

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 STN 125428/0.042 (DATS# 628039) for HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)]

From: Priscilla M. Pastrana, CSO, CBER/OCBQ/DMPQ/MRB2

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

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

Subject: **Review Memo:** Dynavax Technologies Corporation (US License #1883) Amendment to Biologics License Application (BLA) for HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)], in Support of the Manufacture for the Hepatitis B Surface Antigen (HBsAg) at Dynavax GmbH (Formally Rhein Biotech GmbH) in Düsseldorf, Germany and the Manufacture for HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)] at Rentschler Biotechnologie GmbH in Laupheim, Germany.

ADD: December 15, 2016

RECOMMENDATION:

A Complete Response letter should be issued to the firm.

COMPLETE RESPONSE LETTER QUESTIONS:

1. Regarding the Shipping Study of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to (b) (4) and from Rentschler Biotechnologie GmbH to (b) (4):
 - a. Please provide a copy of the summary report for the shipping study of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to (b) (4) and from Rentschler Biotechnologie GmbH to (b) (4). Ensure to include a description and results of the installation, operational, and performance qualification (IOP/Q) studies conducted in this study. In addition, include a description of the shipping configuration, target maximum shipping duration, target shipping temperatures, and acceptance criteria used for the PQ study as well as, during routine shipping of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to (b) (4) and from Rentschler Biotechnologie GmbH to (b) (4).

- b. Please clarify if you conducted any PQ 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).

SUMMARY:

CBER received on March 15, 2015 an amendment for the BLA for HEPLISAV™ [Hepatitis B Vaccine, Recombinant (Adjuvanted)] (HEPLISAV™ Drug Product) under Amendment #125428/0.42 (DATS# 628039). This amendment contains responses to a Complete Response (CR) letter that was issued to Dynavax Technologies Corporation (Dynavax) on February 22, 2013 and updates to the BLA. This CR letter is associated with deficiencies observed during the PLI conducted in Dynavax GmbH (formally Rhein Biotech GmbH) in Düsseldorf, Germany (Drug Substance manufacturing facility) on August 16-23, 2012 and deficiencies in the facility and equipment of Rentschler Biotechnologie GmbH in Laupheim, Germany (Drug Product manufacturing facility) were discussed in separate review memos.

HEPLISAV™ is a recombinant hepatitis B vaccine for active immunization against hepatitis B virus infection. Dynavax explains that the immunogenic component of this vaccine is hepatitis B surface antigen (HBsAg), subtype adw, which is produced in the yeast strain *Hansenula polymorpha* using recombinant technology. The firm indicates that the HBsAg Drug Substance is formulated with 1018 ISS Adjuvant to produce HEPLISAV™ Drug Product.

The amendment to this BLA contains information associated with the following:

- The manufacture of the hepatitis B surface antigen (HBsAg) Drug Substance at Dynavax GmbH (formally Rhein Biotech GmbH) in Düsseldorf, Germany
- The manufacture for HEPLISAV™ Drug Product at Rentschler Biotechnologie GmbH in Laupheim, Germany
- The manufacture of the 1018 ISS adjuvant at Nitto Denko Avecia Inc (formerly Avecia Biotechnology Inc.) in Milford Massachusetts (The review of the 1018 ISS adjuvant is not in the scope of this memo.)
- The labeling, packaging and storage of the vials of this Drug Product at (b) (4)

Therefore, the discussion of (b) (4) and the shipping of the Drug Product from Rentschler Biotechnologie GmbH to this facility are addressed in this memo.

The information from HBsAg Drug Substance Drug Substance and HEPLISAV™ Drug Product included in the amendment to this BLA was repeated in the original BLA for HEPLISAV™. There are no changes in the manufacturing processes of the HBsAg Drug Substance Drug Substance and HEPLISAV™ Drug Product. The original BLA was received by the agency on April 26, 2012 under STN 125428/0.0 (DATS# 534454). The review of the above information for these facilities was addressed in separate memos uploaded in the EDR.

Dynavax provided an updated description of the following items for the HBsAg Drug Substance manufacturing facility in the amendment to this BLA:

- Classification of the manufacturing rooms to comply with ISO-14644-1, “Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness.”
- List of manufacturing equipment to reflect the relocation of exiting equipment and implementation of new equipment in the washing and preparation area.
- Water Systems (Purified Water, Water for Injection and Clean Steam) and Clean Compressed Air System.
- Controls used to measure conductivity, TOC and bioburden in the Water Systems; in addition, to the (b) (4) of the Clean Compressed System and the temperature in the Warehouse Area.
- Manufacturing area.
- Flow pattern diagrams of the manufacturing area.

