

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 Hepatitis B Vaccine, recombinant (HEPLISAV™)

From: Destry M. Sillivan, 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, RPM, OVRR/DVRPA/CMC2

Subject: Review Memo: Dynavax Technologies Corporation Biologics License Application (BLA) for HEPLISAV™ (recombinant hepatitis B vaccine) in support of the manufacture for the hepatitis B surface antigen (HBsAg) Drug Product at Rentschler Biotechnologie GmbH in Laupheim, Germany.

ADD: February 24, 2013

RECOMMENDATION:

A Complete Response letter should be issued to the firm.

Complete Response letter questions:

1. 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, 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.*
2. Please provide, or have provided by your contract manufacturer, Rentschler Biotechnologie GmbH provide via an appropriate regulatory mechanism, a complete list of products filled in Building (b) (4), room (b) (4), for the Laupheim, Germany facility.
3. Your container closure integrity test performed in support of your final drug product container is inadequate, as follows:
 - a. Your (b) (4) test was not performed under extremes of pressure to simulate worst case conditions.
 - b. 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.

- c. 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.

4. Your 100 percent final container visual inspection program is inadequate, as follows:
 - 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 reevaluate your 100% visual inspection program and submit any subsequent validation of the program for review.

5. 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
6. 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.
 - b. Please submit three additional process validation lots that demonstrate that you can produce acceptable product when using this equipment.

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.

*CR comment number 1 is comprehensive to inspectional issues identified during the pre-license inspection.

SUMMARY:

CBER received a BLA from Dynavax Technologies Corporation (Dynavax) on April 26, 2012 for the introduction of HEPLISAV™ (Hepatitis B Vaccine, recombinant), formulated together with a 1018 ISS Adjuvant (a short oligonucleotide segment). Dynavax states that this drug product is a recombinant hepatitis B vaccine intended for active immunization against hepatitis B virus infection. The immunogenic component is hepatitis B surface antigen (HBsAg), subtype adw, and is produced in the yeast strain *Hansenula polymorpha* using recombinant technology. 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 (Rentschler), and label, package and store the vials of this drug product at (b) (4).

This BLA contains all aspects of an eCTD BLA, Modules 1 through 5. The following sections of this submission were reviewed by DMPQ:

1. Form FDA 356h, and selected other sections of Module 1.
2. Cover Letter
3. Module 2
4. Module 3.

The scope of this memorandum is review of ***Drug Product*** manufacture.

The Rentschler facility has a US compliance history dating back to 1998. Of note, the two most recent inspections were one conducted as a pre-approval inspection in November of 2007, and another conducted as a combined pre-approval and compliance inspection in July of 2011. These two inspections combined resulted in one FDA form 483 observation; the last inspection resulted in no observations. On that basis, a decision was made to waive any inspection associated with this BLA for the Rentschler facility.

All review issues were not adequately addressed (see **Complete Response letter questions**, above).

REVIEW:

HBsAg Drug Product Manufacturing Location:

Rentschler Biotechnologie GmbH
Erwin-Rentschler-Strasse 21
88471 Laupheim, Germany
FEI 1000291122

Facility Overview:

Dynavax states that the Rentschler facility has been designed and constructed for the production of drugs for therapeutic and diagnostic purposes as a multiproduct facility. The facilities include areas for cell culture production and downstream processing of proteins, as well as aseptic production of small volume parenterals (sterile liquids and sterile lyophilized products) packaged in vials and syringes. All facilities used in the manufacture of HEPLISAV Drug Product are used on a campaign basis with the potential for other products to be manufactured in the same facilities between HEPLISAV Drug Product campaigns. The manufacturing facility consists of (b) (4) interlinked buildings, named Buildings (b) (4), as summarized:

(b) (4)

Drug Product is formulated and aseptically filled in Building (b) (4). Visual inspection is performed in Building (b) (4) or Building (b) (4). Labeling of trays and bulk packaging is performed in Building (b) (4). Drug Product is stored either in Building (b) (4) or Building (b) (4). Quality Control testing is done in Building (b) (4) or Building (b) (4).

Dynavax provided a general list of product types filled in this facility, but did not provide product specifics, nor if the facility had been inspected by FDA in the past (see **Information Requests** section, June 14, 2012 teleconference).

