

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 125428/0.42 (DATS# 628039) 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: **Complete Response 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 (formerly 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: December 15, 2016

RECOMMENDATION:

Dynavax Technologies Corporation (Dynavax) responses to the Complete Response (CR) Letter issued February 22, 2014 associated with this BLA have been adequately addressed. However, I cannot recommend approval at this time due to the changes to the BLA for Hepatitis B Vaccine, Recombinant (Adjuvanted) [HEPLISAV] submitted by Dynavax on March 15, 2016 under Amendment STN 125428/0.042 (DATS# 628039).

I recommended that a Complete Response (CR) Letter be sent to Dynavax to inform them that we are unable to complete the final approval for this BLA. Refer to the review memo for the amendment to this BLA dated October 24, 2016.

SUMMARY:

CBER received the following two responses from Dynavax to the CR Letter issued February 22, 2014: Amendment STN 125428/0.42 (DATS# 628039 received March 15, 2016) and Amendment STN 125428/0.44 (DATS# 629452 received April 01, 2016). The CR Letter issued is associated with 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). 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.

The firm provided updates to the BLA for HEPLISAV as part of Amendment #125428/0.42 (DATS# 628039). The review of these updates is discussed in a separate review 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. 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)

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 the PLI, a 13-item FDA Form-483 was issued. The inspectional findings are 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) and August 2014 (Amendment #125428/0.37, DATS#591008). Two 483 Responses Review Memos were issued on February 12, 2013 and March 18, 2015 to address the firm's responses to these observations. Dynavax provided acceptable responses that resolved and closed observations 1.a.i., 1.a.ii., 1.b., 1.c., 1.d., 1.e., 2.a., 2.b., 4.a., 4.b., 4.c., 5, 6, 7.a., 7.b., 8, 9, 10, 11, 12 and 13. However, they did not provided satisfactory responses to resolve and close observations 3.a., 3.b., 3.c., 3.d., 3.e., and 3.f.

On February 22, 2013 a CR Letter was issued to Dynavax to address deficiencies observed during the PLI; to deficiencies found in the review of this BLA in 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.

The scope of this CR review memo is the evaluation of the firm's responses to these deficiencies and to the IR submitted to Dynavax on May 24, 2016 for 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 responses to this IR were received on June 06 and 09, 2016.

CBER Comments: Based in the review of Dynavax's responses to this CR letter and the IR sent on May 24, 2016, I can concluded that the issues reviewed in this CR review memo were

resolved and closed. However, a CR letter has to be sent to the firm in regards to the changes to the BLA for Hepatitis B Vaccine, Recombinant (Adjuvanted) [HEPLISAV] submitted by Dynavax on March 15, 2016 under Amendment STN 125428/0.042 (DATS# 628039). **See Recommendation Section.**

Dynavax resubmitted the BLA for HEPLISAV™ in conjunction with these responses to the CR letter received on March 15, 2016. It was noted in the BLA that there are several changes to the Drug Substance and Drug Product Manufacturing Facilities. The changes associated with the Drug Substance manufacturing facility were reviewed during the Pre-License Inspection (PLI) conducted on June 08-16, 2016. They are discussed in the Establishment Inspection Report (EIR) for this PLI. The changes to the Drug Product manufacturing facility are discussed in a separate memo dated October 24, 2016.

CR Review:

This review is for the responses received on March 15, April 01 and June 09, 2016 under Amendments #125428/0.42 (DATS #628039), #125428/0.44 (DATS #629457) and #125428/0.49 (DATS# 634730) for the CR letter issue on February 22, 2013. The CR questions appear italicized and a summary of the firm response and reviewer commentary appear in regular text.

4. *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 1a.ii, 1b, 3.a., 3.b., 3.c., 3.d., 3.e., 3.f., 4b, 5, 8, and 10; the deficiencies identified in these observations have not yet been appropriately corrected.*

Firm Response: Dynavax submitted documentation on August 2014 (Amendment #125428/0.37 (DATS #591008), to demonstrate that all outstanding inspectional issues and deficiencies identified in observations 1a.ii., 1b., 3.a., 3.b., 3.c., 3.d., 3.e., 3.f., 4b., 5, 8, and 10 on the FDA form 483 issued August 23, 2012 had been corrected and closed. The firm provided additional documentation on January 14, 2016 and March 17, 2016, under Amendments #125428/0.39 (DATS# 623588) and #125428.042 (DATS# 628039), which include an updated process control strategy for HBsAg drug substance to demonstrate that the deficiencies identified in observation 3.a., 3.b., 3.c., 3.d., 3.e., 3.f were satisfactory corrected and solved.

