



Our STN: **BL 125428/0**

Dynavax Technologies Corporation
Attention: Mr. William Turner
2929 Seventh Street
Suite 100
Berkeley, CA 94710

Dear Mr. Turner:

This letter is in regard to your biologics license application (BLA) for Hepatitis B Vaccine (Recombinant), Adjuvanted, manufactured at Rhein Biotech GmbH, Düsseldorf, Germany (a wholly owned subsidiary of Dynavax Technologies Corporation, USA) and at your contract manufacturing facility, Rentschler Biotechnologie GmbH, Laupheim, Germany and submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA with the exception of the information in the amendments dated December 29, 2012, January 16, 2013, February 1, 2013, and February 7, 2013. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

CLINICAL ITEMS

1. We consider the size of the safety database in your license application to be insufficient to support the proposed indication and use of your Hepatitis B Vaccine (Recombinant), Adjuvanted, i.e., for prevention of Hepatitis B infection in adults 18-70 years of age. In addition, we are concerned that two subjects may have developed rare granulomatous diseases after receipt of your vaccine. One was a documented case of granulomatous polyangiitis (Wegener's granulomatosis). Another subject may have developed Tolosa-Hunt Syndrome, a serious medical condition of multiple possible etiologies that, in some cases, may be a manifestation of granulomatous polyangiitis. As each of these diagnoses is rare, it would be highly unlikely for both to be observed among the 4,425 recipients of Hepatitis B Vaccine (Recombinant), Adjuvanted, in the clinical trials on the basis of random occurrence. We also note the absence of post-marketing safety experience for any licensed product containing the adjuvant component of your vaccine that could supplement the evaluation of safety. Additionally, we refer you to the discussion of the safety of your vaccine before the Vaccines and Related Biologic Products Advisory Committee on November 15, 2012, and the negative vote by the committee on the question regarding adequacy of the safety information to support the proposed indication and use. Therefore, prior to consideration of licensure of your Hepatitis B Vaccine

(Recombinant), Adjuvanted, for use in adults 18-70 years of age, further clinical evaluation of safety will be necessary, whereby the design and size of the additional safety study or studies will require discussion with CBER.

However, as we indicated in the telephone conversation dated February 12, 2013, between Dynavax and CBER, the safety data required to support licensure of your Hepatitis B Vaccine (Recombinant) Adjuvanted, will depend on the indication and use and a favorable benefit/risk determination associated with that indication and use. We are willing to discuss with you information that would be needed to support a more restricted use of your vaccine, including the size of a safety database and any additional immunogenicity data that may be required.

2. Incomplete information was provided regarding several subjects who experienced adverse events. Please provide the following additional information:
 - a. For subject 32-018, please provide any medical records related to the diagnosis and treatment of narcolepsy.
 - b. Subject 42-320 was discontinued from study due to facial swelling and a rash of unknown etiology. If referral for medical evaluation took place, please provide those documents.
 - c. Subject 21-640 was referred for medical evaluation of a potential autoimmune event. Please provide the records pertaining to that evaluation.
 - d. Please provide the hospital records and neurological outpatient follow-up records for subject 06174.
 - e. Clotting disorder evaluations were performed for three subjects reporting pulmonary emboli (22-601, 21047 and 22070). Please provide the results of those evaluations including any serologic markers of autoimmune disease.
3. Three disks containing radiographic, computed tomography and magnetic resonance images pertaining to the potential case of Tolosa-Hunt syndrome together with a cover letter were submitted to CBER for review. These files could not be accepted for review in the form submitted; therefore, please make the following changes and resubmit the files containing these images.
 - a. To comply with 21 CFR 20.63(b), please remove all patient identifiers from the images and files before they are submitted to the FDA.
 - b. Please resubmit these images to CBER on a disk. The viewing software must be on a separate disk from the images (see item 3 c. below). Please name each image file with the date and radiological test (e.g., MRI, CT) and the subject number (i.e., the number assigned when the subject was entered into the study). Place the patient's image files together in a folder on the disk.

- c. For archiving purposes, please submit a copy of the software required to view these images along with a site license allowing the FDA to use the software on a separate disk. After installing and opening the software, inserting the subject number should take the reviewer to the image files on the disk containing the image files. The software should then allow those files to be opened and viewed.
- d. Please provide detailed instructions on how to install the viewer software and to view the images, with each set of disks.
- e. Please submit five copies of each disk as soon as possible. To expedite review of these images it is acceptable to respond to this comment and submit these five copies as soon as possible and before you respond to the other items in this Complete Response Letter.
- f. Please amend your eCTD submission through the Electronic Submission Gateway (ESG). The cover letter for the submission which responds to this item should state the contents of each disk. Please notify the review team when the disks have been mailed and when the eCTD amendment has been sent through the ESG. Please provide at that time, the CoreId, which is the number conveyed to you when the ESG received your submission.

