

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 for HEPLISAV™
From: Priscilla M. Pastrana, CSO, OCBQ/DMPQ/MRB II, HFM-676
Through: Marion Michaelis, Branch Chief, OCBQ/DMPQ/MRB II, HFM-676
CC: Richard Daemer, Ph.D, RPM, OVRR/DVRPA/CMC2
Katherine Berkousen, CAPT, RPM, OVRR/DVRPA/CMC2
Destry Sullivan, CDR, Director, RRO/OCBQ/DMPQ/MRB II, HFM-676
Subject: **Review Memo:** Dynavax Technologies Corporation (US License #1883) Biologics License Application (BLA) for HEPLISAV™ (recombinant hepatitis B vaccine) in support of the manufacture for the hepatitis B surface antigen (HBsAg) Drug Substance at Rhein Biotech GmbH (Dynavax Europe) in Düsseldorf, Germany.
ADD: February 24, 2013

RECOMMENDATION:

Based on the information reviewed for this submission, amendment and associated with the Pre License Inspection (PLI) conducted on August 16-17 and 20-23, 2012, I recommend a Complete Response (CR) letter should be sent to Dynavax Technologies Corporation for the following;

Pre License Inspection (PLI) Issues:

- Please submit documentation that demonstrates that all outstanding inspectional issues identified on the FDA form 483 issued August 23, 2012, have been corrected. Outstanding inspectional issues include observations 1.a.ii, 1.b., 2.a., 2.b., 3.a., 3.b., 3.c., 3.d., 3.e., 3.f., 4.b., 5, 7.a, 8, 9 and 10. The deficiencies identified in these observations have not yet been appropriately corrected.

All BLA Submission Review Issues have been resolved.

SUMMARY:

CBER received a BLA from Dynavax Technologies Corporation (Dynavax) on April 26, 2012 for the introduction of HEPLISAV™ (recombinant hepatitis B vaccine). Dynavax stated that this drug product is a recombinant hepatitis B vaccine 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. They stated 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 (Dynavax Europe) in Düsseldorf, Germany; 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. Labeling, packaging and storage of the vials of this drug product is at (b) (4). However, information related to (b) (4) was not included in the BLA. **See IR Questions #1a., #1b, #1c, #1d, and #1e.**

In addition, this BLA included information regarding the manufacturing of the adjuvant at Avecia Biotechnology, Inc., Milford Massachusetts. However, this material will not be covered in the scope of this review.

Primarily, this review is limited in scope to review of the manufacturing for the HBsAg Drug Substance, and some aspects of the packaging facility. A listing of overall facilities involved in the manufacture of Heplisav is provided below.

The following sections of this submission were reviewed by DMPQ:

1. Form FDA 356h
2. Cover Letter
3. Section 2.3.S, Quality Overview Summary - HBsAg Drug Substance Manufacturer
4. Section 2.3.A.1, Quality Overview Summary – Facilities and Equipment - HBsAg Drug Substance Manufacturer
5. Module 3.

Furthermore, the firm also provided a request for categorical exclusion from an environmental assessment for the drug substance, adjuvant and drug product manufacturing facilities, referencing 21 CFR 25.31 and (c), and this request is addressed in a separate memo in the EDR.

A Pre-License inspection (PLI) for the drug substance manufacturing was conducted from August 16 to 23, 2012. Upon completion of the PLI, 13 FDA form 483 observations were issued to the firm (see EIR and FDA form 483 associated with the inspection). Issues identified included: deficiencies in quality system procedures, inadequate cleaning validation studies, in-process control (IPCs) limits applicable during the manufacturing of the HBsAg did not reflect manufacturing process capabilities, inadequate qualification studies conducted for process equipment, open seams, cracks and incompletely sealed defects observed in walls and ceiling surfaces, extractable and suitability testing was not conducted for the (b) (4) used for the filling of this drug substance, inadequate Container Closure Integrity Test (CCIT) methodology, lack of procedures for batch to batch changeover, routine calibration was not conducted for compressed air system critical instrumentation, process and instrumentation diagrams (P&IDs) of utility systems did not reflect the actual configuration of the installed systems, training procedures were not followed, and process equipment was not operated at the validated operational parameters.

