

DEPARTMENT OF HEALTH & HUMAN SERVICES



Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Administrative File BL STN 125428/0.74 (DATS# 660745) for HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)]

From: Priscilla M. Pastrana, Consumer Safety Officer, CBER/OCBQ/DMPQ/MRB2

Through: CDR Qiao Bobo, Ph.D., RAC, Branch Chief, CBER/OCBQ/DMPQ/MRB2

CC: Katherine Berkhausen, RPM, CBER/OVRR/DVRPA/CMC2
Richard Daemer, Ph.D., RPM, CBER/OVRR/DVRPA/CMC2

Subject: **Second Complete Response (CR) Review Memo:** Dynavax Technologies Corporation (US License #1883) for Biologics License Application (BLA) for HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)], in support of the manufacture for the hepatitis B surface antigen (HBsAg) (Drug Substance) at Dynavax GmbH (formally Rhein Biotech GmbH) in Düsseldorf, Germany and the manufacture for HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)] (Drug Product) at Rentschler Biotechnologie GmbH in Laupheim, Germany.

ADD: August 10, 2017

RECOMMENDATION:

I recommend approval of the BLA.

SUMMARY:

CBER received a response from Dynavax Technologies Corporation (Dynavax) to the CR Letter issued November 10, 2016 under Amendment STN 125428/0.74 (DATS# 660745) on February 07, 2017. This is the second CR Letter issued to the BLA for HEPLISAV in support of the manufacture for the hepatitis B surface antigen (HBsAg) Drug Substance at Dynavax GmbH (formerly Rhein Biotech GmbH) in Düsseldorf, Germany and for the manufacture of HEPLISAV Drug Product at Rentschler Biotechnologie GmbH in Laupheim, Germany.

The original BLA was received by the agency on April 26, 2012 under STN 125428/0.0 (DATS# 534454). On February 22, 2014, the first CR Letter was issued to this BLA. Then, two responses for this CR Letter were received on March 15 and April 01, 2016 under Amendment #125428/0.42 (DATS #628039) and 125428/0.44 (DATS# 629452), respectively. In addition, the firm responded on June 09, 2016 under Amendment #125428/0.49 (DATS# 634730) to an Information Request (IR) submitted on May 24, 2016 for this CR Letter. The responses to the first CR Letter and IR have been adequately addressed. They were discussed in a separate memo issued on October 26, 2016.

It was noted in Amendment #125428/0.42 (DATS# 628039), that Dynavax provided additional changes to the BLA for HEPLISAV. The review of these changes was addressed in a separate review memo issued on October 24, 2016. However, a second CR Letter was issued to Dynavax on November 10, 2016, due these changes. Then, the responses to this CR Letter were received February 07, 2017 under Amendment STN 125428/0.74 (DATS# 660745). An IR was sent to the firm on March 30, 2017 and they provided their responses on March 31, 2017 under Amendment #125428/0.79 (DATS# 670585). These responses were discussed with Dynavax on a Telecon held on April 03, 2017. They submitted additional clarification to these responses in Amendments #125428/0.80 (DATS# 671640) on April 10, 2017 and #125428/0.82 (DATS# 675584) on May 01, 2017. The responses to the second CR Letter and IR sent on March 30, 2017 have been adequately addressed. They were discussed in this memo.

Background:

CBER received a BLA from Dynavax on April 26, 2012 under STN 125428/0.0 (DATS# 534454) for a recombinant hepatitis B vaccine HEPLISAV. Dynavax stated that this recombinant vaccine drug product is for active immunization against hepatitis B virus infection. They explained that the immunogenic component is hepatitis B surface antigen (HBsAg), subtype adw and is produced in the yeast strain *Hansenula polymorpha* using recombinant technology. The firm indicated that the HBsAg Drug Substance is formulated with 1018 ISS Adjuvant to produce HEPLISAV drug product.

In this BLA, Dynavax proposes to manufacture the HBsAg Drug Substance at Rhein Biotech GmbH (name changed to Dynavax GmbH) in Düsseldorf, Germany. Then formulate this drug substance with 1018 ISS Adjuvant to produce HEPLISAV Drug Product and fill in vials at Rentschler Biotechnologie GmbH & Co. KG, Laupheim, Germany. The labeling, packaging and storage of this drug product is at (b) (4).