These items were reviewed during the Pre-License Inspection (PLI) conducted in the HBsAg Drug Substance manufacturing facility on June 08-16, 2016. They were addressed in the Establishment Inspection Report (EIR) for this PLI.

As mentioned previously, in the amendment to this BLA, Dynavax provided the responses to the CR letter issued on February 22, 2013. The review of these responses to the CR letter from DMPQ was discussed in a separate memo.

It was decided to waive the PLI of the facilities in support for the manufacture, testing, labeling, packaging and storage of HEPLISAV™ Drug Product per SOPP 8410, *Determining When Pre-Licensing/Pre-Approval Inspections are Necessary*. The PLI waiver of these facilities is addressed in a separate inspection waiver memo in the EDR (issued June 30, 2016).

The scope of this review memo includes the following:

- Additional facilities for the testing, labeling, packaging and storage of HEPLISAV™ Drug Product
- Changes to the name of facilities involved in the manufacturing of the HBsAg Drug Substance and 1018 ISS adjuvant.
- Discussion of (b) (4) as additional location for vial labeling and finished product packaging
- The shipping validation of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to (b) (4) for distribution.

The following sections of this submission were reviewed by DMPQ:

- Form FDA 356h
- Cover Letter
- Section 2.3.P. –Quality Overview Summary - Manufacturer, HEPLISAV™, Solution for Injection
- Section 2.3.A.1 - Quality Overview Summary - Facilities and Equipment [HEPLISAV, (b) (4)]

- Section 3.2.P.3 –Quality - Manufacturer, HEPLISAV™, Solution for Injection
- Section 3.2.P.5 - Quality - Process Validation and/or Evaluation [HEPLISAV, Solution for Injection]
- Section 3.2.A.1 - Quality - Facilities and Equipment [HEPLISAV, (b) (4)]

Dynavax did not provide a copy of the summary report for the shipping of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to (b) (4)

. **See Complete Response Letter Questions #1.a. and #1.b.**

SUBMISSION REVIEW:

As stated in the summary section of this memo, the scope of this amendment to the BLA review memo includes the implementation of additional facilities in support for the testing, labeling, packaging and storage of HEPLISAV™ Drug Product; changes in the name of facilities involved in the manufacturing of the HBsAg Drug Substance and 1018 ISS adjuvant. In addition, to the discussion of (b) (4) as additional location for vial labeling and finished product packaging and the shipping validation of HEPLISAV™ from the Rentschler Biotechnologie GmbH to (b) (4); as well, from (b) (4) to third-party logistics provider (b) (4) for distribution.

REVIEW:

Facilities:

Dynavax stated that additional facilities involved in the testing and storage, labeling and packaging of HEPLISAV™ Drug Product were included in the amendment to the BLA as follows:

Company Name	Address	Operation Performed	FDA Registration Number
(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)

Dynavax notified in the updated BLA that the following facilities change their name:

Former Company Name	Former FDA Registration	Activities Conducted	Updated Company Name	Updated FDA Registration
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

	Number			Number
Drug Substance				
Rhein Biotech GmbH (A wholly owned subsidiary of Dynavax Technologies Corporation)	1000350748	<ul style="list-style-type: none"> • Manufacture DS • In-process and stability testing • Storage • QA release • Release testing: Master Cell Bank (MCB) and Working Cell Bank (WCB): <ul style="list-style-type: none"> • Storage • Testing • Stability testing • QA release • WCB Production Drug product release testing	Dynavax GmbH	3010165220
Drug Product				
Avecia Biotechnology	No Change	1018 (Adjuvant) <ul style="list-style-type: none"> • Manufacture • In-process and stability testing • Storage • QA release Release testing 	Nitto Denko Avecia Inc.	No Change

Reviewer Comments: The facility information provided in the amendment to the BLA was reviewed and found acceptable.

(b) (4) :

Dynavax stated in the amendment to this BLA that HEPLISAV™ Drug Product can be labeled and packaged either in (b) (4)

They indicated that both facilities are multiproduct labeling and packaging facilities for US licensed products such as capsules, powders, tablets, vials and ampoules. The firm explained that both facilities have the same room classification for labeling and packaging processes; as well as the same gowning, containment, segregation, changeover and line clearance controls in-place for these processes.

Dynavax stated that the labeling and packaging of HEPLISAV™ Drug Product in (b) (4) consists of the following steps:

- Removal of unlabeled Drug Product vials from cold storage room
- Vial labeling
- Manual cartooning and PIL insertion
- Carton Overprinting

- Cartons placed in shipper box and shipper labeling
- Shipper boxes containing labeled Drug Product vials transferred and stored in cold storage room.

