



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

BLA RESUBMISSION REVIEW

DATE: 11/15/2016

From: Iryna Zubkova, PhD
Product reviewer

SUBJECT: STN# 125428
Response to CR letter and BLA resubmission review

Sponsor: Dynavax Technologies Corporation
Product: Hepatitis B Virus (recombinant) Vaccine [Hepelisav[®]]

TO: Richard J. Daemer, PhD
Katherine Berkhousen, PhD

THROUGH: Marian Major, PhD
Robin Levis, PhD
Sara Gagnetten, PhD

ACTION DATE: December 15, 2016

Background

HEPLISAV is a sterile, preservative-free solution for intramuscular administration. An administrated dose of 0.5 mL contains 20 µg of HBsAg and 3000 µg of 1018 adjuvant formulated in 8 mM sodium phosphate, 154 mM sodium chloride, and 0.01% w/w polysorbate 80, pH 7.0 buffer.

A BLA for HEPLISAV was submitted on April 26, 2012, a complete response letter was issued on February 22, 2013 and a full response was submitted by Dynavax on March 15, 2016

(Amendment 42). This memo covers a review of the resubmission which included a response to the Complete Response Letter from February 22, 2013. This review also covers changes proposed within the resubmission for the manufacturing process, specifications, and stability data submitted in support of HEPLISAV (recombinant hepatitis B vaccine for active immunization against hepatitis B virus infection). This review covers Sections 2.3.S.1- 2.3.S.7, 2.3.P, 2.3.A.2 (HBsAg, Drug Substance), 2.3.A.2 (HEPLISAV, Solution for injection), 2.3.R (HBsAg Drug Substance and HEPLISAV Drug Product), 3.2.S (HBsAg), 3.2.P.1-8, 3.2.A.2 (HBsAg and HEPLISAV) of BLA 125428.

This memo contains information requests sent to the sponsor and responses received followed by a review of the additional data contained within the resubmission. Information requests are shown in bold with review of the responses shown in unbolded font.

The HEPLISAV HBsAg Drug Substance and Drug Product manufacturing, in-process testing, validation and specification were summarized in my review memo of the original BLA submission STN125428/0.

The information in this memo is presented as follows:

1. Information request sent on September 26, 2012 - Response received on January 16, 2013
2. Response to CR letter February 22, 2013 - Response received on March 16, 2016
3. Information Request sent on July 07, 2016 - Response received on August 16, 2016
4. Information Request sent on September 16, 2016 - Response received on September 28, 2016
5. Review of CMC information submitted in STN# 125428/0042
6. Conclusions and recommendation

1. Information request sent on September 26, 2012 - Response received on January 16, 2013

This information request was sent to the sponsor during the initial review but a response was not received until January 2013 after the review was finalized. Therefore, a review of the response is included in this memo.

1. **CBER does not agree with your proposal to remove the following tests from the stability plan for the HBsAg Drug Substance:**

(b) (4)

Please submit a revised stability plan for the Drug Substance that includes these tests.

A response was received on January 16, 2013.

The sponsor submitted a revised stability plan for HBsAg Drug Substance that included (b) (4) testing.

(b) (4)

(b) (4)

(b) (4)

2. CBER does not agree with your proposal to remove the following tests from the stability plan for the HEPLISAV Drug Product:

pH
Particle size
1018 ISS adjuvant content
HBsAg concentration
HBsAg (b) (4)

Please submit a revised stability plan for the Drug Product that includes these tests.

A response was received on November 30, 2012.

Dynavax acknowledged the Agency's request and committed to maintain the tests for pH, particle size, 1018 ISS Adjuvant content, HBsAg concentration, and HBsAg (b) (4) for HEPLISAV Drug Product stability testing.

A revised stability plan for HEPLISAV Drug Product was received on December 29, 2012 and was found to be acceptable.

3. Please include into the HEPLISAV Drug Product Commercial Release Specification the following test:

(b) (4)

Please submit the test procedure, method validation protocol, validation report and SOP to the BLA for review.

A response was received on December 29, 2012.