MANUFACTURING FACILITIES AND 483 RESPONSES

Manufacturing Inspection (Dynavax's Responses to FDA Form 483)

4. Issues remain from our prelicensure inspection of your facility at Rhein Biotech GmbH, Düsseldorf, Germany which resulted in the issuance of FDA Form 483 on August 23, 2012. Outstanding inspectional issues include observations 1a ii, 1b, 3a, 3b, 3c, 3d, 3e, 3f, 4b, 5, 8, and 10; the deficiencies identified in these observations have not yet been appropriately corrected. When you have implemented the corrections and have been notified by the Office of Compliance and Biological Quality that your responses to the FDA Form 483 are acceptable, please submit confirmation of this status to this BLA.

Facilities and Equipment

5. Please provide, or have your contract manufacturer, Rentschler Biotechnologie GmbH provide, via an appropriate regulatory mechanism, a complete list of products filled in Building ^(b)(), Room ^(b)(4), for the Laupheim, Germany facility.
6. The container closure integrity tests performed in support of the final drug product (DP) container is inadequate, as follows:
 - a. The ^(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 utilize an aperture/defect.
- c. The (b) (4) test does not provide qualification data to demonstrate that it 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 a critical threshold (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 submit results from a container closure integrity test that is performed under worst case conditions and that utilizes appropriate positive controls.

- 7. Your 100 percent final container visual inspection program is inadequate, as follows:
 - a. The qualification defect test is set such that the acceptable percentage of defects is too high. The defect test should generally be set to allow a maximum of 5% defects.
 - b. 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 limit (percentage) of defects per batch above which 100% re-inspection is required and also does not specify how many 100% re-inspections will be allowed before a given batch should be rejected.
 - d. You have not stated or provided details regarding the use or the 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 updates of the program for review.

- 8. With respect to Cleaning Validation performed in support of product contact equipment used in the manufacture of the final DP, 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 would ensure that residual cleaning solution would not be carried over into the final product.

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 are inadequate to determine if this equipment is suitable for use. Please submit complete validation/qualification final reports for review.
 - b. Please submit data from three additional process validation lots that demonstrate that you can produce acceptable product when using this equipment.
 - 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 in item 8.

QUALITY CONTROL AND TESTING PROCEDURES

Lot Release and In-support Testing

10. We provided a lot release protocol template on August 16, 2012, to assist you in the development of a lot release protocol for Hepatitis B Vaccine (Recombinant), Adjuvanted. Please submit a lot release protocol template for your product.
11. On August 16, 2012, and in the follow-up teleconference of October 15, 2012, we provided a list of required final container samples and reagents for identity and potency testing to be provided to the Agency. Please submit these reagents and samples. One exception to the agreed upon request is that we will not require that you send the Qualified Immunoassay Test Kit for Detection of anti-HBsAg antibodies (i.e., the (b) (4)

Quality Control Tests and Method Validations for the Drug Substance (DS)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted text block containing multiple paragraphs of information, all obscured by grey boxes.]

Quality Control Tests and Method Validations for the Drug Product (DP)

- 23. 1018 ISS Adjuvant Content by (b) (4) Assay
 - a. Please explain how the extinction coefficient cited in Section 3.2.1 (p. 3) of the SOP QC109-02 is determined.
 - b. Please provide the description of Sample 1 and Sample 2 used for the System Suitability study in the method validation report, Document No. VAL-Q139C-R.

- c. Please explain how the concentrations of (b) (4) used in the specificity study are related to those in the formulated product. If the concentrations are not similar, please explain why specificity studies in the presence of (b) (4) are relevant.
 - d. What are the (b) (4) of the diluents (b) (4) , and 1018 ISS, in the specificity study? Did the diluents contribute to (b) (4) of the analyte, when the analytes are diluted with them?
 - e. We do not agree that accuracy of an assay can be inferred automatically once linearity, precision and specificity are established. Please provide data to show accuracy over the range of the assay (b) (4) . At a minimum, accuracy should be evaluated at three concentration levels, the target concentration, and the lowest and the highest concentrations of the assay range.
24. Please address the following comments regarding validation report HBsAg Concentration by (b) (4) Assay:
- a. Please identify which of the results included in Table 2 of the validation report (Document # VAL-DE A090-4-R) were performed at the Dynavax Berkeley laboratory and which were performed at the Dynavax Europe laboratory.
 - b. Section 7.2 (specificity) of the validation report (Document # VAL-DE A090-4-R) states, “Dynavax Berkeley qualification report QUAL-Q116C-R demonstrates that (b) (4) and provide the qualification report QUAL-Q116C-R.
 - c. Please provide the results showing specificity, intermediate precision and reproducibility (inter-laboratory precision) using (b) (4) concentrations over the assay range, (b) (4) .
 - d. Please explain how the Expected Concentrations reported in section 7.3.2 of the validation report (Document # VAL-DE A090-4-R) are determined. Please clarify whether you used the same assay method or a different (orthogonal) assay method.
 - e. We do not agree that accuracy of an assay can be inferred automatically once linearity, precision and specificity are established. Please provide data to show accuracy over the range of the assay. At the minimum, accuracy should be evaluated at three concentration levels, the target concentration, and the lowest and the highest concentrations of the assay range.