CBER Comments: Responses from observations 1a.ii., 1b., 4b., 5, 8, and 10 had been reviewed by DMPQ. They were found corrected and resolved. Responses from observations 3.a., 3.b., 3.c., 3.d., 3.e., 3.f. had been reviewed by the Product Office (PO) reviewer. A 483 response review memo was issued on March 18, 2015 to address that observations 1a.ii., 1b., 4b., 5, 8, and 10 were satisfactory corrected and closed. The 483 response memo found observations 3.a., 3.b., 3.c., 3.d., 3.e., 3.f. were not satisfactorily resolved.

The PO reviewer evaluated the additional information provided on January 2016 and requested the firm to provide an updated process control strategy for HBsAg drug substance. The updated process control strategy for HBsAg drug substance was received in the re-submitted BLA on March 17, 2016. The PO reviewer evaluated the firm's new responses to observations 3.a., 3.b., 3.c., 3.d., 3.e., 3.f. and they were found acceptable. The PO reviewer documented this in a 483 response review memo issued on April 26 2016.

(b) (4)			

CBER Comments: The above list was reviewed and found acceptable.

6. *Your container closure integrity test performed in support of your final drug product container is inadequate, as follows:*
- Your (b) (4) test was not performed under extremes of pressure to simulate worst case conditions.*
 - Positive controls employed as part of the (b) (4) test are not appropriate, in that they do not approach a worst case leak, and do not define an aperture size, or even utilize an aperture/defect.*
 - Your (b) (4) test does not provide qualification data that demonstrates that they can reliably detect a (b) (4) within test vials that would approach the amount that would migrate into a defective vial with a defect size approaching critical (i.e., (b) (4)) under your chosen test conditions. Additionally, you have not provided any information regarding positive controls incorporated into the test.*

Therefore, please perform a container closure integrity test that is performed under worst case conditions that utilizes appropriate positive controls.

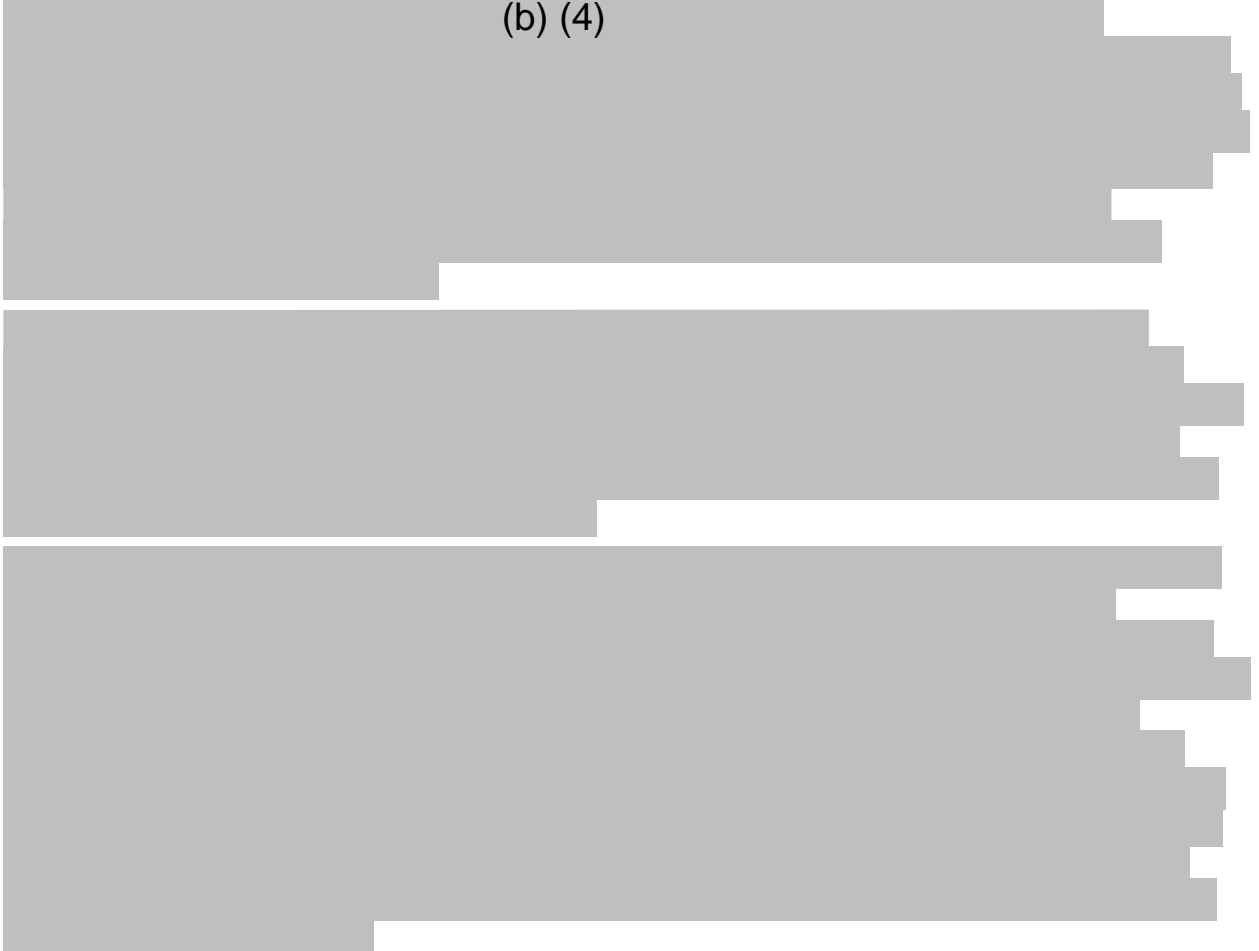
Firm Response: Dynavax explained that a teleconference held with the agency on May 13, 2013 to notify that the CCIT study will be repeated for the drug product container/closure system of HEPLISAV™ using the (b) (4) method with a positive control (with a defect size of