A Pre-License Inspection (PLI) was conducted in the Drug Substance manufacturing facility on August 16-17 and 20-23, 2012. This inspection revealed objectionable conditions regarding quality systems, cleaning validation, in-process testing criteria, qualification activities, facilities, extraction profile, environmental monitoring, container closure integrity testing, changeover procedures, calibration, process and instrumentation diagrams, training and process equipment. At the end of this PLI, a 13-item FDA Form-483 was issued. The inspectional findings were documented in the Establishment Inspection Report (EIR). The firm provided responses to these observations on October and November 2012 (Amendment #125428/0.11, DATS# 546597 and Amendment #125428/0.20, DATS# 54721), August 2014 (Amendment #125428/0.37, DATS#591008) and March 2016 (Amendment #125428/0.42 DATS #628039). Three 483 Response Review Memos were issued on February 12, 2013, March 18, 2015 and April 26, 2016 to address the firm's responses to these observations. Dynavax provided acceptable responses that resolved and closed all 13 observations.

On February 22, 2013 the first CR Letter was issued to Dynavax to address deficiencies observed during the PLI. In addition, to deficiencies found during the review of this BLA; in specific the Chemistry, Manufacturing and Control (CMC) section for the drug product manufacturing facility and equipment and Bioresearch Monitoring (BIMO) section for clinical quality control and testing procedures. Two responses for this CR Letter were received on March 15 and April

01, 2016 under Amendment #125428/0.42 (DATS #628039) and 125428/0.44 (DATS# 629452). Also, an IR was sent to the firm on May 24, 2016 to request additional clarification regarding the CCIT study conducted to the final container and the Cleaning and Depyrogenation Validation Studies conducted to the components used in the formulation and filling of the Drug Product. The firm provided the responses on June 09, 2016 under Amendment #125428/0.49 (DATS# 634730). The responses to this CR Letter and the IR have been adequately addressed and they were discussed in a separate memo issued on October 26, 2016.

A second PLI was conducted in the Drug Substance manufacturing facility on June 08-10 and 13-16, 2016. This inspection revealed objectionable conditions regarding disinfection effectiveness studies, cleaning validation, cleaning and sanitization of process equipment, *in vivo* potency release assay data analysis and Good Documentation Practices (GDPs). At the end of the PLI, a 5-item FDA Form-483 was issued. The inspectional findings were documented in the EIR. The firm provided responses to these observations on July 08, 2016 under Amendment #125428/0.53 (DATS# 636911), which are discussed in a 483 Response Review Memo issued on October 24, 2016. Dynavax provided acceptable responses that resolved and closed all five observations.

Dynavax provided changes to the BLA for HEPLISAV as part of Amendment #125428/0.42 (DATS# 628039), which were discussed in a separate memo issued on October 24, 2016. Then, a second CR Letter was issued to this firm on November 10, 2016, due these changes. The responses to the second CR Letter were received February 07, 2017 under Amendment STN 125428/0.74 (DATS# 660745).

The scope of this CR review memo is the evaluation of the firm's responses to the second CR Letter received on February 07, 2017 under Amendment STN 125428/0.74 (DATS# 660745) and the responses to an IR sent to Dynavax on March 30, 2017 regarding the shipping of the drug product from Rentschler Biotechnologie GmbH & Co. KG, Laupheim, Germany to (b) (4)

In addition, this memo includes the firm's responses received on March 31, 2017 under Amendment #125428/0.79 (DATS# 670585) to an IR sent on March 30, 2017 and additional clarification to these responses in Amendments #125428/0.80 (DATS# 671640) on April 10, 2017 and #125428/0.82 (DATS# 675584) on May 01, 2017.

Reviewer's Comments: Based in the review of Dynavax's responses to this second CR letter and the responses to the IR sent on March 30, 2017, I concluded that the issues reviewed in this CR review memo were resolved and closed. I recommend the approval of this BLA.

CR Review:

This review is for the responses received on February 07, 2017 under Amendments STN 125428/0.74 (DATS# 660745). In addition, this memo includes the responses received on March 31, 2017 under Amendment #125428/0.79 (DATS# 670585) to an IR sent on March 30, 2017 and additional clarification to these responses in Amendments #125428/0.80 (DATS# 671640) on April 10, 2017 and #125428/0.82 (DATS# 675584) on May 01, 2017. The CR questions appear italicized and a summary of the firm response and reviewer commentary appear in regular text.

45. Regarding the Shipping Study of the drug product from Rentschler Biotechnologie GmbH to your labeling and packaging contract manufacturers (b) (4)

- a. Please provide a copy of the summary report for the shipping study and include a description and results including a description of the shipping configuration, target maximum shipping duration, target shipping temperatures, and acceptance criteria. Please also compare this with your routine shipping conditions.