To date, outstanding inspectional issues observations identified on FDA form 483, issued on August 23, 2012, include observations 1.a.ii, 1.b., 2.a., 2.b., 3.a., 3.b., 3.c., 3.d., 3.e., 3.f., 4.b., 5, 7.a, 8, 9 and 10; A CR letter is recommended for this file to address the outstanding inspectional issues. See the “Recommendation Section.

REVIEW:

The facilities involved in the manufacturing and testing of HBsAg Drug Substance, in addition to the storage, labeling and packaging of HEPLISAV™ Drug Product are the following:

Table No. 1 - HBsAg Drug Substance Manufacturing and Testing Information

Company Name and Address	Contact Name and Number	Activities	Reference
Hepatitis B Surface Antigen (HBsAg) Drug Substance			
(b) (4)	Site no longer active	<ul style="list-style-type: none">• Master Cell Bank Production	<ul style="list-style-type: none">• None
(b) (4)	(b) (4)	<ul style="list-style-type: none">• Master Cell Bank Storage	<ul style="list-style-type: none">• FDA Establishment Identifier: Not Applicable
Rhein Biotech GmbH (a wholly owned subsidiary of Dynavax Technologies Corporation) Eichsfelder Strasse 11 40595 Duesseldorf Germany	Dr. Thomas Menne Head Quality Assurance Quality Assurance tmenne@eu.dynavax.com +49 (0) 211 / 75845-164	<ul style="list-style-type: none">• HBsAg Drug Substance Manufacture• HBsAg Drug Substance In-process Testing• HBsAg Drug Substance Release Testing(b) (4)• HBsAg Drug Substance Stability Testing• HBsAg Drug Substance Storage• HBsAg Drug Substance Manufacturer's QA Release• Master Cell Bank Storage• Master Cell Bank Testing• Working Cell Bank Production• Working Cell Bank Testing• Working Cell Bank Storage	<ul style="list-style-type: none">• FDA Establishment Identifier: 1000350748
(b) (4)	(b) (4)	<ul style="list-style-type: none">• HBsAg Drug Substance Release Testing - Sterility	<ul style="list-style-type: none">• FDA Establishment Identifier: (b) (4)
(b) (4)	(b) (4)	<ul style="list-style-type: none">• HBsAg Drug Substance Release Testing - Sterility	<ul style="list-style-type: none">• FDA Establishment Identifier: (b) (4)

Dynavax Technologies Corporation 2929 Seventh Street, Suite 100 Berkeley, CA 94710 USA	William Turner VP, Regulatory Affairs and Corporate Quality Systems (510) 665-7296 wturner@dynavax.com	<ul style="list-style-type: none"> • BLA Sponsor • HBsAg Drug Substance QA Release 	<ul style="list-style-type: none"> • FDA Establishment Identifier: Application submitted
Rentschler Biotechnologie GmbH Erwin-Rentschler-Strasse 21 88471 Laupheim Germany	Dr. Hans-Joachim Zoller Vice President Quality Assurance +49 7392 701 864 HansJoachim.Zoller@rentschler.de	<ul style="list-style-type: none"> • HBsAg Drug Substance Storage 	<ul style="list-style-type: none"> • FDA Establishment Identifier: 1000291122
HEPLISAV™ Drug Product (Storage, Labeling and Packaging)			
(b) (4)	(b) (4)	<ul style="list-style-type: none"> • Bulk HEPLISAV Drug Product Storage • HEPLISAV Drug Product Secondary Labeling and Packaging • Finished HEPLISAV Drug Product Storage 	<ul style="list-style-type: none"> • FDA Establishment Identifier: (b) (4)

HBsAg Drug Substance Manufacturing Location:

Rhein Biotech GmbH (Dynavax Europe)
Eichsfelder Strasse 11 D-40595 Düsseldorf Germany

HBsAg Drug Substance Manufacturing Facility Overview:

Rhein's facility consists of a complex of (b) (4) Buildings (b) (4) consist of a total area of approximately (b) (4) square feet on (b) (4) floors ((b) (4) and used for development, manufacturing, quality control, quality management, storage, and administrative functions. Quality Control (QC), microbiology and other laboratories, in addition to the administrative offices are located in the (b) (4) floor of Building (b) (4). In addition, the (b) (4) houses the material/personnel airlock leading into Suite (b) (4) personnel changing rooms and a corridor leading into the manufacturing area within Building (b) (4). The (b) (4) is dedicated for the manufacturing of HBsAg (GMP Suite (b) (4), GMP Suite (b) (4) utilities and raw material sampling area.

Building (b) (4) is approximately (b) (4) square feet and partially utilized as a GMP warehouse, technical supply area, administrative offices and general storage. Building (b) (4) consist of an area of approximately (b) (4) square feet and is partially used as a document archive and office space. The remaining space in Buildings (b) (4) will be use for a future expansion.

Building (b) (4) houses the manufacturing facility. Manufacturing began in (b) (4) and operated as a process development site under non GMP conditions until (b) (4). This building was upgraded to a GMP facility in (b) (4). From (b) (4), physical modifications were done in this building to upgrade the classification in the manufacturing area from Class (b) (4) to Class (b) (4) and segregate the manufacturing area into (b) (4) GMP suites identified as Suite (b) (4) and Suite (b) (4). Suite (b) (4) is a dedicated area of approximately (b) (4) square feet for the production of *Hansenula polymorpha* HBsAg cell banks and Drug Substance. Suite (b) (4) is approximately (b) (4) square feet and not used. Other work conducted during this renovation was the implementation of a (b) (4) storage area in Building (b) (4). Prior to the mentioned renovation, this facility was a multi-product manufacturing facility, however none of the products manufactured in this facility have been approved by the Agency.

Dynavax clarified that this facility is dedicated to the manufacturing of the HBsAg Drug Substance after the completion of the mentioned renovation and they are not manufacturing other products. Dynavax indicated that they were manufacturing other products prior the submission of this application. Clarification was requested with respect to the controls that are in-place to demonstrate that there are no residues of the other products that were manufactured at Rhein Biotech GmbH after the change of multiproduct manufacturing facility to single product manufacturing facility. **See IR Question #4.**

HBsAg Drug Substance Manufacturing Process Overview:

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

Cleaning, Containment, Segregation, Change Over, Prevention of Contamination Controls:

Dynavax indicated that the Rhein Biotech GmbH manufacturing facility is dedicated to the manufacturing of the HBsAg Drug Substance, however within the BLA, the firm stated that they have in place procedures for the cleaning of facilities, containment, change-over and prevention of contamination, cross-contamination and mix-ups, in addition to routine environmental monitoring to manufacturing areas, product contact utilities and personnel.

Cleaning, Containment, Segregation, Change Over, and Prevention of Contamination Controls were reviewed primarily during the PLI.

Moreover, they indicated that the frequency of routine cleaning is adapted for different surfaces in the clean rooms and hygiene zones (HZ). They explained that a basic facility cleaning is conducted every ^{(b) (4)} months and include the cleaning and disinfection using a sporicidal agent, in addition this type of cleaning is conducted as part of their change over procedure and when the environmental monitoring data requires a specific corrective action. Moreover they use a (b) (4) ^{(b) (4)} after the reconditioning project conducted in the manufacturing area. In addition, class ^{(b) (4)} area and HZ ^{(b) (4)} and ^{(b) (4)} are cleaned (b) (4) and class ^{(b) (4)} and HZ ^{(b) (4)} are cleaned based a established cleaning schedule. Dynavax stated that they use cleaning agents and disinfectants that provide a broad range of antimicrobial effectiveness and disinfection efficacy studies were conducted to them using local isolates to evaluate the antimicrobial spectrum of the mentioned agents against those organisms. They provided a list of cleaning and disinfection agents and cleaning frequency intervals in the clean rooms and hygiene zones in Section 3.2.A.1.1.6, Facility Cleaning and Disinfection from BLA STN 125428/0.