The (b) (4) test was included in the HEPLISAV drug product commercial release specification.

SOP 113 (version 04 Dated 29 December 2012) and validation report were submitted.

Response is acceptable.

2. Response to CR letter February 22, 2013 - Response received on March 16, 2016

The following CMC comment from DVP was included in the Complete Response Letter (CRL) sent to the sponsor on February 22, 2013. The original comment in the CRL is included in bold followed by a review of the response from the sponsor received in the March 16, 2016

resubmission. The numbering represents the numbering of comments in the CRL of February 22, 2013.

CRL#41. 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.

In a response received on November 30, 2012 Dynavax acknowledged the request and committed to include testing for (b) (4)

in the HBsAg Drug substance commercial release specification. At that time the sponsor provided validation protocols and validation reports only for the test methods for (b) (4)

Subsequent to the CRL a communication was received from Dynavax on December 24, 2014 requesting clarification on CRL#13 and CRL#41. Within this communication Dynavax requested to exclude testing for (b) (4) from the release testing of the HBsAg Commercial Release specifications based on demonstration of manufacturing controls. This communication was reviewed by members of DBSQC and based on the information provided by Dynavax, members of DBSQC agreed with Dynavax's proposal to monitor (b) (4) against a specification as a parameter in the Continuous Process Verification (CPV) program for HBsAg Drug Substance and that it was not necessary to include this test as a commercial release specification. However, it was pointed out to Dynavax that the method should be adequately validated as a Process Verification test and should be carried out accordingly during manufacturing of each batch of product.

In the March 16, 2016 resubmission response to CRL#41 Dynavax proposed that (b) (4) be excluded from commercial HBsAg drug substance release testing. On July 7, 2016 an information request (see below) was sent to Dynavax which stated that the (b) (4) test should be included as an HBsAg Drug substance commercial release specification and requested updates to the HBsAg release tests and specification tables.

3. Information Request sent on July 07, 2016 - Response received on August 16, 2016

- 1. During review of Heplisav stability data, we note that several time points for potency assay results were invalid or invalidated (Lots (b) (4)). Please provide the original potency results for these batches and justify the invalidation of these results.**

Dynavax provided an explanation for the invalid stability results for potency. Lot (b) (4) demonstrated invalid stability potency results at 12 and 24 months and lot (b) (4) had invalid stability potency results at month 12. The potency assay for both lots was invalid because the (b) (4) value of the test article was outside the range between the highest and the lowest dose that had been used for the evaluation. However, testing at week 36 showed potency assay results for both lots were valid.

Lot (b) (4) had an invalid potency assay at 24 months. This invalid result was related to a Parvovirus infection in mice. The testing at 36 months demonstrated valid results for the potency assay.

Potency assay results for Lot (b) (4) was invalidated at 0 and 12 months when reference material (b) (4) was disqualified after failing the annual requalification. The potency results at 0 and 12 months were determined relative to (b) (4) reference standard. At the later time points (24 and 36 months) potency was determined relative to the new reference standard RI285 and results were valid.

Lots (b) (4) were used in Phase 3 clinical studies and Process Performance Qualification. Lot (b) (4) was used in Continued Process Verification.

Response is acceptable.

- 2. You propose a shelf-life of 36 months for the Heplisav Drug Product stored at 5°C±3°C. Please provide 36 months stability data for the Heplisav Drug Product lots formulated with HBsAg bulk held for the proposed bulk shelf life of (b) (4) and with the 1018 ISS drug substance held in the (b) (4). These lots should be manufactured using the proposed commercial scale using the validated manufacturing process.**

Dynavax provided information about HEPLISAV lots that were manufactured at the proposed commercial scale since the beginning of the process performance qualification and have been evaluated for stability. Only 1 lot (b) (4) met manufacturing criteria requested in the IR. This lot was formulated from aged HBsAg Bulk (b) (4) but it was manufactured using a (b) (4) process (b) (4) not a commercial scale manufacturing process (b) (4). The oldest HBsAg drug substance lot used for HEPLISAV manufactured at the proposed commercial scale was (b) (4) old.