Firm Response: Dynavax stated that copy of the summary report for the Performance Qualification (PQ) for the shipment of the drug product from Rentschler Biotechnologie GmbH Laupheim, Germany (Rentschler) to the labeling and packaging contract manufacturer in (b) (4) was included in the original BLA under STN 125428/0.0 (DATS# 534454). This report was approved by the firm on February 15, 2012. They explained that this report provides the a summary from the Installation/Component, Operational and Performance Qualification (ICOP/Q) studies conducted in support for the shipping of the drug product from Rentschler to the labeling and packaging contract manufacturer (b) (4). In addition, this report describes shipping configuration, target maximum shipping duration, target shipping temperatures, and acceptance criteria in support for the shipping of this drug product from Rentschler to (b) (4).

Dynavax stated that the ICQ study consisted of the verification of the calibration certificates for (b) (4) temperature dataloggers and the qualification package for the shipping container (b) (4). This qualification package includes the following testing conducted by the manufacturer of this shipping container using a climate controlled chamber and temperature dataloggers:

(b) (4)

(b) (4)

(b) (4)

Dynavax provided copies of the summary reports from the above testing conducted to this shipping container in the original BLA. They indicated that no deviation was initiated in the ICQ study. The firm concluded in the ICQ study that the interior of the shipping container is capable to maintain a temperature of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for not less than (b) (4) and the dataloggers have the ability to monitor the above temperature for not less than (b) (4)

The firm explained that the OQ study consisted of the (b) (4)

(b) (4)

CBER Comments: Summary report PD-2012-09 was not discussed in the drug product review memo dated on February 12, 2013. This report and the qualification package for the shipping container (b) (4) were discussed as part of the response to the CR item #45.a. They were found acceptable. However, it is unclear if the (b) (4) testing at a temperature between 2°C to 8°C conducted in the OQ study simulate the (b) (4) of the vials and duration during (b) (4) shipment conditions. Also, it is unclear if Dynavax conducted any testing to the unlabeled drug product vials to determine if there are changes in the product quality, at the end of the OQ study. **See IR Questions #1.a. and #1.b. – 03/30/2017 and Telecon - 04/03/2017 (Below).**

1. Regarding page 4 of 63 from the Summary Report PD-2012-09, in which the results of the OQ study were documented in the Distribution Simulation Final Report, (b) (4) (b) (4) in support for the response to the CR item #45.a.
 - a. You stated that this OQ study was a simulation of the (b) (4) (b) (4) at a temperature between 2°C to 8°C. However, it is unclear if the (b) (4) testing conducted at a temperature between 2°C to 8°C are representative of the (b) (4) of the vials during (b) (4) shipment conditions. Please clarify if the (b) (4) testing at a temperature between 2°C to 8°C conducted in this OQ study simulate the (b) (4) of the vials and duration during (b) (4) shipment conditions.

Firm Response: Dynavax stated that the simulation of the (b) (4) for HEPLISAV drug product vials during (b) (4) shipment conditions was conducted in the Container Closure Integrity Testing (CCIT) study using (b) (4) method under the following worst-case conditions:

(b) (4)

The firm explained that this study was conducted on 2013 and according to guidance for high altitude conditions defined in (b) (4)

(b) (4) The summary report for this CCIT study was approved on October 2014 and submitted in response to the CR items# 6.a., #6.b. and #6.c. addressed in the CR Letter issued on February 22, 2013.

Dynavax clarified that the (b) (4) transportation of the drug product unlabeled vials will be via (b) (4)

CBER Comments: The simulation of the (b) (4) for HEPLISAV drug product vials during (b) (4) shipment conditions conducted in the Container Closure Integrity Testing (CCIT) study using d (b) (4) method on 2013 was reviewed and found acceptable.

- b. *You did not state if any testing has been conducted to the unlabeled drug product vials to determine if there are changes in the product quality at the end of the OQ study. Please corroborate if any product quality testing has been conducted to these vial at the end of the OQ study. If so, please indicate the testing conducted to these vials and results.*

Firm Response: Dynavax stated that CCIT has been conducted to the unlabeled drug product vials to determine if there are changes in the product quality. This CCIT study was discussed in the Firm Response to the IR question #1.a.

CBER Comments: CBER Comments of this IR question was discussed in the CBER Comments to the IR question #1.a. In addition, the chairman for this file has indicated that this protein is pretty robust so agitation should not cause problems to the product.