- a. *The qualification defect test set is comprised of too large a percentage of defects. The defect test set should generally be composed of no more than 5% defects.*
- b. *The defect test set is inadequately described in that the total number of vials in the defect test set is not specified, and defects themselves are not specifically defined beyond a general description, such as “particles.”*
- c. *The overall visual inspection program does not specify a percentage of defects observed per lot where you will initiate a 100% re-inspection of a batch, nor how many 100% re-inspections will be allowed before rejection of a given batch.*
- d. *You have not stated nor provided details regarding use or implementation of an Acceptable Quality Limit (AQL) or Lot Tolerance Percent Defective (LTPD) acceptance sampling program to be performed routinely.*

Therefore, please re-evaluate your 100% visual inspection program and submit any subsequent validation of the program for review.

Firm Response: Dynavax explained that SOP-DYN-PF-006, “Qualification, Visual Inspection and Random Sample Inspection of HEPLISAV” and “Defect Types and Description Summary Report for HEPLISAV” were implemented to improve the 100% visual inspection of HEPLISAV™ vials at Rentschler Biotechnologie. Copies of both documents were included in the response to this CR item. They were reviewed and found acceptable.

(b) (4)



(b) (4)

The firm explained that a yield calculation is conducted at the end of the 100% visual inspection and random samplings. It includes an analysis of the critical, major and minor defects identified in the vials and total amount of rejected vials.

CBER Comments: The firm's response and SOP-DYN-PF-006, "*Qualification, Visual Inspection and Random Sample Inspection of HEPLISAV*" and "*Defect Types and Description Summary Report for HEPLISAV*" were reviewed and found acceptable.

8. *With respect to Cleaning Validation performed in support of use of product contact equipment used in the manufacture of the final drug product, your (b) (4) criterion of (b) (4) is inappropriate, as use of this criterion may allow carryover of residual cleaning solution into the final product. Therefore, please submit a revised cleaning validation (b) (4) acceptance criterion that is appropriate for cleaning validation performed for product contact equipment used in the manufacture of final drug product.*

Firm Response: Dynavax provided two summary reports for the Cleaning Verification Studies of the (b) (4), which were approved on December 2013. These studies were conducted in 2013 to demonstrate that the washing cycles used for product contact components (such as glassware, single use items, small components and filling line components) during routine production and in the manufacture of HEPLISAV drug product, comply with the (b) (4) acceptance criterion of (b) (4) and (b) (4) criterion of (b) (4). Copy of both reports was included in the response to this CR item. They were reviewed and found acceptable.