Facility cleaning, product changeover, contamination control:

The transition between the manufacturing of different products within the multiproduct facilities of Rentschler occurs using a defined and controlled procedure. The basic aspects of the procedure are summarized in the section that follows. However, for this product, the product-contact equipment is either dedicated or single use material. To support the changeover, the timelines for required activities are defined to ensure timely conduct of subsequent steps. A list of equipment required for the next product campaign is compiled. Available equipment is assessed to ensure its appropriateness for the subsequent process and, if necessary, further equipment qualification or cleaning validation activities are requested.

Following the completion of product manufacturing, the equipment is removed, cleaned, and stored in interim storage. A final inspection of the applicable rooms is performed to verify the complete removal and relocation to the interim storage of all equipment before each new production process.

Cleaning of facilities is performed according to detailed written procedures using cleaning agents (PW, WFI, and disinfection agents, as appropriate) to reduce viable and nonviable particles on floors, walls, bench tops, as well as on ceilings. In general, cleaning is performed using an appropriate cleaning agent and applied on the floors, walls, and bench tops as well as on ceilings. In addition, production equipment is cleaned after each production process and subsequently sterilized. Each working place described below is cleared of all foreign materials and cleaned prior to the start of a new production process. The area is checked prior to use to ensure cleanliness and operational statuses are acceptable. The check is documented in the relevant batch record or log book, if applicable.

For cleaning of rooms in Grades (b) (4), a disinfectant cleaning agent is dissolved in (b) (4). For Grade (b) (4), a disinfectant cleaning agent is dissolved in (b) (4).

The firm provided diagrams of facility flows and differential pressures between rooms/classified areas, as well as descriptions of facility utilities. Flows appear appropriate, and have been reviewed previously during at least two inspections. The firm also provided diagrams and qualification summaries of utilities used in manufacture of final drug product. Utilities include a WFI system, a Purified Water system, and a Pure Steam system. The qualification summaries will not be discussed here, as these systems have been reviewed during inspection, additionally, information present in EIRs written for inspections conducted for this facility in July of 2011, and December of 2007 was reviewed. During these two inspections, one FDA form 483 observation was given.

Manufacturing Process Overview:

(b) (4)

(b) (4)

(b) (4)

Media fills:

Dynavax did not provide sufficient information regarding media fills performed in support of aseptic processing activities (see **Information Requests** section, August 6, 2012, Questions 8 and 9).

Visual inspection:

Dynavax states that unlabeled vials are 100% visually inspected according to an internal inspection SOP that utilizes (b) (4) fields. Any vial that does not meet the criteria of the SOP is rejected. No other information regarding this inspection process was supplied (see **Information Requests** section, August 6, 2012, Question 5)

Storage, Labeling, and Shipment of Vials:

The bulk packaged vials are stored and, subsequently, shipped to (b) (4) at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ to the vial labeling and finished product packaging site. The bulk vials are placed into (b) (4)

Labeling is performed at (b) (4) as well.

Major Process Equipment:

Major process equipment includes the following:

(b) (4)

(b) (4)

Qualification of this machinery will not be covered here, other than cleaning validation, depyrogenation and sterilization validation, as this is a facility with an acceptable compliance history. Note, however, that the firm has implemented new critical equipment during the course of the BLA review (see CR Question 6, above).

Equipment Sterilization:

(b) (4)

[Redacted]

- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted text block]

[Redacted text block]

Cleaning Validation:

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

Product Final Container and Container Closure Integrity Testing (CCIT):

The container closure system of HEPLISAV Drug Product consists of a (b) (4) glass vial ((b) (4) Type (b) (4) glass) manufactured by (b) (4), a 13 mm (b) (4) stopper [chlorobutyl 13 mm serum stopper with (b) (4) film and (b) (4)-coating and is manufactured (b) (4)

(b) (4), and an aluminum cap. Letters of Authorization to cross reference the respective Drug Master Files (DMF) were provided. The firm's testing of the vials is as follows:

(b) (4)

The stoppers are (b) (4)
The stoppers are tested by the vendor to meet the requirements of (b) (4) (C of A included and reviewed). Additional tests include (b) (4)
Incoming stoppers are additionally tested for (b) (4) at Rentschler. Identity

is confirmed by visual inspection with comparison against a reference standard for stopper dimensions and color.

CCIT:

(b) (4)



A large rectangular area of the document is redacted with a solid grey fill, obscuring several lines of text.



A rectangular area of the document is redacted with a solid grey fill, obscuring several lines of text.