- 45.b. *Please clarify if you conducted any Performance Qualification runs for the shipping of HEPLISAV Drug Product from Rentschler Biotechnologie GmbH to (b) (4). If no shipping validation studies were performed, please provide the rationale why none were conducted for shipments from Rentschler Biotechnologie GmbH to (b) (4)*

Firm Response: Dynavax clarified that no PQ study has been conducted in support for the shipping of HEPLISAV Drug Product from Rentschler to (b) (4). They conducted an assessment (PD-2016-04) to compare the results and conclusions from PD-2012-09 with the expected routine shipping of the unlabeled vials of this drug product from Rentschler to (b) (4). PD-2016-04 was approved on January 2016. The firm explained that there are no changes in the shipping configuration, target shipping temperatures and acceptance criteria in support for the shipping of unlabeled vials from Rentschler to (b) (4). Dynavax stated that the expected shipping time from Rentschler to (b) (4) is less than (b) (4) which is less than the shipping time of (b) (4) challenged as the worst-case shipping time in PD-2016-04.

The firm explained that 3009PM22002, (b) (4) *Verification Tests Container Exposed to Realistic Conditions, Measuring Container Air Temperature*, and 3009PM21804, (b) (4) *Verification Tests Container Exposed to Varying Ambient Temperature, Measuring Container Air Temperature*, were conducted as part of the qualification package for the shipping container (b) (4) to demonstrate that the interior of the shipping container maintained a temperature of 5°C ± 3°C during the simulation of (b) (4) transportation.

CBER Comments: PD-2016-04 was reviewed. However, additional clarification was required from Dynavax to consider this assessment acceptable, since they did not compare the (b) (4) transportation methods of the unlabeled vials from Rentschler to the labeling and packaging locations located in (b) (4). In addition, Dynavax did not state if there is no

changes in the shipping configuration, target shipping temperatures and acceptance criteria as evaluated in PD-2012-09. Also, it is unclear how the firm determined that the expected shipping time from Rentschler to (b) (4). The firm did not indicate if identity testing has been or will be conducted to the labeled drug product vials according to 21 CFR 610.14. **See IR Questions #2.a., #2.b., #2.c. and #2.b. – 03/30/2017 and Telecon - 04/03/2017 (Below).**

2. *Regarding assessment PD-2016-04, which describe the comparison of the results and conclusions from PD-2012-09 with the expected routine shipping of the unlabeled vials from Rentschler to (b) (4) in support for the response to the CR item #45.b.*
 - a. *It is unclear if you compared the (b) (4) transportation methods of the unlabeled vials from Rentschler to the labeling and packaging locations located in (b) (4). Please clarify if you conducted a comparison of the (b) (4) transportation methods of the unlabeled vials from Rentschler to these labeling and packaging locations. If so, please provide a summary of this comparison and an assessment of the impact the differences have on the product. If not, please provide a rationale to not conduct this comparison.*

Firm Response: Dynavax clarified that a comparison of the (b) (4) transportation methods of the unlabeled vials from Rentschler to the labeling and packaging locations located in (b) (4) has not been conducted, yet. They indicated that risk assessment will be conducted to demonstrate that any differences between both transportation methods do not impact the product quality. However, the firm did not state in their responses, when this risk assessment will be provided to CBER.

CBER Comments: In the telecom conducted on April 03, 2017, Dynavax stated that the above risk assessment will be provided to the agency on the week of May 01, 2017. This risk assessment was received in CBER on May 01, 2017 under Amendment #125428/0.82 (DATS# 675584) (See Below).

Firm Response: Dynavax provided copy of PD-2017-04-R v1, *Risk Assessment for Shipment of HEPLISAV (HBsAg 1018) Drug Product Bulk Unlabeled Vials*, approved on April 28, 2017. This risk assessment evaluated the differences between the (b) (4) transportation methods of the unlabeled vials from Rentschler to the labeling and packaging locations located in (b) (4) to demonstrate that both transportation methods do not impact the product quality. They indicated that this assessment was conducted using the same shipping configuration evaluated in PD-2012-09. This assessment consisted in the failure mode and effect analysis (FMEA) of the following transportation conditions:

Transportation Conditions	(b) (4)
(b) (4) Transportation	<p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4)</p>

Transportation Conditions	(b) (4)
(b) (4) Transportation	(b) (4)
Storage During Transportation	(b) (4)

