

MEMORANDUM

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To Administrative File for STN: BL 125428/0

From Anil Choudhary, Ph.D., DBSQC, OCBQ, HFM-681
Muhammad Shahabuddin, Ph.D., DBSQC, OCBQ, HFM-681

Through William M. McCormick, Ph.D. Director DBSQC, OCBQ HFM-681

Applicant: Dynavax Technologies Corporation

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

Submissions Reviewed:

STN125428/0, Dated: April 26, 2012
STN125428/0.1, Dated: July 17, 2012
STN125428/0.3, Dated: August 9, 2012
STN125428/0.5, Dated: September 13, 2012

Methods and Validation documents Reviewed:

1. Method Validation Report QS784: Method validation of the (b) (4) assay for the determination of (b) (4) in Drug Substance.
2. Method Validation Report QS677: Method validation of the (b) (4) assay for the determination of (b) (4) in Drug Substance.
3. Method Validation Report QS720: Method validation of the (b) (4) assay for the determination of HBsAg (b) (4) and identity in Heplisav Drug Product.
4. Method Validation Report QS491: Re-validation of the HBsAg (b) (4) for measurement in Heplisav.
5. SOP A012-5: Standard Operating Procedures, Validation of Analytical Procedures.
6. Validation Report VAL-Q209A/QC128-01-R: Determination of (b) (4) of HBsAg Drug Substance by (b) (4).
7. Validation Report QS498: Re-validation of (b) (4) method for the determination of **Identity** of samples of Heplisav.
8. **Validation Protocol VAL-248A/QC128 03-P:** HBsAg Stability study by (b) (4) - the Validation plan and report.

9. Method description **SOP QC 128-03** Determination of (b) (4) of HBsAg DS and its Validation Plan and Report (VAL QC209A/QC 128-01-R).
10. Method description SOP QC 129-02: Determination of the (b) (4) of HBsAg in HEPISAV Drug product by (b) (4).
11. Method Validation Report VL014: Method validation of quantitative (b) (4) assay for determination of (b) (4) of HBsAg in HEPISAV Drug product.
12. **SOP QC006** Method for (b) (4).
13. **SOP QC 008** Method for (b) (4).
14. **SOP 006/013** Method description for determination of HBsAg (b) (4) by (b) (4) and for stability by visually comparing test article to reference standard.
15. Method description SOP A118-05: Determination of HBsAg Identity and (b) (4) for HEPLISAV Drug Product for release and stability testing, by (b) (4).
16. HEPLISAV Drug Product Development: Analytical Procedures Proposed for Removal.
17. Method Validation Report VAL-QC113/089-R Rev.1: Validation of Heplisav *in vivo* potency assay.
18. Method Validation Protocol: VAL-QC113/089-P Rev.1: Validation of Heplisav *in vivo* potency assay.
19. Method Validation Report VL-022: Method Validation of (b) (4) for determination of anti-HBs antibody titers in (b) (4) mouse sera.
20. Method Validation Plan VL022: Method Validation of (b) (4) for the determination of anti-HBs antibody titers in (b) (4) mouse sera.
21. Method description QC113-02 and QC113-03 (Heplisav Potency: Part I- Preparation of vaccine dilutions)
22. In vivo Potency Assay Part II: Vaccinations and Serum Sampling of (b) (4) mice (Animal Protocol).
23. Method description for Potency Assay: SOP QC089-05 (Heplisav Potency: Part III).
24. **QX011** Method Validation and Protocol/Plan for comparison of (b) (4) assay kit

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 and a number of issues with regard to adequacy of method and its validation were found. Based on DBSQC's review, additional clarification and documents are needed from the sponsor for a complete review of this application at this time.

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. The sponsor had submitted an

Investigational New Drug Application (BB-IND 12692, Effective October 30, 2005 and BB-IND 13332, Effective April 26, 2007).

HEPLISAV™ is a recombinant hepatitis B vaccine for active immunization against hepatitis B virus infection. The immunogenic component, hepatitis B surface antigen (HBsAg), is produced in the yeast strain *Hansenula polymorpha* (subtype adw) using recombinant technology at Rhein Biotech GmbH (a wholly owned subsidiary). HBsAg is (b) (4)

The 1018 ISS Adjuvant is a novel 22-mer immunostimulatory phosphorothioate oligonucleotide with a molecular mass of (b) (4) that is produced by (b) (4). HBsAg Drug Substance (DS) is formulated with 1018 ISS Adjuvant to produce HEPLISAV Drug Product.

HEPLISAV Drug Product (DP) is a sterile, liquid dosage form that is administered as an intramuscular injection. The finished vial (0.7 mL) contains 4200 mcg of 1018 ISS Adjuvant and 28 mcg of HBsAg Drug Substance of which the dose of 0.5 mL contains 3000 mcg of 1018 ISS Adjuvant and 20 mcg of HBsAg Drug Substance is administered.

Preliminary review of the analytical methods in 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. Subsequently, sponsor submitted additional documents (not in response to CBER's response to additional documents) on July 17, 2012 as amendment 125428/01. Sponsor submitted the animal protocol used for potency determination of the HEPLISAV product on August 9, 2012 as amendment 125428/ 03. Additional documents requested by CBER on June 18, 2012 were provided by the sponsor on Sept 13, 2012 as amendment 125428/ 05.