(b) (4)

(b) (4)	

[REDACTED]

[REDACTED]

[REDACTED]

CBER Comments: The summary reports for the Cleaning Verification Studies of the (b) (4) [REDACTED] were reviewed and found acceptable. They demonstrated that the (b) (4) [REDACTED] criterion of the washing cycles used to wash product contact components used during routine production and in the manufacture of HEPLISAV drug product, comply with the (b) (4) [REDACTED] acceptance criterion of (b) (4) [REDACTED]. However, the firm did not explain the reason to demonstrate the effectiveness of the change in the (b) (4) [REDACTED] acceptance criterion in a single verification run of the washing cycles used to wash product contact components (such as glassware, single use items, small components and filling line components) during routine production and in the manufacture of HEPLISAV drug product. **See IR Question #2 - May 24, 2016 (Below).**

2. *Regarding the response to the CR item #8 from the CR letter issued on February 22, 2013, It was noted in the two summary reports for the Cleaning Verification Studies of the (b) (4) [REDACTED], that a single cleaning verification run was conducted. Please provide your rationale why a single cleaning verification run instead of three cleaning validation runs is sufficient to demonstrate the effectiveness of the change in the (b) (4) [REDACTED] acceptance criterion.*

Firm Response: Dynavax explained that a developmental study was conducted in 2013, to demonstrate that the “Single-Use Equipment,” (b) (4)

(b) (4)

CBER Comments: The firm response was found acceptable. In addition, copies of the summary reports for the developmental study in support for the change in the (b) (4) acceptance criterion and addendum for the Cleaning Verification Studies of the (b) (4) were reviewed and found acceptable.

9. *You have stated that since the time of the original BLA submission a Rentschler Biotechnologie GmbH change control has been approved which authorized the implementation and qualification of a (b) (4) for use at the Laupheim location. With respect to implementation of this new equipment:*

a. The validation/qualification summaries provided in support of this equipment are inadequate to determine if this equipment is suitable for use. Please submit complete validation/qualification final reports for review.

Firm Response: Dynavax provided summary reports of the Cleaning Validation Studies conducted to the (b) (4); as well, Performance Qualification (PQ) studies conducted to the (b) (4)

In addition, the summary reports from the latest Re-Qualification studies conducted to the autoclave and depyrogenation oven in 2015 and

verification studies conducted to the washer in 2013. They stated in these reports that the above equipment is suitable for use at their contract manufacturing facility located at Laupheim location.

(b) (4)

Dynavax stated that the summary reports from the Cleaning Validation (CV) Studies and Cleaning Verification Studies of the (b) (4) were approved on September 2012 and December 2013.

Cleaning Validation:

(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 summary reports associated to the Qualification and Re-Qualification Studies conducted to the (b) (4)

; in addition, to the Cleaning Validations Studies of the (b) (4) were reviewed and found acceptable.

CBER Comments associated to the discussion of the summary reports for the Cleaning Validation Studies of the (b) (4) from this CR item was addressed in the CBER Comments to the CR item #8.

Additional clarification is required in the summary reports of the Cleaning Validation Study of the (b) (4)

). As well, additional confirmation is required from the firm if at least one qualification run was conducted in the depyrogenation ovens (b) (4) using the Loads #1, #2 and #3. **See IR Questions #3.a., #3.b. and #3.c. –May 24,2016. (Below):**

3. *Regarding the response to the CR item #9.a.from the CR letter issued on February 22, 2013,*

- a. *You stated in Section 15 from summary report of the Cleaning Validation Study RBT_GAS_A1696_RVP_v1.0 that Deviation DEV007/12 was issued due to no re-testing of the samples for SST at the maximum testing time of (b) (4) days after the first test. Please clarify what SST stands for.*

Firm Response: Dynavax clarified that SST stand for System Suitability Test.

CBER Comments: The firm response is acceptable.

- b. You stated in the summary report RBT_GAS_A1696_RVR_Addendum_v1.0 that a second Cleaning Validation Study was conducted 2012 to demonstrate the reduction of the (b) (4) acceptance criterion from (b) (4) of the items washed according to the (b) (4) historical data and an agreement with the Agency on August 2012. However, you did not indicate the DHT of the items soiled in (b) (4) in this report. Please provide the DHT for these items.