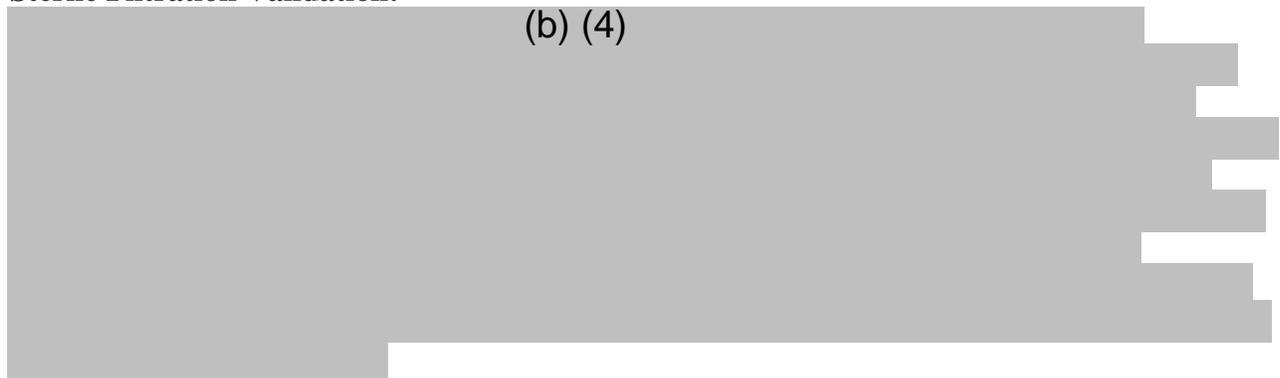
A rectangular area of the document is redacted with a solid grey fill, obscuring several lines of text.



A large rectangular area of the document is redacted with a solid grey fill, obscuring a significant portion of the text.

Sterile Filtration Validation:

(b) (4)



A large rectangular area of the document is redacted with a solid grey fill, obscuring the majority of the text in this section.

Information Requests:

(FDA information requests in normal font, applicant responses in *italics*.)

June 14 teleconference (with Rentschler):

To better determine if a pre-license inspection is necessary for the Rentschler facility, we request a complete listing of all products manufactured within this filling line/area and formulation area. We also request that you confirm that all areas used to manufacture Heplisav were covered under previous FDA inspections of your facility.

Rentschler representatives confirmed that all areas used to manufacture Heplisav were covered under previous FDA inspections of this facility. They also stated that they would forward to us a listing of all products manufactured/filled in areas used to manufacture Heplisav.

To date, a list of products manufactured/filled in areas used to manufacture Heplisav has not been submitted to FDA (see **Complete Response Questions**, Question 2).

August 6, 2012

1. With respect to filling of the final drug product, you state that a “target extractable (b) (4) is monitored....” Is this process a fill (b) (4) check? If not, please describe this procedure in greater detail.

(b) (4)

This response is acceptable, and provides appropriate methodology to perform a (b) (4) check.

2. You have described both a (b) (4) final formulation and fill process and a (b) (4) final formulation and fill process. Please clarify if you currently prepare intermediate final formulation volumes, or plan to in the future.

(b) (4)

3. With respect to container closure integrity testing (CCIT), please provide the following:
 - a. A justification of your choice of (b) (4) challenge organisms. Please note that the organisms you have chosen are not generally considered worst case with respect to organism size.
 - b. Clarification if you utilized extremes of pressure during CCIT testing.
 - c. Results of post testing growth promotion tests for the growth medium.
 - d. The aperture size of positive controls utilized during testing.

3a response:

Dynavax responded that the (b) (4) microorganisms, (b) (4) were used for the container closure integrity test of HEPLISAV Drug Product vials. The microorganisms were selected for the container closure integrity test for the following reasons:

(b) (4)

(b) (4) species were detected at the Rentschler manufacturing facility during the microbiological routine monitoring of personnel, water, and environment and are therefore representative for the microbiological environment.

3b response:

Dynavax stated that the (b) (4) test was not performed under extremes of pressure.

3c response:

Dynavax stated that (b) (4) was performed for all bacterial species, and media was growth promoting.

3d response:

The positive controls ((b) (4) Test) within the (b) (4) test were actively inoculated with defined microorganisms with a (b) (4). No artificial defects with a defined aperture size were created for the positive controls.

