

MEMORANDUM

Date 15 November, 2016

To Administrative File for STN: BL 125428/0

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Through Muhammad Shahabuddin, Ph.D., DBSQC, OCBQ, CBER, FDA

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Applicant: Dynavax Technologies Corporation

Subject: Review Memo of IR responses for Biologics Licensure Application (BLA) for HEPLISAV [Hepatitis B Vaccine (Recombinant)] STN 125428/0

Recommended Action:

Documents submitted to support Analytical Methods (Section 3.2.S.4.2 and 3.2.S.4.3) of Quality Section of the BLA for HEPLISAV, were reviewed for test methods and their validation reports for determination of **Purity**, (b) (4) **and In-Vivo Relative Potency** for HBsAg (b) (4) drug product (DP) and were found adequate for the use of the method for intended purposes. Based on DBSQC's review, the above said test methods of this application are approvable.

Summary:

In the current submission, sponsor has provided the responses to all DBSQC questions on validation of analytical test methods for testing of purity, (b) (4) (b) (4) and in-vivo relative potency for (b) (4) drug product. The test methods- DUS-SOP-QC-0172, [DUS- QC-168-01, SOP-QC-169-01], [DUS- QC-0113-07 and DUS-QC-0089-09] have been properly validated in the new validation reports for purity and (b) (4) (VL116), (b) (4) (VL100 and VL101) and in-vivo potency (VL099), respectively. VL22 was previously submitted for validation of (b) (4) kit to estimate the seroconversion of (b) (4) for anti-HBsAg titers. Sponsor also submitted the comparability protocol for *in-vivo* and *in-vitro* potency assay for Heplisav DP, to establish the equivalency of the two methods for a future replacement of the *in-vivo* test method. DBSQC reserves making comments on the comparability study at this time.

Submissions Reviewed:

STN125428/0, Dated: March 16, 2016

Methods and Validation documents Reviewed:

1. VL101- (b) (4) Method Validation Report for HEPLISAV DP.
2. VL100- Method Validation Report- Determination of (b) (4) .
3. VL99- Validation report for determination of relative Potency for HEPLISAV DP.
4. DUS- QC-0113-07 (Preparation of vaccine dilutions of Heplisav-Part I and II Potency assay).
5. DUS-QC-0089-09 (In vivo potency measurement of titers, Part III)
6. VL022- Validation report for Potency for DP by (b) (4) .
7. DUS-SOP-QC-0172- Determination of HBsAg purity, Identity and (b) (4) .
8. VALQ209A/QC128-R2-Method Validation Report – for Identity for (b) (4) .
9. VL116- Method Validation Report- Determination of Identity, Purity, and (b) (4) of HBsAg (b) (4)
10. DUS- QC-168-01 -for determination of (b) (4) of HBsAg (b) (4)
11. SOP-QC-169-01 - (b) (4) test methods for determination of HBsAg (b) (4) in HEPLISAV.
12. AD-2016-03-P- *In vitro* and *in vivo* potency assays comparability.

Background:

Dynavax Technologies Corporation submitted a BLA on April 26, 2012 for licensing of HEPLISAV for immunization against infection caused by all known subtypes of Hepatitis B virus in adults 18 through 70 years of age.

Preliminary review of the analytical methods in CMC quality section of the application found the need of additional documents for a complete review by DBSQC, a list of which were communicated to the sponsor on June 18, 2012.

Below is a chronology of the subsequent communication between Dynavax and CBER;

1. On July 17, 2012- Sponsor submitted documents as amendment 125428/01, to the file.
2. On August 9, 2012- Sponsor submitted the animal protocol used for IVRP assay as amendment 125428/ 03.
3. On September 13, 2012- Sponsor provided additional documents to CBER as amendment 125428/ 05.
4. On February 22, 2013- a Complete Response Letter (CRL) was issued by CBER.
5. On July 30, 2014- Dynavax submitted follow-up questions regarding general method validation issues and seeking to clarify issues raised by DBSQC in the February 22, 2013 CRL.

6. On October 17, 2014- CBER provided clarifications of Dynavax questions from July 30, 2014 communication.
7. On March 16, 2016- Dynavax submitted a full response to CBER CRLs.
8. On April 18, 2016- CBER issued a Major Amendment letter due to major information missing on CMC and clinical data.
9. On November 10, 2016- CBER issued second CRL to the sponsor following major clinical safety issues on November 10, 2016.

DBSQC Review of Dynavax Response to CR Letter of March 16, 2016:

Original CR questions are provided in italics preserving the original numbering from the CR letter (CRL items 26-40); DBSQC's review and conclusions follow each issue.

(b) (4) [Redacted]

(b) (4) [Redacted]

[Redacted]

[Redacted]

(b) (4) [Redacted]

5. Specificity: [REDACTED] (b) (4)

Stability Indicating Properties of the *in vitro* Test Method will be evaluated using HELPLISAV DP exposed to different factors including, but not limited to (b) (4)

Sponsor commits to providing the validation and characterization results for (b) (4) test method, along with stability data to CBER prior to distributing the product made with the change.

A discussion regarding the justification of “Target Range of (b) (4) of the relative potency” will be needed when sponsor submits the validation results of this study. DBSQC reserves the comments at this time for the above mentioned study plan.