The response is not found to be acceptable in terms of justifying the proposed shelf life. A corresponding comment was sent to the Sponsor on September 16, 2016. See comments below.

- 3. We note that within your current submission under Section 1.11.1 “Information Request 10 Dynavax Proposes” on page 4 of 6 you request “2. Removal of Sterility Test as a Release Parameter for HBsAg (b) (4)”. However, the text**

discusses the removal of the sterility test during stability studies, not at release. Please clarify if this request is to remove sterility testing for the (b) (4) at release or during stability testing.

Dynavax responded that Sterility will be tested as a release parameter for HBsAg (b) (4).

Response is acceptable.

- 4. In Section 1.11.1 “Information Request 10 Dynavax Proposes”, you propose to remove (b) (4) as a release test for HBsAg bulk. We do not agree with the removal of this test. Please include this test with acceptance criteria and submit a revised list of release tests for the HBsAg bulk and also submit a revised Lot Release Protocol that includes this test.**

Dynavax agreed to include (b) (4) as a release test for HBsAg. Proposed acceptance criterion is (b) (4). The proposed acceptance criterion for (b) (4) of HBsAg drug substance is the same as the proposed acceptance criterion for (b) (4) of HEPLISAV drug product. Dynavax will update the relevant BLA sections for HBsAg following Agency acceptance of Dynavax’s proposal.

Dynavax submitted a new draft Lot Release Protocol with the following corrections:

- ‘Sterile’ was replaced by ‘No growth’ for the sterility test specification.
- (b) (4) has been added as an HBsAg drug substance release test.
- The specification for HBsAg (b) (4) in drug product was updated to (b) (4)

Response is acceptable.

- 5. (b) (4)**

(b) (4)

Response is acceptable.

Dynavax requested to remove (b) (4) testing from the list of in-process tests. At this time CBER does not agree with the proposal to remove this test as in-process test. Comments were sent to the sponsor on September 16, 2016. See below.

6. In your response to CRL #41, you propose that (b) (4) be excluded from commercial HBsAg drug substance release testing. We do not agree with the proposal. Please submit a revised list of release tests for HBsAg bulk that includes testing of (b) (4) together with release specifications.

Dynavax proposed to perform (b) (4) testing as an in-process test. At this time we do not agree with the proposal to discontinue (b) (4) testing as a release test and perform it only as in-process test.

The response is not acceptable. Corresponding comments with a request to submit an updated list of release tests was sent to the sponsor on September 16, 2016. See below.

7. In response to a CBER request in 2012 to include (b) (4) as a commercial release test for the HBsAg bulk, Dynavax acknowledged this request and committed to include a test for (b) (4) in the HBsAg Drug Substance release specification (September 26, 2012). This test is not included as a release specification. Please include this test and submit a revised list of release tests for HBsAg (b) (4)

Dynavax responded that during the Type C meeting (30 July 2014) they proposed the following: "Given the absence of (b) (4) in the HBsAg process, the buffers, or the protein, does the Agency agree (in) eliminating the (b) (4) content assay from the release control?" The Agency responded in a FAX dated 17 October 2014 as follows: "CBER response: we agree with your proposal; based on the reason provided in your meeting request document."

The response is acceptable.

4. Information Request sent on September 16, 2016 - Response received on September 28, 2016

In response to CBER's Information Request from July 7, 2016 Dynavax requested several changes to in-process and release testing for the HBsAg bulk. After review of the proposed changes the following comments were sent to the sponsor on September 16, 2016.

1. We note that in Section 3.2.S.2.3.3.6 (New Working Cell Banks) you propose to manufacture, test, and release new working cell banks according to the protocol "Manufacturing and Testing of Working Cell Banks". Requests to use new working cell banks and/or a comparability protocol for qualification of new working cell banks should be submitted as supplement(s) post licensure. Please be advised that any supplement certifying a new working cell bank for use in the manufacturing process should include test results for the new working cell bank qualification and results of analytical tests performed on the first drug substance lot manufactured

with the new working cell bank. Please confirm that no new working cell banks will be qualified and introduced into the manufacturing process without prior review and approval by CBER.