Firm Response: Dynavax indicated that the DHT of the item soiled in (b) (4) on the second Cleaning Validation Study conducted in 2012 and included in the summary report RBT_GAS_A1696_RVR_Addendum_v1.0 was (b) (4) days. They clarified that the duration of this DHT is the same as the first cleaning validation study included in this report.

CBER Comments: The firm response is acceptable.

- c. You stated in the summary report RBT_TSQua_A2734-09II24-E_LQR_v1.0 that depyrogenation of glassware using Loads #1, #2 and #3 are currently depyrogenated during routine production in (b) (4). Also, you stated that you used the glassware Load #2, which is considered as the worst-case load for the qualification of these ovens.

Please provide a copy of the summary report from the latest re-qualification study of the (b) (4); in which one requalification run was conducted using glassware Load #2.

Firm Response: Dynavax provided copy of the summary reports from the latest re-qualification study of the (b) (4); in which include one re-qualification run was conducted using the glassware Load #2. They stated that these re-qualifications were conducted in the following years:

Table No. 13: Re-qualification of (b) (4) Using Glassware Load #2

(b) (4)

The firm explained in these reports that the same Load #2 evaluated in the PQ Study and (b) (4) Re-qualification Study of the (b) (4) were evaluated in the re-qualification of these (b) (4). The same components, amount of TC's, and (b) (4) were also used. They stated that the TC's and (b) (4) were placed in the same worst case locations of this load configuration, as in the PQ and Re-qualification Study of the (b) (4). Dynavax stated that the exposure time and temperature stage from these re-qualification runs are the same as stated in Table No. 11 of this memo. They indicated that these re-qualification runs complied with the same acceptance criteria as states in Table No. 12 of this memo. The firm stated that no deviation was generated in these re-qualification studies.

CBER Comments: The summary reports from the latest re-qualification study of the (b) (4) were reviewed and found acceptable.

- b. Please submit three additional process validation lots that demonstrate that you can produce acceptable product when using this equipment.

Firm Response: Dynavax submitted the Certificate of Analysis (CoA), which details the final release results from three consecutive lots of drug product manufactured as follows:

Table No. 14: Final Release Data from HEPLISAV Drug Product Lots

Final Release			Drug Product Lot No. Manufacturing Date and Expiration Date		
Testing	Test Method	Specification	(b) (4)	(b) (4)	(b) (4)
Physical Characteristics					
Appearance	(b) (4)	Color: NMT (b) (4) Opalescence: NMT (b) (4) Essentially free of visible particles	(b) (4)	(b) (4)	(b) (4)
pH	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Extractable volume	(b) (4)	≥ 0.5mL	(b) (4)	(b) (4)	(b) (4)
Particulate contamination: sub-visible particles/ particulate matter	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Identification and Purity					
HBsAg identity	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
HBsAg concentration	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
HBsAg (b) (4) (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
1018 identity	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
1018 content	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

	assay	(b) (4)			
Endotoxin	(b) (4)				
Sterility	(b) (4)	Sterile, no growth	(b) (4)		
General Safety Test	(b) (4)	Pass	(b) (4)		
Activity					
HBsAg (b) (4)	(b) (4)	(b) (4)	(b) (4)		
Potency	(b) (4)		(b) (4)		

The firm stated that the final release results of these lots comply with the final release specifications of HEPLISAV drug product. They indicated that (b) (4) (b) (4)) were used for the cleaning, sterilization and depyrogenation of components used in the manufacture of these lots.

CBER Comments: The final release results from (b) (4) were reviewed and found acceptable.

- c. Finally, please note that your (b) (4) value reported as part of cleaning validation (b) (4) performed in support of the (b) (4) is not appropriate for cleaning validation of filling equipment, as stated above.

Firm Response: Dynavax stated that two Cleaning Verification Studies of the (b) (4) were conducted on 2013 to demonstrate that the washing cycles used to wash product contact components (such as glassware, single use items, small components and filling line components) and cleaning components during routine production and used in the manufacture of HEPLISAV drug product, comply with the (b) (4) acceptance criterion of (b) (4)

These reports were discussed in the Firm Response to the CR item #8.

CBER Comments: CBER Comments of this CR item were discussed in the CBER Comments to the CR item #8.