

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	20-APR-2017 11:00 AM
Author	AGNIHOTHRAM, SUDHAKAR
EDR	No
Post to Web	No
Outside Phone Number	1 (877) 746-4263
FDA Originated?	Yes
Communication Categories	IR - Information Request
Related STNs	None
Related PMCs	None
Telecon Summary	IR regarding the Endotoxin Testing
FDA Participants	James Kenney, DBSQC; Simleen Kaur, DBSQC; Hyesuk Kong, DBSQC; Katherine Berkousen, DVRPA; Sudhakar Agnihothram, DVRPA;

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Applicant Participants	Elaine Alambra , Senior Director, Regulatory Affairs; Mike Berry VP, Process Dev. & Manuf. Sciences, Technical Operations , Denis Celentano Vice-President and Site Head, Dusseldorf Martin Gohlke Senior Director, Analytical Technologies, David Novack Senior VP, Operations & Quality, Technical Operations Catherine Pederson Senior Director, Quality Assurance Andreas Richter Head of Quality Control Operations, Dusseldorf
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Telecon Body:

Background:

DBSQ/CBER performed (b) (4) endotoxin licensing support testing of the Heplisav conformance lots submitted in support of Heplisav`s license application. The samples were tested as per the sponsor`s (b) (4) method validation/qualification report at a (b) (4) sample dilution using the same (b) (4) reagent kit. CBER experienced more product enhancement of the positive product control (PPC) than reported in the sponsor`s laboratory. This disparity in method qualification criteria could delay or prevent the release of product lots post licensing. Therefore, DBSQ/CBER requested a teleconference with Dynavax`s team who performed sample testing for the (b) (4) method validation report to determine if there is subtle difference between the methods that could explain the observed differences in positive product control recovery. Email exchanges (4/6/2017 to 4/18/2017) regarding the details on the testing protocol and issues to be discussed during the teleconference can be found in Annexure I to this document.

Introduction

CBER thanked Dynavax for being responsive to CBER`s concerns by discussion materials prior to the meeting. CBER explained their concerns as indicated below.

During averaging of results in the licensing support testing, CBER observed a 50% more enhancement in Positive Product Control compared to what was observed in Dynavax`s laboratory. CBER was concerned that this will lead to disparity for product lots post licensing that could delay regulatory lot release.

Dynavax indicated that they understand the concerns. CBER explained that they hope to obtain more information that may help resolve the observed discrepancy. CBER recalled a similar experience in the past where they had observed discrepancies in endotoxin testing when they had used (b) (4) Method, and stated that this discrepancy was resolved with an Information Request. The impact of the following parameters on the observed results was discussed during the telecon.

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Endotoxin, Buffer and (b) (4)

CBER indicated that they use (b) (4) as a PPC instead of the (b) (4), and requested confirmation that Dynavax has been using (b) (4). Dynavax responded that they used the (b) (4), and agreed with CBER that this could be one of the potential factors leading to observed discrepancy. Dynavax further raised concerns that several other factors including the buffers used and the (b) (4) of the solution may impact the observed results. CBER indicated that they had used (b) (4) for diluting the endotoxin and that they do not foresee that being an issue affecting the results. Dynavax questioned whether (b) (4) adjustments were performed by CBER as a part of their routine testing protocol. CBER responded that they follow the sponsor's protocols and will perform (b) (4) verification only if it is mentioned in the manufacturer's protocol.

Calibration Curve, Software Parameters

Dynavax raised concerns that the calibration curve (as used by the CBER to calibrate the use of positive product control) might impact the readouts observed. Dynavax pointed out that the CBER's calibration curves span a wider range (from (b) (4) of endotoxin), whereas the Dynavax's calibration curves run from (b) (4) of endotoxin. Dynavax questioned CBER on why they applied a different calibration range, and CBER responded that resource limitations were the primary reason and added that CBER's analyst who ran these results has years of ISO 17025 proficiency reports comparing manufacturer results with those from our (b) (4) testing laboratory, indicating equipment and software differences do not significantly impact results of this compendial assay; these proficiency results also indicate (b) (4) use instead of (b) (4) has a minimal impact compared to the use of different (b) (4) reagents. Dynavax further claimed that the use of wider calibration ranges in the past have accounted for a (b) (4) enhancement of positive product control, and may explain the observed differences in the slopes and intercept. CBER explained that they do not envision the calibration curve to impact the results, but they believe that the use of the different endotoxin standard might impact the spike recovery and the results observed.

Timing after reconstitution of the samples and Details on the Spiking

CBER questioned whether the reconstituted samples were immediately used in the assay or was there a time lag between reconstitution and their testing in the assay. Dynavax responded that the samples were measured in the assay (b) (4) after reconstitution, and that there was (b) (4). Dynavax questioned CBER whether the spiking was done at a value corresponding to the middle of the calibration curve, and CBER responded that the spiking was performed at (b) (4) which falls in the middle of the calibration curve. CBER further commented that they do not foresee this to be a problem for the discrepancy in the observed results and pointed out that Dynavax was not spiking their PPC in the middle of their calibration curve.

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Potential reasons for the outlying PPC % recoveries for the 'end' measurements of lot number 1033385 and 1017099

The observed PPC % recoveries for lot # 1033385 were (b) (4) and for the lot # 1017099 was (b) (4). CBER questioned Dynavax on the potential reasons for the outlying PPC % recoveries. Dynavax responded that they do not consider these numbers as outliers, and the differences observed are part of the normal variability observed between the assays. CBER informed Dynavax that the assay validation criteria is a carryover from the (b) (4) Method, which is a (b) (4) method, and for the (b) (4) methods CBER expects the selected testing dilution to provide optimal consistent results in the middle of this method validation criteria of (b) (4) recovery of the PPC.

Potential reasons to explain CBER's observed greater PPC % recovery for lot number 1033385 than the other two lots whose results were submitted (i.e., 1017099 and 1017100)?

Dynavax indicated that both the lots were exactly manufactured using the same way and questioned CBER on why they observe a difference. CBER indicated that they used the same (b) (4) dilution during testing, and that the observed variability is only concerning as the lot with the greater PPC recover was the only lot tested that was not expired at testing and CBER's greater PPC recover could result in the delay of the lot-release process.

CBER agreed that they will address the issues discussed and will update Dynavax on the results obtained.

The telecon concluded at noon EST.