An argument may be made that at least two of the (b) (4) organisms chosen for the (b) (4) test may be suitable; however, neither is optimal. This could be overlooked, but the responses for 3b and 3d are not acceptable, because this type of test should be performed under extremes of pressure to simulate worst case conditions, and the firm's positive controls 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 (see **Complete Response Questions**, Question 3)

4. In Table 7 of the FMEA report for Heplisav Drug Product Manufacture, you list a bioburden in process specification of (b) (4). Please confirm that this is an actual (b) (4) test to be performed routinely. If so, this in-process specification should be amended or removed, as bioburden found after (b) (4) would indicate a (b) (4) failure that should be investigated.

Dynavax acknowledged that all (b) (4) are sterilizing grade (b) (4) and have the capacity to yield a sterile (b) (4). However, in the HEPLISAV process summarized in the FMEA report and Section 3.2.P.3.3 (SEQ 0000 dated 26 April 2012), several of the sterilizing Grade (b) (4) are considered bioburden reduction (b) (4) as only the (b) (4) is identified as the sterile (b) (4).

While this response is not optimal because a positive bioburden result a (b) (4) would indicate a failure that should not normally happen, it is acceptable because of the (b) (4) redundancy of (b) (4) in their process when the firm manufactures at the (b) (4) .

5. Please submit complete information regarding your final drug product 100% visual inspection program, to include the final defect test set, validation of the program, qualification of inspectors.

Dynavax replied as follows:

The unlabeled vials are 100% visually inspected according to an internal SOP in a (b) (4) (corresponding to the acceptance criterion given in (b) (4) . Any vial that does not meet the evaluation criteria defined in the SOP is rejected.

Visual Inspection Procedure Including Evaluation Criteria:

Preparatory activity

Prior to visual inspection of liquid drug products, the work space and equipment are cleaned and line clearance (removal of all material from previous inspections) is performed; these steps are documented by (b) (4) . In order to avoid mixing of products, (b) (4) . The light of the (b) (4) prior to the start of visual inspection and is checked for functionality by the operator. The (b) (4) , and appropriate corrective actions are taken if the intensity is not within the specified limit per SOP.

Unlabeled, capped vials are placed in the (b) (4) for at least (b) (4) prior to visual inspection. The vials are removed from the (b) (4) room and transferred to the visual inspection area in trays. Visual inspection is performed at (b) (4) . The time the vials are held at (b) (4) is kept as short as possible and is documented in the batch record.

Visual inspection

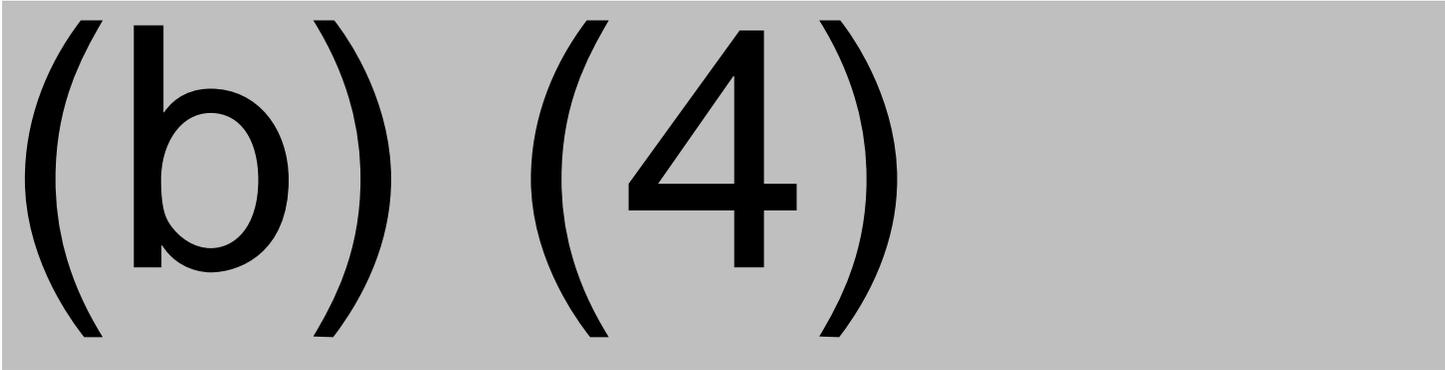
The operators wear (b) (4) gloves. The inventory of vials at the beginning of the visual inspection is documented in the batch record. (b) (4)

The parameters and requirements are set for the visual inspection of liquid filled vials based on common practice

in the pharmaceutical industry and failure rating categories used by suppliers within the pharmaceutical industry (Table 8 of the response).