Dynavax agreed that the new working cell banks (WCB) will be used for manufacturing (b) (4) only after approval by CBER after submission of a supplement post-licensure.

Response is acceptable.

- 2. Regarding the proposed shelf life of the two drug substances and the final drug product. At this time, we will allow a shelf life for the HBsAg drug substance of no longer than (b) (4) , a shelf life for the 1018 adjuvant drug substance of no longer than (b) (4) (when stored in (b) (4) containers) and a Heplisav drug product shelf life of no longer than 36 months. We are (b) (4) your proposed shelf life due to insufficient data in support of a 36 month shelf-life for Drug Product manufactured from (b) (4) HBsAg and (b) (4) 1018 adjuvant produced at commercial scale. In addition, we are concerned about the loss of (b) (4) during accelerated stability studies of the (b) (4) . Please note that the proposed shelf life for the 1018 adjuvant does not include 1018 stored in (b) (4) containers as the available data is limited and show that the (b) (4) is out-of-specification beginning at (b) (4) . Until sufficient and satisfactory data is obtained, 1018 adjuvant stored in (b) (4) containers cannot be used for formulation of Heplisav drug product. Please acknowledge this communication and submit new stability protocols that incorporate these designated time periods.**

Dynavax acknowledged the assigned (b) (4) shelf-life for 1018 (b) (4) container), (b) (4) shelf-life for HBsAg Drug Substance, and 36 month shelf-life for HEPLISAV Drug Product. Response is found to be acceptable.

Follow-up from the response to question #5 from the July 07, 2016 Information request.

- 3. Regarding your request to exclude (b) (4) testing from routine in-process testing, at this time we do not agree with the removal this test from in-process testing during HBsAg Bulk manufacturing. Please submit a revised process control strategy for Sections 3.2.S.2.4 and 3.2.S.2.5 that include the following in-process tests:**

(b) (4)

Dynavax acknowledged the CBER request and submitted revised sections 3.2.S.2.2 (Description of Manufacturing Process and Process Controls [HBsAg Drug Substance]), 3.2.S.2.4 (Control of Critical Steps and Intermediates [HBsAg Drug Substance]), and 3.4.S.2.5 (Process Validation and Evaluation [HBsAg Drug Substance]) that included the requested tests.

Response is found to be acceptable.

Follow-up from the response to the question #6 from the July 07, 2016 Information request.

- 4. Regarding your proposal to perform testing of (b) (4) only as an in-process test and exclude it from the release testing. At this time we do not agree with this proposal. Please submit a revised list of release tests for HBsAg Bulk that includes testing for (b) (4) together with the release specification.**

Dynavax included (b) (4) as a release test for HBsAg bulk. Proposed release specification is NMT (b) (4). Dynavax updated Section 3.2.S.4.1 (Control of Drug Substance [HBsAg Drug Substance]), Section 3.2.S.2.1 (Manufacturer), Section 3.2.S.4.2 (Analytical Procedures), Section 3.2.S.4.3 (Validation of Analytical Procedures), Section 3.2.S.4.5 (Justification of Specification). Also, Dynavax provided a Lot Release Protocol, draft version 3.0, to reflect the current specification.

Response is found to be acceptable.

5. Review of CMC information submitted in STN# 125428/0042

Overview

Heplisav-B is a recombinant hepatitis B vaccine indicated for immunization against infection caused by all known subtypes of hepatitis B virus (HBV) in adults 18 years and older.

Manufacturing of HEPLISAV™ consists of the following major steps:

- HBsAg Drug Substance preparation
- HBsAg Drug Product formulation.

All steps of HEPLISAV manufacturing, testing and storage, except Master Cell Bank and HBsAg Drug Substance Final QA Release, take place in different locations in Germany. The Master Cell Bank was manufactured in (b) (4), but this site is no longer active. HBsAg Drug Substance Final QA Release is performed at Dynavax Technologies Corporation in USA. All facilities involved in Drug Substance testing and storage have an FDA EIN.