Review of Analytical Procedures

Following three analytical methods used for analysis of DS and DP are reviewed:

1. **Determination of** (b) (4) **of HBsAg in** (b) (4) **DP by** (b) (4)
2. **Determination of Potency** of HBsAg in DP by (b) (4) immunization and testing the anti-HBsAg antibody titers by (b) (4).
3. **Determination of** (b) (4) **and purity** of the HBsAg by (b) (4) DP.

1. Determination of HBsAg (b) (4) **:**

A. Validation of (b) (4) **in Drug Substance;**

(b) (4)

(b) (4)

B. Validation of HBsAg (b) (4) in Drug Product and Vaccine Sample;

Section 3.2.P.5.2 and 3.2.P.5.3 of the submission describes the Analytical Procedures and Validation of Analytical Procedures for Drug Product. Sponsor has submitted validation reports (QS 491 and QS 720) to support the Validation of (b) (4) of HBsAg drug product in accordance with ICH Q2A, ICH Q2B and ICH Q2(R1) guidelines and sponsor's SOP A012. The HBsAg drug product has been evaluated for its (b) (4) based method. In this study the Heplisav drug product/vaccine samples were compared with HBsAg standard.

DBSQC Review for HBsAg (b) (4) in DP;

(b) (4)

(b) (4)

2. Potency Determination of HBsAg in HEPLISAV DP

The potency of HEPLISAV Drug Product is measured by an in vivo potency assay in (b) (4) as described in (b) (4)

The immunoassay includes several steps that are summarized here:

(b) (4)

The anti-HBsAg antibody concentration is determined

(b) (4)

Relative potency of the test article is determined against a reference material. The reference material is part of a representative lot shown to be as immunogenic in (b) (4) as a lot that showed immunogenicity in a clinical study in humans.

The potency assay is part of the release and stability testing for Heplisav vaccine lots.

The potency assay of hepatitis B vaccine is described in three parts:

(b) (4)

Validation of (b) (4) kit is provided by sponsor in Validation report VL 022 (Method Validation Plan VL022), wherein following parameters have been evaluated: Accuracy, Precision (Repeatability, Intermediate Precision), Specificity and Detection Limit (determination of cut-off). Robustness will be addressed in a separate study. This method validation was performed according to ICH Q2(R1) and SOP A012.

A. Validation Study for

(b) (4)

Assay for Determination of Anti-HBsAg Titers (QX011: July, 2010)

The immunogenicity of Hephisav was determined by measuring the titer of anti-HBsAg antibodies in serum. Anti-HBs antibody titers were previously determined using the

(b) (4) following SOP QC089-04. As mentioned above this product line (b) (4)

and was validated. Prior to the full method validation however, a comparison of the (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

C. Validation of *in vivo* Potency Assay for DP (Val-QC113/089-R Revision 1: Feb,2012)

The *in vivo* potency assay for Hepisav DP was validated following the validation protocol (Val-QC113/089 Revision 1) for validating SOP QC113 and SOP QC 089. The validation described in this protocol includes all steps to determine the relative potency of Hepisav, The *in-vivo* study was done at (b) (4) and sample analysis using an anti-HBsAg (b) (4) was done at Rhein Biotech. The validation includes data from prospective studies and historical data, which will be retrospectively analyzed. The use of historical data is justified to minimize the use of animals for validation experiments.

The method described in (b) (4) was adopted for the potency test. (b) (4)

B. Determination of (b) (4), Purity, and (b) (4) of Drug Product by (b) (4) Analysis

The Purity of Heplisav DP was reported in VL014 (Determination of the (b) (4) of Heplisav drug product by (b) (4)) following SOP QC129-02 (draft). The same SOP was also adapted for evaluating two of the stability parameters for HBsAg: (b) (4)

(b) (4), developed in DE facility as SOP QC128-03 and DBK facility as Q209 (b) (4). The two methods *SOP 128-03 and 129-02* are technically considered equivalent and differ in treatment of HBsAg DP, wherein the later require the HBsAg DP being (b) (4). Therefore, this study was limited to evaluation of repeatability, specificity and precision due to inclusion of the (b) (4) step in the SOP 129-02 (draft). The accuracy, linearity, range and LOD/LOQ have been documented in Val-Q209A/QC 128-01-R.

Review for (b) (4), Purity, and (b) (4) of HBsAg DP;

The stability of the HBsAg DP was evaluated by (b) (4)

(b) (4)

(b) (4)

The validation parameters evaluated in this study (VL 014): precision, Repeatability, Intermediate precision and specificity are shown to meet the acceptance criteria for the (b) (4) method for stability of Heplisav DP by (b) (4)

The **Identity** of the HBsAg in the HBsAg DP was evaluated in validation report QS-498 : (Re-validation of the (b) (4) method for the determination of Identity of samples of Heplisav). The study was performed using two characterized lots of standards , (b) (4) and adw-subtype, validated in Study QS 235 and Study VP 03/00, respectively.

(b) (4)

(b) (4)

(b) (4)

(b) (4)