The firm indicated that the equipment used in the labeling and packaging of HEPLISAV™ Drug Product in (b) (4) consist of a labeler and a secondary packaging printer, which are shared equipment and non-product contact.

The storage, labeling and packaging of HEPLISAV™ Drug Product in (b) (4) facility was addressed in Drug Product review memo for the original BLA supplement.

Dynavax explained that the labeling and packaging of HEPLISAV™ Drug Product in (b) (4) is conducted in Room (b) (4), which is a dedicated room for the labeling and packaging of vials at a temperature between (b) (4) and relative humidity of less than (b) (4). They indicated that this room is controlled non-classified area, which is served by an air handling unit (AHU) with HEPA filters capable of maintaining a Class (b) (4) in static conditions. The firm stated that Drug Product is stored in a cold storage area at a temperature 2°C to 8°C. They stated that this area is segregated for unlabeled and labeled products for each type of product.

The firm explained that there are gowning, control of materials, containment, segregation, changeover and line clearance controls in-place in this facility to prevent the contamination, cross-contamination and mix-up of products in the labeling and packaging area as well as in the cold storage area. They stated that the personnel involved in the labeling and packaging operations are trained in these controls. Dynavax indicated that one lot of each type of product is labeled and packaged at the same time in the corresponding labeling/packaging room. The firm provided the material and personnel flow patterns diagram associated to the storage, labeling and packaging of HEPLISAV™ Drug Product in (b) (4) as part of this supplement. This diagram illustrates a unidirectional flow pattern of material and personnel from/to the cold storage area.

Reviewer Comments: Information associated to the storage, labeling and packaging of HEPLISAV™ Drug Product in (b) (4) was reviewed and found acceptable.

Shipping of HEPLISAV™ Drug Product vials from Rentschler Biotechnologie GmbH to (b) (4)

Dynavax explained that a controlled environmental shipping container (b) (4) at a temperature of 2°C to 8°C is used for the shipping of unlabeled HEPLISAV™ Drug Product vials from Rentschler Biotechnologie GmbH, Laupheim, Germany (Rentschler) to (b) (4). In addition, this type of container is used for the shipping of labeled Drug Product vials from (b) (4) for distribution.

The firm indicated in the amendment to this BLA that the shipping of unlabeled HEPLISAV™ Drug Product vials from Rentschler to (b) (4) consists of the placement of unlabeled vials in (b) (4) at the completion of the visual inspection, then packaging these (b) (4) (b) (4) This container is shipped from Rentschler to (b) (4) for labeling

and packaging. Dynavax stated that the controlled environmental shipping container is shipped to (b) (4).

They explained that the shipping of the labeled HEPLISAV™ Drug Product vials from (b) (4) for distribution consists of the placement of the shipping boxes containing the labeled Drug Product vials inside of the controlled environmental shipping container and shipping to the distribution center through (b) (4).

Shipping Validation Studies:

Dynavax stated that shipping validation studies had been conducted to demonstrate that the controlled environmental shipping container can maintain a temperature of 2°C to 8°C for extended period of time and this container is capable of maintaining the integrity of HEPLISAV™ Drug Product vials during transit. They provided a summary report of these studies in the updated BLA. They included a description of the IOP/Q studies conducted to the controlled environmental shipping container; the simulation of the shipping of HEPLISAV™ Drug Product, and to validate the shipping processes from Rentschler to (b) (4).

The IQ study consists of the verification of the calibration certificate from the temperature dataloggers to be used for the temperature monitoring inside the controlled environmental shipping container and the qualification package for the controlled environmental shipping container provided by the manufacturer. Dynavax indicated that this qualification package demonstrated that this container is capable of maintaining the required temperature range of 5°C ± 3°C over a period of more than (b) (4).

(b) (4)

(b) (4)

(b) (4)

Reviewer Comments: Dynavax stated in Section 2.3.P.3.5.2.4 from the amendment to this BLA that shipping validation was conducted in support of the shipping of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to either (b) (4)

Limited information associated with the shipping of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to (b) (4) was provided. Information such as shipping configuration, target maximum shipping duration, acceptance criteria, and target shipping temperatures associated with the shipping validation study of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to (b) (4) was not provided. A copy of the summary report in support of this shipping validation was requested. In addition, Dynavax did not specify in the amendment to the BLA if the Performance Qualification Study associated to the shipping of HEPLISAV™ Drug Product from Rentschler Biotechnologie GmbH to (b) (4) was conducted. **See Complete Response Questions #1.a. and #1.b.**

Information about shipping from (b) (4) was reviewed and found acceptable.