Table 1 (Table 3.2.S.2.1–1 from the resubmission)

Facility	Responsibility
(b) (4)	Master cell bank production
(b) (4) FDA Establishment Identifier: Not applicable	Master cell bank storage Working cell bank storage
Dynavax GmbH (formerly Rhein Biotech GmbH) Eichsfelder Strasse 11 40595 Duesseldorf, Germany FDA Establishment Identifier: 3010165220	HBsAg: <ul style="list-style-type: none"> x Manufacture x In-process and stability testing x Storage x QA release x Release testing: (b) (4) Master cell bank and working cell bank: <ul style="list-style-type: none"> x Storage x Testing x Stability testing x QA release Working cell bank: x Production
(b) (4) FDA Establishment Identifier: (b) (4)	HBsAg release testing <ul style="list-style-type: none"> x Sterility

(b) (4)

Drug Product

HEPLISAV is a sterile, preservative-free solution that is administered as an intramuscular injection. The product is clear to slightly opalescent, colorless to slightly yellow, and essentially free of visible particles. A single unit of HEPLISAV (0.7mL) consists of 28ug of HBsAg drug substance, 4200ug of 1018, formulated in 8 mM sodium phosphate, 154 mM sodium chloride, and 0.01% w/w polysorbate 80, pH 7.0 buffer. The administered dose is 0.5mL.

The HEPLISAV manufacturing process is divided into the following stages:

(b) (4)

Although the manufacturing process for HEPLISAV remains unchanged from the original submission, Dynavax implemented several minor changes as follows:

1. Added an (b) (4) test to the Drug Product release specification in response to an IR from September 26, 2012
2. Updated acceptance criteria for HBsAg (b) (4) y and Particles size
3. Introduced a new reference standard (RI285) for use in the in vivo potency test
4. Discontinued the (b) (4)
5. Proposed to use up to (b) (4) HBsAg (b) (4)
6. Updated stability information in order to support a 36 month shelf-life for the Drug Product.

(b) (4) test

In response to the Information request from September 26, 2012 the sponsor added an (b) (4) test to the Drug Product Commercial Release Specification (SOP113-04, version 04 Dated 29 December 2012). This test was validated and the Validation Protocol was included in the resubmission. This test method and validation were reviewed by members of DBSQC.

Release and stability specification

Particle Size

Dynavax proposed an adjustment to the particle size commercial stability specification from NMT (b) (4). In order to measure particle size Dynavax will employ the same (b) (4) method.

The proposed commercial specification acceptance criterion is derived using information from long-term stability studies and release data. (b) (4) HEPLISAV batches (b) (4) have been manufactured since the beginning of the process performance qualification. The lower specification acceptance criterion of (b) (4) is based on the (b) (4). The upper specification acceptance criterion of (b) (4) is based on the particle size data determined for (b) (4) HEPLISAV batches and considerations of the test method.

HBsAg (b) (4)

(b) (4)

(b) (4)

New reference standard for potency assay

RI285 is derived from vials of HEPLISAV lot (b) (4) was manufactured on (b) (4) using HBsAg drug substance lot (b) (4) and 1018 lot (b) (4). The lot release results for HEPLISAV lot (b) (4) complied with the specifications in place at the time of release. HEPLISAV lot (b) (4) has shown safety and immunogenicity in a phase 3 clinical study (DV2-HBV-23), and thus complies with (b) (4) Assay of Hepatitis B Vaccine, recommendations for hepatitis B vaccine reference material.

A total of (b) (4) vials of (b) (4) were designated as reference material RI285 and stored at (b) (4). The sponsor performed qualification of RI285 as a reference material. RI285 met all acceptance criteria and has been qualified for use as a reference material in the *in vivo* potency test for HEPLISAV.

RI285 will be re-qualified per protocol at (b) (4) intervals, starting with the end of shelf life of HEPLISAV Lot (b) (4), from which it is derived.

Commercial batch size

In the original BLA Dynavax used (b) (4) scales for the commercial batch production: (b) (4). In the resubmission Dynavax proposed to (b) (4). The (b) (4) scale process uses the same platform and process technology as the (b) (4) scale process. The primary difference between the (b) (4) process and the (b) (4) process, aside from scale, is that the (b) (4) process requires (b) (4). As a result, (b) (4) was implemented.