Vials with defects evaluated as critical, major or minor are rejected and documented together with the description of the defect in the batch documentation. If multiple defects are observed for a vial, the rejected vial is evaluated based on the most critical feature (critical > major > minor). Inspected and uninspected vials are kept strictly separated. Following inspection, inspected vials are directly packed into trays with dividers and lids, a product specific label is inserted, and the trays are sealed. Rejected vials are packed separately and labeled accordingly. If the number of rejected vials in a batch exceeds the specified limit (Table 9), a deviation and a failure investigation are initiated. In this case, all vials in the batch that were not rejected are visually inspected for a second time to ensure that no defective vials are overlooked.

Alert levels for Rejects are defined as follows:



Qualification of Operators (including defect test set)

Setup of a test batch

The test batch is comprised of

(b) (4)

Out of the defects listed in Table 10 the required number of defect vials is selected at random and mixed with compliant vials to form the test batch.

Training and qualification of new operators

(b) (4)

(b) (4)

(b) (4)

Qualified operators are re-qualified (b) (4) a year via randomly arranged re-inspections of a portion of an inspected Drug Product batch that was previously inspected by the supervisor or another qualified operator.

The firm's inspector qualification program is generally acceptable with one exception: the 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. Further, 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." With respect to the overall visual inspection program, it is inadequate in that it does not specify a percentage of defects observed where the firm will move to a 100% re-inspection of a batch, how many 100% re-inspections will be allowed before rejection of a given batch, and they do not state nor provide details regarding any Acceptable Quality Limit (AQL) or Lot Tolerance Percent Defective (LTPD) acceptance sampling performed routinely (see **Complete Response Questions**, Question 4).

6. In Table 3.2.P.3.5-18: Step 7 – Capping Evaluation, you list a Container Closure integrity test that has been performed on vials filled using the (b) (4) batch size. Please completely describe this test, and state why this test was not performed for the (b) (4) batch size.

The CCIT (Rentschler SOP QCA 213 v2) utilizes (b) (4) to confirm that the integrity of the container closure system is sufficient for the prevention of microbial contamination. To perform this test, a (b) (4)

(b) (4)

The CCIT test described above was performed on test vials produced at these settings to confirm that the tested settings for the capping machine were successful in maintaining the integrity of the container closure system. After fill completion and line clearance for each validation batch,

(b) (4), and subsequently tested for container closure integrity. No (b) (4) was observed inside any of the test vials, thereby indicating that the primary container closure system for HEPLISAV maintained container closure integrity when capped with a (b) (4) height setting for the capping machine.

This test appears to be a more stringent CCIT than those previously described, as it uses a (b) (4). However, there are two apparent flaws with the test as described. The first is that they do not detect the presence of (b) (4) and do not provide qualification data for their operators with respect to their ability to 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)). The second flaw is that they do not provide information regarding positive controls incorporated into the test (see **Complete Response Questions**, Question 3).

7. With respect to cleaning validation, please provide/respond to the following:
 - a. A listing and brief description of all non single use product contact equipment, and please re-state that all product contact equipment is dedicated.
 - b. Complete cleaning validation final reports. These reports should include sufficient detail, such as swab locations, configurations of equipment within wash loads, etc.
 - c. Your chosen cleaning validation acceptance criteria for (b) (4) are not stringent enough for cleaning validation studies for final fill equipment, and also do not appear to meet your process capability, base on the validation data submitted in the BLA. Please explore holding a teleconference with CBER/DMPQ to discuss your cleaning validation program.

7a

Dynavax confirmed that all product contact equipment is dedicated. Equipment is dedicated by being single-use (eg, discarded after first use) or dedicated by not being shared, but re-used (multiuse).

7b

Dynavax provided the cleaning validation final report.

Dynavax stated that (b) (4) with direct product contact have (b) (4) for the cleaning (b) (4) to access. They are therefore considered a worst-case load and are used for (b) (4) samples for the validation. Among glass equipment, the (b) (4) is the worst-case equipment because as an individual piece of equipment it has the largest surface area and direct product contact. As noted previously, acceptance criteria for (b) (4) (final rinse for both criteria) were (b) (4). Additionally, their rationale for choosing a product specific criterion of (b) (4) has not been provided. Swabbing locations were described, and appear to be adequate. As noted previously, actual numbers observed during testing were generally at or approaching (b) (4) specifications for (b) (4) levels demonstrated a maximum value of (b) (4).