25. Extractable Volume (b) (4)

Please provide data to show that you consistently meet the required specification.

Analytical Methods Validation

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

CHEMISTRY, MANUFACTURING, AND CONTROL (CMC) INFORMATION

Drug Substance (DS)

41. On November 5, 2012, CBER requested that you include in the HBsAg Drug Substance Commercial Release Specification the following tests:

- (b) (4)
- [redacted]

At this time SOPs, method validation protocols and validation reports for these tests have not been received by CBER. Please provide this information.

1018 ISS Adjuvant

- (b) (4)
- [redacted]
- [redacted]
- [redacted]

(b) (4)

Drug Product

53. In your November 20, 2012, response to the November 2, 2012, CBER Information Request regarding release tests for the final product, you proposed the release specification limit of NLT (b) (4) of 1018 ISS adjuvant by (b) (4) in the Hepatitis B Vaccine (Recombinant), Adjuvanted, and you stated that you do not agree to include the (b) (4). We note that the release test specification for the 1018 ISS adjuvant alone (b) (4) is NLT (b) (4). Please incorporate a release specification of NLT (b) (4) in the Hepatitis B Vaccine (Recombinant), Adjuvanted drug product or explain why you would need to have a lower limit for the (b) (4) in the final product than that for (b) (4) in the 1018 ISS adjuvant (b) (4). Regarding the (b) (4) test specification of “confirmed” we will allow it to remain; however, you will also need to state the (b) (4) as previously requested by CBER. Please provide the method validation protocol and report for the revised (b) (4) test method using the (b) (4) and revised (b) (4) of 1018 ISS adjuvant proposed for the release of the Hepatitis B Vaccine (Recombinant), Adjuvanted drug product and include data from the analysis of several lots of drug product via the revised test to support your specification limits.

BIORESEARCH MONITORING (BIMO) ITEMS

54. The BIMO inspection of the clinical investigator for DV2-HBV-16 (study data at site #38) revealed the presence of three protocol deviation logs with discrepant data: Log A, Log B, and Log C. For example, it appears that diaries for five subjects were not collected during the study visit(s) and that in some cases diary data were reconstructed, and/or diaries were collected at subsequent visits that were not reported in the submitted BLA in the line listings 16.3. One of the logs, Log A, contained numerous corrections and cross outs on the data entries. During the inspection, the site received a letter dated October 23, 2012, from Dynavax stating that Dynavax revised the cumulative list of deviations that occurred at the site prior to the BLA submission. The letter further instructed the clinical investigator to review the list and sign the pages, and return them to Dynavax. Please explain the following:
- a. How did Dynavax derive the cumulative list of deviations that was sent to the site?
 - b. Please provide a list of subjects for whom the logs were discrepant from the data submitted in the BLA with the identification of the data that are discrepant.

- c. If diary data were missing when subjects lost their diaries, how were the data reconstructed?
55. Please describe the events and the timeline for the unblinding of the study personnel in study DV2-HBV-16 at site #24. Please include the dates the subjects received the vaccine and the dates when the site, the monitor responsible for the study, and when Dynavax was made aware of the deviations. Please include the database lock date for the study and explain the effect of unblinding of the blinded personnel at the study site prior to the database lock.

We reserve comment on the proposed pharmacovigilance plan and the proposed labeling until the application is otherwise acceptable.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our “Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants,” dated May 2009. This document is available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf> or may be requested from the Office of Communication, Outreach, and Development, at (301) 827-1800. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER’s SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. This document also is available on the internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

We acknowledge receipt of your amendment(s) dated December 29, 2012, January 16, 2013, February 1, 2013, and February 7, 2013. You may cross reference applicable sections of these amendments in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Managers, Richard Daemer, Ph.D. or Katherine Berkhausen, CAPT., USPHS at (301) 796-2640.

Sincerely yours,

Wellington Sun, M.D.
Director
Division of Vaccines and
Related Products Applications
Office of Vaccines
Research and Review
Center for Biologics
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