Dynavax claimed that the manufacturing process of HBsAg Drug Substance and the HVAC system were designed to prevent contamination; in addition the processing rooms of Suite ^{(b) (4)} are physically segregated with airlocks. Furthermore, they explained that the equipment used in the manufacturing of the HBsAg Drug Substance is dedicated, and is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use, cleaning and maintenance.

They provided a description of the mentioned controls in Section 3.2.A.1.2.2, Segregation and Prevention of Contamination from BLA STN 125428/0.

They explained that routine environmental monitoring is conducted to manufacturing areas under dynamic conditions (in operation) to ensure the clean room classification is maintained during operations. In addition it is conducted to product contact utilities and personnel. The firm stated that procedures are in-place for gowning, flow of personnel and GMP practices inside the manufacturing area such as hygiene, techniques while handling products, cleaning and disinfecting gloves or hands, and basic health requirement. They provided a description of the environmental monitoring and personnel controls in Section 3.2.A.1.2.3, Environmental Controls and Monitoring from BLA STN 125428/0.

Clarification was requested to the firm regarding the controls that they have in-place to demonstrate that there are no residues of the other products manufactured at Rhein Biotech GmbH after the change of multiproduct manufacturing facility to single product manufacturing facility. **See IR Question #4.**

However the following deficiencies were observed during the PLI:

- Inadequate procedures for Environmental Monitoring, since the environmental monitoring procedure did not indicate the sampling location and environmental monitoring sampling was not conducted during the filling set-up activities;
- There are no procedures that define the requirements necessary for batch to batch changeover;

Refer to discussion of 483 Observation No. 5, No. 7a and No. 9 in Rhein Biotech GmbH (Dynavax Europe) EIR.

Heating, Venting, and Air Conditioning (HVAC) System and Environmental Monitoring (EM):

HVAC systems and control were reviewed primarily during the PLI.

Briefly, Dynavax stated that ^{(b) (4)} independent HVAC units ^{(b) (4)} supply air to the manufacturing area and the incoming air from outside to supply the Grade ^{(b) (4)}, Grade ^{(b) (4)}, in addition to “hygiene zones (HZ)” areas are filtered by terminal HEPA filters with an efficiency of 99.95%, in addition it is humidified and tempered as needed (during the PLI it was determined that HZ are roughly equivalent to a controlled, not classified area). They indicated that the pressure differentials between Grade ^{(b) (4)} corridors and controlled, not classified (HZ ^{(b) (4)}) areas are maintained at ^{(b) (4)} Pa and it is measured using magnehelic gauges. Furthermore, they explained that the air over pressurization was established to achieve a directed flow from rooms of low potential emission of particles and microorganisms to those rooms with a higher potential emission and the air change rate for the Grade ^{(b) (4)} rooms is not less than ^{(b) (4)} to ensure proper recovery times of the rooms. They stated that local protection up to HZ ^{(b) (4)} is provided for critical operations in the functional areas by using ^{(b) (4)}. They claimed that the Recirculation rate of the clean room air is ^{(b) (4)} except for Manufacturing Room ^{(b) (4)} and the air is not recirculated in the Upstream Manufacturing Room ^{(b) (4)}, Supply Room ^{(b) (4)} and Storage ^{(b) (4)} Room ^{(b) (4)} and the exhaust air is ^{(b) (4)}. The firm stated that a visual and audible alarm is triggered by the AHUs in the affected areas if limits

are exceeded or a critical technical alarm occurs to allow operator intervention, in addition an automated printout of the alarm messages is generated.