According to the FMEA, the firm indicated that any damage in the shipping container caused by handling, compression and shock during (b) (4) transportation; as well, during storage is detected during the visual inspection conducted in the labeling and packaging locations located in (b) (4). In addition, they stated that excessive vibration is not easily detected in this type of shipping container, because it is secured and monitored during (b) (4) transportation. Dynavax explained that there is minimum or no pressure impact during the simulation of (b) (4) transportation, since the crimps from the Drug Product vials function as a physical barrier to prevent the displacement of the stoppers from the vials. Therefore, the integrity of the Drug Product closure/container system is not affected by pressure during (b) (4) transportation. The firm stated that there is no impact in the temperature and time during (b) (4) transportation; as well, during storage, since, the shipping container can maintain a temperature of 5°C ±3°C for a maximum of (b) (4) at an (b) (4) temperature of - (b) (4) as well for a maximum of (b) (4) at a (b) (4) temperature of (b) (4).

Dynavax concluded in this risk assessment that the differences between the (b) (4) transportation methods of the unlabeled vials from Rentschler to the labeling and packaging locations located in (b) (4) demonstrate minimum or none impact in the product quality.

CBER Comments: The risk assessment to demonstrate that any differences between both transportation methods do not impact the product quality was reviewed and appears acceptable.

- b. You did not specify in this assessment if there is any change in the shipping configuration, target shipping temperatures and acceptance criteria evaluated in PD-2012-09, since the shipping of HEPLISAV unlabeled vials from Rentschler to (b) (4) are through (b) (4) transportation. Please clarify if there is any change in the shipping configuration, target shipping temperatures and acceptance criteria evaluated in PD-2012-09, since the shipping of HEPLISAV unlabeled vials from Rentschler to (b) (4) are through (b) (4) transportation.*

Firm Response: Dynavax clarified that there is no change in the shipping configuration, target shipping temperatures and acceptance criteria evaluated in PD-2012-09, during the (b) (4) transportation of HEPLISAV unlabeled vials from Rentschler to (b) (4).

CBER Comments: The firm response is acceptable.

- c. *You stated in page 3 of this assessment that the expected shipping time from Rentschler to (b) (4) is less than (b) (4). However, it is unclear how you determined this shipping time since it appears that no shipment was sent to (b) (4) yet. Please clarify if you sent any shipment of unlabeled HEPLISAV Drug Product from Rentschler to (b) (4) to corroborate that the expected shipping duration is less than (b) (4). Alternative, please justify how you determined the shipping time to be less than (b) (4).*

Firm Response: Dynavax clarified that no shipment of HEPLISAV unlabeled vials has been sent from Rentschler to (b) (4) yet. They determined the shipping duration of less than (b) (4) based on expected shipping times from Europe (b) (4).

CBER Comments: The response to this IR question was discussed with Dynavax in a telecom on April 03, 2017. It was requested to the firm to provide a table with a breakdown of the activities with their duration in support for the (b) (4) shipment of HEPLISAV unlabeled vials from Rentschler to (b) (4) to demonstrate that the shipment duration is less than (b) (4). The firm made the commitment to provide this table on the week of April 10, 2017. This table was received in CBER on April 10, 2017 under Amendment #125428/0.80 (DATS# 671640) (See Below).

Firm Response: Dynavax stated that the (b) (4) shipment of HEPLISAV unlabeled vials from Rentschler to (b) (4) will be conducted by (b) (4). They stated that the duration of the above transportation is between (b) (4), which is less than (b) (4) as claimed in assessment PD-2016-04 and less than (b) (4) as evaluated in the Validation Study PD-2012-09. The firm provided a table with a breakdown of the activities with their duration in support for the (b) (4) shipment of HEPLISAV unlabeled vials from Rentschler to (b) (4) to demonstrate that the shipment duration is less than (b) (4) as follows:

(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

CBER Comments: The table with a breakdown of the activities with their duration in support for the (b) (4) shipment of HEPLISAV unlabeled vials from Rentschler to (b) (4) to demonstrate that the shipment duration is less than (b) (4) was reviewed and found acceptable.

d. Please corroborate if identity testing has been and will be conducted to the labeled drug product vials according to 21 CFR 610.14 and where this testing is conducted.

Firm Response: Dynavax indicated that identity testing will be conducted to the commercial shipments of HEPLISAV according to 21 CFR 610.14. This testing will be conducted in (b) (4) .

The firm clarified in the Telecon conducted on April 03, 2017, that identity testing was not conducted to the clinical lots of HEPLISAV that were labeled and packaged in (b) (4) facility..

CBER Comments: The firm response is acceptable.