Of note, in their response to this question, Dynavax states the following:

Since the time of the original BLA submission a Rentschler change control has been approved that authorized the implementation and qualification of a (b) (4)

... (b) (4) were qualified using the same acceptance criteria and approach as described in Section 3.2.A.1.1.2.4.2 for the (b) (4) (summary of new equipment qualification attached). A complete copy of the (b) (4) Cleaning Validation Report is provided, including swab locations. Load configurations are described in the information that follows as these are routinely included within a SOP.

This information will not be reviewed, as it was not annotated in the cover letter for this response, and major changes of this sort made during the middle of a BLA review and submitted as part of an information request are not acceptable (see **Complete Response Questions**, Question 6). However, Dynavax notes that the (b) (4) final rinse (b) (4) value, as demonstrated during cleaning validation performed in support of this (b) (4). This is noteworthy, as this value is not as robust as achieved when using their (b) (4) (also see **Information Requests**, January 7, 2013).

7c

We acknowledge that a limit of (b) (4) is not stringent enough for final fill equipment cleaning validation studies and that it is not reflective of the capability of the (b) (4). A new limit of (b) (4) will be implemented for both rinse and swab

samples, as reflected in the addendum to the Cleaning Validation Report for the newly implemented (b) (4). The information that follows provides background regarding the development of the acceptance criteria.

The (b) (4) cleaning validation summary Section 3.2.A.1.1.1.1.5, Acceptance Criteria states in Table 2 that the (b) (4) acceptance criterion is (b) (4). The intention for the (b) (4) limit was not to be used as a single limit per piece of equipment, but to be used in a total carryover calculation for a series of equipment. We acknowledge that this was not properly implemented for the reporting of the rinse (b) (4) results, as individual points were evaluated against the (b) (4) acceptance criteria (Section 3.2.A.1.1.1.2.1.4).

Dynavax proposed to implement new (b) (4) cleaning validation acceptance criteria of (b) (4) (see Information Requests, January 7, 2013).

8. Please provide the results of media fills performed in support of filling of Heplisav, or results of media fills that have been performed using either the same vials used to fill Heplisav, or results of media fills that you believe to be supportive of use of the final Heplisav container configuration.

Dynavax provided a list of all media fills performed since 2007 for room (b) (4) total runs. Of the (b) (4) vial sizes listed, only the (b) (4) types are filled on the line used to manufacture HEPLISAV. The HEPLISAV process uses the (b) (4) vials. The filling line also supports other vial manufacturer types (eg, (b) (4) vials), but they are bracketed by the dimensions of the (b) (4) vials. One of the runs was performed for the (b) (4) vial used for Heplisav, and most others performed were for vials of different sizes made by the same manufacturer. Numbers of filled units range from a minimum of (b) (4) to a maximum of (b) (4). No media fill failures were observed.

9. Please submit your SOP for media fills.

Dynavax submitted the media fill SOP for the Rentschler site.

Media fill practices and procedures outlined in the SOP are adequate for their intended purpose, and specify worst case interventions to be performed, and that environmental monitoring is performed; these aspects were not provided previously. The firm did not submit media fill environmental monitoring data with the requested additional information for media fills. This is acceptable in this instance for two reasons: 1), there is the expectation that this information was reviewed during the last inspection performed for the facility, and 2), since the firm has implemented major new process equipment for their filling line and support activities, we will request new media fill data, to include environmental monitoring data, as part of the review of the qualification of that equipment, should the firm respond to the CR letter and restart the review process.

January 7, 2013

With respect to your Cleaning Validation results at your contract filler, Rentschler Biotechnologie, we accept your final rinse (b) (4) validation acceptance criterion of (b) (4), as the filling equipment is dedicated. Should you ever choose to share this equipment with another product, the appropriate criterion would be (b) (4).

We do not accept your final rinse (b) (4) criterion of (b) (4). This criterion should be essentially in line with (b) (4) specifications, and we regard the upper end of values you have reported (up to (b) (4)) as failing results (see **Complete Response Questions**, Questions 5 and 6).

Conclusions:

Dynavax has not responded adequately to all information requests and a Complete Response letter should be issued to the firm.