Dynavax explained that Rhein Biotech's environmental monitoring program includes 2 control classifications (grades and HZs). The Grade (b) (4) and Grade (b) (4) classification has been adapted for processing rooms within the manufacturing area and raw material sampling where there is the most risk to the product and their specification are defined in the (b) (4). Moreover the classification for each HZ was assigned internally based on the potential impact to product quality, where the impact on product quality has been categorized based on direct (HZ (b) (4)), indirect (HZ (b) (4)) or no impact (HZ (b) (4)). The environmental monitoring is performed in dynamic condition to confirm that the status of the clean room classifications in Suite (b) (4) and the other classified GMP areas is maintained. Routine monitoring sites have been established based upon a review of performance qualification data and an identification of worst case locations.

Facility Utilities:

Facility Utilities were reviewed entirely during the PLI.

The facilities utilities included Purified Water (PW), Water for Injection (WFI), Clean Steam (CS) and Compressed Air System. Dynavax stated that the PW is used for the (b) (4)

. They indicated that the WFI is used for the (b) (4) step. The CS is used for (b) (4). The firm explained Compressed Air System is used to actuate valves and (b) (4).

Process Equipment:

Process Equipment systems and control were reviewed primarily during the PLI.

Briefly, Dynavax stated that the equipment used in the manufacturing of the HBsAg Drug Substance is dedicated, and is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use, cleaning and maintenance. They provided a list of the major processing and ancillary equipment in Section 3.2.A.1.2.1, Major Equipment Identification and Location of Operation from BLA STN 125248/0. The qualification, preventive maintenance and calibration of the manufacturing equipment were evaluated in the PLI. During the PLI, it was observed that the firm did not adequately conduct qualification studies for process equipment, and that process equipment is not operated at the validated operational parameters. Refer to discussion of 483 Observation No. 4.a and No. 13 in Rhein Biotech GmbH (Dynavax Europe) EIR.

Process Equipment Cleaning:

Process Equipment cleaning validation was reviewed primarily during the PLI.

Dynavax stated that product dedicated equipment and single use (disposable) components are used in the HBsAg manufacturing process. They indicated that their cleaning validation program focused on demonstrating that the cleaning of product contact and non-product contact equipment between batches of HBsAg is consistent and reduces residues to acceptable levels.

(b) (4)

A copy of the Report for the Process Equipment Cleaning Validation Study detailing the cleaning method and cleaning validation acceptance criteria was included in Section 3.2.A.1 Quality Information - Facilities and Equipment - HBsAg Drug Substance Manufacturer of BLA STN 125428/0.

Dynavax did not provided information regarding the equipment used for sterilization and depyrogenation of product contact equipment and components in the BLA. However they were reviewed as part of the process equipment system and controls during the PLI.

Clarification was requested to the firm regarding to the use of potable water for the (b) (4) cleaning steps and the evaluation of the validated condition of the cleaning process. **See IR Questions #6 and #7.**

During the PLI, it was observed that the firm conducted inadequate cleaning validation studies for the process equipment. Refer to discussion of 483 Observation No. 2.a and No. 2.b in Rhein Biotech GmbH (Dynavax Europe) EIR.

Container Closure System:

(b) (4)

Responses received for inquiries appear italicized and a summary of firms response and reviewer commentary appear in regular text.

The firm's responses to IR questions 1.a, 1.b, 1.c, 1.d, 1.e, 2.a, 2.b, 3.b, 5, 6.a, and 6.b are considered acceptable. However the firm's responses to IR questions 3.a, 4 and 7 are not considered acceptable since they were cited with 483 Observations No. 2.a, No. 2.b, No. 5, No. 7a, No. 8 and No. 9. Final review of these issues will be covered as part of the responses to FDA form 483 observations.

[Redacted content]

(b) (4)

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Conclusions:

Dynavax has not addressed all FDA form 483 observations as noted above as Recommended Action. Therefore, a CR letter should be issued to the firm.