

RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125428/0.0
Review Office	OVRR
Applicant	Dynavax Technologies Corporation / Lic. # 1883
Product	Hepatitis B Vaccine (Recombinant), Adjuvanted
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	27-APR-2016 02:32 PM
Author	BERKHOUSEN, KATHERINE
EDR	Yes
Post to Web	No
Outside Phone Number	
FDA Originated?	Yes
Communication Categories	IR - Information Request
Related STNs	None
Related PMCs	None
Telecon Summary	IR for QC, CMC, facilities, clinical
FDA Participants	Katherine Berkhausen; Richard Daemer
Applicant Participants	Elaine Alambra

Telecon Body:

From: Berkhausen, Katherine
Sent: Wednesday, April 27, 2016 2:16 PM
To: Alambra, Elaine
Cc: Daemer, Richard J.; Berkhausen, Katherine
Subject: 125428/0 Information Request

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Dear Elaine,

We have the following Information Requests regarding your submission 125428/0.42:

Regarding Quality Control Testing (**Please provide your response by May 13, 2016**):

1. In your response to CRL Comment 41a, you requested that the assay for (b) (4) be excluded from commercial drug substance release testing based on results from (b) (4) lots of HBsAg drug substance. However, you have not provided information on the assay method and the method validation, including how you determined LOQ. This does not permit us to consider your request. Please provide a detailed description of your (b) (4) assay method and the method validation data.
2. In CBER's response to Dynavax on October 17, 2014, (regarding Dynavax's general method validation questions submitted on July 30, 2014), you sought agreement from CBER that "monitoring (b) (4) against a specification as a parameter in the Continuous Process Verification (CPV) program for HBsAg Drug Substance is acceptable rather than including as a commercial release specification." CBER agreed. However, in 125428/0.42 you indicated that CPV has been completed with 3 PPQ lots and (b) (4) CPV lots. Please note that a CPV program should continue over the product life cycle and the method needs to be validated. Furthermore, for consideration of your request, we need to review the assay method and the method validation. Please provide a detailed description of the (b) (4) assay method and the method validation data.
3. You assessed the accuracy of (b) (4) content in your product by (b) (4) method, by (b) (4), and determined the range after baseline correction. The range for Accuracy measurement should be assessed by evaluating the (b) (4) content in spiked samples. The data presented in Table 6 in Document ID VAL-100717 (section 5.2) shows that two of the (b) (4) levels are above the range of your assay and the proposed specification of (b) (4). Please provide data to demonstrate accuracy within your proposed validated range by including at least (b) (4) levels between the method LOQ and the specification limit of (b) (4).

Regarding CMC:

4. We note that in Section 2.3.P.5, in Table 2.3.P.5-1, the acceptance criterion for HBsAg (b) (4) for HEPLISAV Drug product at release and during stability monitoring was changed from (b) (4), as in the original BLA, to (b) (4). Please justify this change.

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5. In Table 3.2.P.6-1 the acceptance criterion for HBsAg (b) (4) for the Reference Standard (b) (4) while the acceptance criterion for HBsAg (b) (4) for HEPLISAV Drug Product at release and during stability monitoring is (b) (4) (Table 2.3.P.5-1). Please justify the use of a different acceptance criterion for (b) (4)

Regarding Manufacturing Facilities (**Please provide your responses by May 2, 2016**):

6. You state in Table 2.3.P.3-1, Section 2.3.P.3, that the potency (in vivo study) drug product release testing is conducted at (b) (4). It was noted that this facility does not have a FDA Establishment Identifier (FEI). Please clarify if this facility has been inspected by any foreign regulatory agencies. If so, please provide a summary of the inspections conducted in this facility, including the agency name(s), dates of the inspection, and the outcome of the inspection.
7. You stated in Table 2.3.P.3-1, Section 2.3.P.3, that Final QA Release is conducted in Dynavax Technologies Corporation. However, you did not list the Final QA Release Testing conducted in this facility. Additionally, this facility was inspected by the agency in 2012.
 - a. Please provide a list of the Final QA Release Testing conducted in this facility.
 - b. Please clarify if this facility has been inspected by any foreign regulatory agencies after the latest inspection conducted by FDA in 2012. If so, please provide a summary of the inspections conducted in this facility, including the agency name(s), dates of the inspection, and the outcome of the inspection.

Regarding Clinical:

8. In your cover letter you state that the previous pivotal studies (DV2-HBV-10 and DV2-HBV-16) were revised in response to observations during a European Medicines Agency (EMA) inspection of a trial not included in this BLA. Please provide additional details about the EMA regulatory inspection and inspection outcome and how this was addressed in the revised data analyses. Please justify the revision of the clinical results based on the EMA's comments.
9. In submission 125428/0.45 you submitted revised datasets for studies DV2-HBV-10 and DV2-HBV-16. Please provide details of all of the changes that were made to all datasets, including the datasets supporting the Integrated Summaries of Safety and Efficacy, since the time of the original BLA submission

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(125428/0). These details should specify a line listing of any values that were changed and the original value, such that a reviewer external to Dynavax could identify their location within the dataset. They should include any subjects, events, assessments, or other items that may have been removed from the dataset. Please include a justification for each change.

Kind regards,

Katherine

Katherine Berkousen
CAPT., US Public Health Service

FDA/CBER/Office of Vaccines
Div. of Vaccines & Related Products Applications
10903 New Hampshire Ave. WO71-3022
Silver Spring, MD 20993-0002

Tel: (301) 796-1296
katherine.berkousen@fda.hhs.gov