAL-Q139C-R.
- c. How do the concentrations of (b) (4) used in the specificity study compare to those in the formulated product?
- d. What are the (b) (4) of the diluents (b) (4), 1018 ISS, in the specificity study? Did the diluents contribute to ^(D) (4) of the analyte, when the analytes are diluted with them?
- 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 assay range (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.

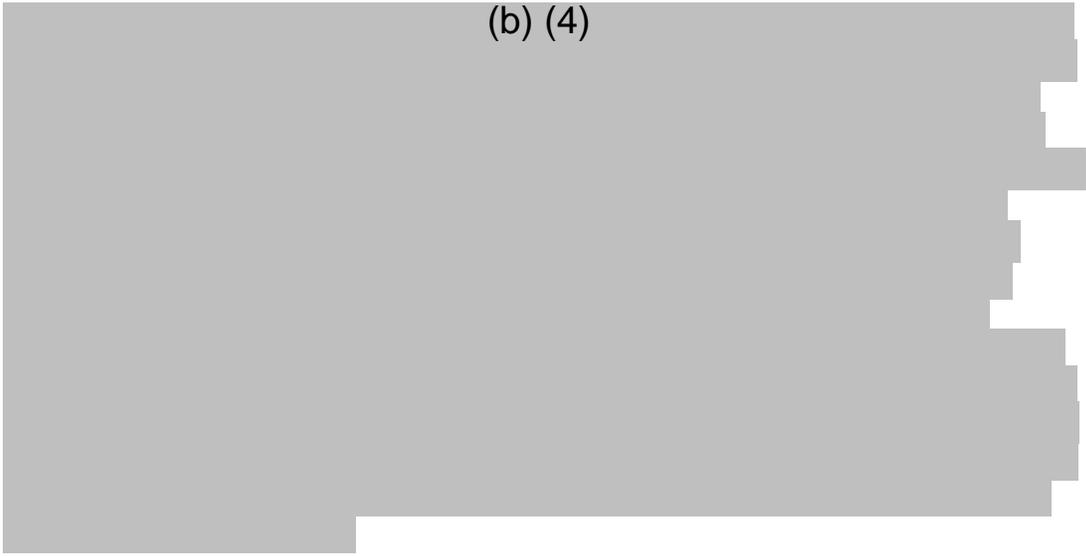
Conclusion

Additional information is necessary to complete review of this procedure and its validation. We requested additional information on this assay through an IR submitted on August 16, 2012. As of the time of writing this memo, we have not received response from the sponsor on any of the questions on this assay. It is not possible to complete review of this procedure and its validation without sponsor's response. It is recommended that a CR letter be issued at this time requesting the sponsor to submit the requested information.

3. HBsAg Concentration by (b) (4) Assay

Method

(b) (4)



Validation

(b) (4)



(b) (4)

Information Request and Review of Response

The following Information Request (IR) was sent to Dynavax Technologies Corporation on August 16, 2012. None of the IR questions have been addressed by the sponsor as of the time of writing this memo.

- 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.
- b. Section 7.2 (specificity) of the validation report (Document # VAL-DE A090-4-R) states, “Dynavax Berkeley qualification report QUAL-Q116C-R demonstrates tha (b) (4) means. Provide the qualification report QUAL-Q116C-R.
- c. Provide results showing specificity, intermediate precision and reproducibility (inter-laboratory precision) using protein concentrations over the assay range, (b) (4)
- 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?
- 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.

Conclusion

A significant amount of additional information is necessary to complete review of this procedure and its validation. We requested additional information on this assay through an IR submitted on August 16, 2012. As of the time of writing this memo, we have not received response on any of the questions. These information are necessary to complete review of this procedure and its validation without sponsor's response. It is recommended that a CR letter be issued at this time requesting the sponsor to submit the requested information.

4. pH

The pH of Heplisav Drug Product is measured as described in (b) (4) [REDACTED]
SOP (document number 016) for the method was not included in the submission. Since this is a compendial method validation of this method is not necessary.

Information Request

None.

Conclusion

The method is appropriate and it was validated adequately. There is no outstanding issue. The method can be approved for lot-release testing.

5. Particulate Contamination: Sub-visible Particles/Particulate Matter

Heplisav drug product is tested for Particulate Contamination: Sub-visible Particles/Particulate Matter as described in (b) (4) [REDACTED]

[REDACTED] SOP for the method was not included in the submission, and the document number not provided. Since this is a compendial method validation of this method is not necessary.

Information Request

None.

Conclusion

The method is appropriate and it was validated adequately. There is no outstanding issue. The method can be approved for lot-release testing.

6. Extractable Volume (b) (4)

Heplisav drug product is tested for extractable volume (b) (4) as described in (b) (4) (harmonized compendial method). The SOP has not been included in the BLA submission, but the submitted method description (Document reference number SOP PH04-10: Method Description for Extractable (b) (4) describes the method in sufficient details to permit complete review. Extractable (b) (4) is measured at (b) (4) intervals during the manufacturing of Heplisav drug product. (b) (4)

(b) (4). Given that the drug product containers will contain a nominal volume of less than 2 mL, (b) (4)

(b) (4). However, the actual number of vials is not mentioned in the method description. The (b) (4) volume must be not less than the sum of the nominal values of the containers taken collectively. SOP (document number QC111) for the method was not included in the submission. Since this is a compendial method validation of this method is not necessary.

Information Request

None.

Conclusion

The method is appropriate and it was validated adequately. There is no outstanding issue. The method can be approved for lot-release testing.

In-Process Testing

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Conclusion

A new BLA is submitted by Dynavax Technologies Corporation for Heplisav [Hepatitis B Vaccine (Recombinant)], STN: 125428. Analytical chemistry methods for lot-release and in-process testing and validation of the methods, included in the submission were reviewed. This includes lot-release tests for antigen drug substance (HBsAg), adjuvant drug substance and the formulated final product as well as In-process tests for (b) (4). Based on the review, several deficiencies were identified. An IR was sent to the Sponsor on August 16, 2012. As of the time of writing this memo, only a few of the questions/comments were addressed. The information provided by the sponsor up to this point does not permit complete review. It is recommended that the application is not approved at this time but a Complete Response (CR) letter is sent to the sponsor asking them to address the outstanding issues and comments, which are summarized below.

CR Letter

Based on the review of the analytical chemistry methods for lot-release and in-process testing and validation of the methods for antigen drug substance (HBsAg), adjuvant drug substance and the formulated final product, included in the initial submission and subsequent amendments several deficiencies were identified. These deficiencies were brought to the attention of Dynavax Technologies Corporation in an Information Request (IR) sent on August 16, 2012. As of the time of writing this memo, only a few of the questions/comments were addressed. The information available at this point does not permit complete review of the application. The sponsor must address all outstanding issues and comments within a mutually

agreeable timeline. These unaddressed issues and comments are summarized below by test method.

Drug Substance

(b) (4) [Redacted text block containing multiple paragraphs of information, all obscured by grey bars.]

(b) (4)

[Redacted]

[Redacted]

Adjuvant

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted text block]

Drug Product

1. 1018 ISS Adjuvant Content by (b) (4) Assay

Please address the following comments:

(b) (4)

[Redacted text block]

(b) (4)

2. HBsAg Concentration by (b) (4) Assay

Please address the following comments:

(b) (4)

[Redacted content]

3. Extractable Volume (b) (4)

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