(b) (4) scales, including the Hold Time Study, were reviewed in the original BLA submission (STN 125428/SEQ No.0000).

(b) (4) batches for DP formulation

(b) (4)

(b) (4)

36 month Drug Product shelf life

Stability studies for HEPLISAV were performed at long-term conditions ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) for 36 months and accelerated conditions (b) (4) according to International Conference on Harmonization (ICH) Guideline Q1A(R2), Stability Testing of New Drug Substances and Drug Products.

Dynavax proposed a 36 month shelf live for the Heplisav final product. In order to support this request Dynavax provided stability data for (b) (4) HEPLISAV lots (b) (4) manufactured at commercial scale using the validated commercial manufacturing process.

Lot release of commercial lots and stability specifications

The HEPLISAV specifications are defined based on manufacturing and clinical experience, pharmacopoeial standards, and stability studies. The specifications ensure that the identity, potency, purity, and safety are maintained throughout the proposed shelf-life period.

Table 4 below includes Lot Release and Stability specifications.

Table 4. HEPLISAV Specifications (Table 3.2.P.5.1-1 from the resubmission)

Parameter	Test Method	Acceptance Criteria for Release	Acceptance Criteria for Stability
Appearance	(b) (4)	Color: (b) (4) Opalescence: (b) (4) Essentially free of visible particles	Color: (b) (4) Opalescence: (b) (4) Essentially free of visible particles
pH	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
HBsAg identity	(b) (4)	Confirmed	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

HBsAg concentration	(b) (4)	(b) (4)	(b) (4)
HBsAg	(b) (4)	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)	(b) (4)
1018 identity	(b) (4)	Confirmed	(b) (4)
1018	(b) (4)	(b) (4)	(b) (4)
1018 content	(b) (4)	(b) (4)	(b) (4)
Particle size	(b) (4)	(b) (4)	(b) (4)
Particulate contamination: sub-visible particles/ particulate matter	(b) (4)	(b) (4)	(b) (4)
Extractable volume	(b) (4)	≥ 0.5 mL	(b) (4)
Endotoxin	(b) (4)	\leq (b) (4)	(b) (4)
Sterility	(b) (4)	Sterile, no growth	(b) (4)
Container closure integrity	(b) (4)	NA	(b) (4)

(b) (4) NA = not applicable, no release or stability specification; NLT = not less than; NMT = not more than; (b) (4) (b) (4); UCL = upper confidence limit.

^a Test method adjusted for single-use vials; septa are not pierced for test.

The sponsor committed to monitor stability of (b) (4) lot of Heplisav (b) (4) under long term conditions ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$).

Batch analysis

Two presentations of HEPLISAV have been used during clinical development: a single-vial presentation that will be the commercial presentation, and a dual-vial presentation that was used for Phase 1/2 clinical studies. The dual-vial presentation consisted of a vial of formulated 1018 and a vial of formulated HBsAg drug substance. The 2 vials were mixed together immediately prior to injection. Starting with batch (b) (4) HEPLISAV was manufactured as a single-vial presentation. The current HEPLISAV formulation was used for batch (b) (4) and all subsequent batches. All HEPLISAV batches used in clinical studies since 2006 were manufactured by Rentschler Biotechnologie GmbH (Laupheim, Germany). Since 2013 Dynavax has manufactured (b) (4) new batches of HEPLISAV. Certificates of analysis for the last (b) (4) HEPLISAV batches (b) (4) were provided in this submission. All batches of HEPLISAV complied with the specifications in place at the time of release.

Conclusions and recommendation

Review of BLA 125428/0042 resubmission showed that Dynavax responded to all CMC questions in the CR letter issued on February 22, 2013. Minor new changes implemented in the manufacturing process described in the BLA resubmission will not affect quality or immunogenicity of HEPLISAV. Thus, from the perspective of the CMC information submitted to the BLA, I recommend approval of this application.