

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	03 April 2017, 11:00AM (EST)
Author	Sudhakar Agnihothram
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	Discussion of Information Request (IR) Associated to the Responses of Shipping Validation Study for the Drug Product Received on February 07, 2017 in Support for CRL Items #45.a. and #45.b.
FDA Participants	<u>FDA Participants:</u> Priscilla Pastrana (CMC-Facility Reviewer/DMPQ), Ellen Huang (CMC-Facility Consult Reviewer/DMPQ), Marian Major Ph.D (Committee Chair/DVP), Richard Daemer (RPM/DVRPA), Sudhakar Agnihothram (RPM/DVRPA) and Katherine Berkousen (RPM/DVRPA)

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Applicant Participants	Elaine Alambra (Senior Director, Regulatory Affairs), Mike Berry (VP, Process Development and Manufacturing Sciences), Aashis Bhatia (Senior Director, Engineering and Validation), David Novack (SVP, Operations and Quality) and Maureen Urban (Director, Process Development and Manufacturing Sciences)
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Background

CBER/DMPQ requested a telecon with Dynavax to discuss Dynavax' s responses to CRL Items #45.a. and #45.b (Shipping Validation Study for the Drug Product) submitted on February 07, 2017. On March 30, 2017, CBER emailed Dynavax the questions to be discussed in the telecon (see listed questions below). Dynavax responded to the questions via email on March 31, 2017. CBER/DMPQ reviewed the Dynavax responses and found them acceptable; however, a discussion was still needed to clarify questions 2.a. and 2.c.

For the sake of clarity of this telecon discussion, the original DMPQ (emailed) questions along with Dynavax` s responses are listed below.

FDA questions are in **bold** followed by Dynavax` s response in blue.

1. **Regarding page 4 of 63 from the Summary Report PD-2012-09, in which the results of the OQ study were documented in the Distribution Simulation Final Report, (b) (4) in support for the response to the CR item #45.a.**

- a. **You stated that this OQ study was a simulation of the (b) (4) at a temperature between 2°C to 8°C. However, it is unclear if the (b) (4) testing conducted at a temperature between 2°C to 8°C are representative of the (b) (4) of the vials during (b) (4) shipment conditions. Please clarify if the (b) (4) testing at a temperature between 2°C to 8°C conducted in this OQ study simulate the (b) (4) of the vials and duration during (b) (4) shipment conditions.**

Dynavax Response:

In 2013, Dynavax successfully performed simulation of the (b) (4) of the (b) (4) vials (which represents 'worst case' as compared to the packaged vials) during (b) (4) shipment conditions, using the guidance for (b) (4)

. These tests were performed by (b) (4)
. These test conditions

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represent 'worst case' conditions, since (b) (4) transportation of Dynavax unlabeled vials will be via (b) (4), which are typically (b) (4) to approximately (b) (4) (as stated in Section X1.1 of (b) (4)).

The results of this study are documented in [Summary Report 20130001705-B Rev. 0](#) (attached).

- b. **You did not state if any testing has been conducted to the unlabeled drug product vials to determine if there are changes in the product quality at the end of the OQ study. Please corroborate if any product quality testing has been conducted to these vial at the end of the OQ study. If so, please indicate the testing conducted to these vials and results.**

Dynavax Response:

Dynavax has successfully performed Container Closure Suitability testing of the unlabeled drug product vials at the end of simulated (b) (4) testing, as described in [Summary Report 20130001705-B Rev. 0](#).

2. **Regarding assessment PD-2016-04, which describe the comparison of the results and conclusions from PD-2012-09 with the expected routine shipping of the unlabeled vials from Rentschler to (b) (4) in support for the response to the CR item #45.b.**

- a. **It is unclear if you compared the (b) (4) transportation methods of the unlabeled vials from Rentschler to the labeling and packaging locations located in (b) (4). Please clarify if you conducted a comparison of the (b) (4) transportation methods of the unlabeled vials from Rentschler to these labeling and packaging locations. If so, please provide a summary of this comparison and an assessment of the impact the differences have on the product. If not, please provide a rationale to not conduct this comparison.**

Dynavax Response:

Dynavax has not documented the comparison of the (b) (4) transportation methods of the unlabeled vials from Rentschler to the labeling and packaging locations. The rationale is that the difference in the two transportation methods is primarily due to (b) (4), which have been adequately tested and documented as summarized in [Summary Report 20130001705-B Rev. 0](#). However, Dynavax commits to performing a detailed Risk Assessment to ensure that any differences between the transportation methods have no impact on the product quality of the unlabeled vials.

- b. **You did not specify in this assessment if there is any change in the shipping configuration, target shipping temperatures and acceptance criteria evaluated in PD-2012-09, since the shipping of HEPLISAV unlabeled vials from Rentschler to (b) (4) are through (b) (4) transportation. Please clarify if there is any change in the shipping configuration, target shipping temperatures and acceptance criteria**












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evaluated in PD-2012-09, since the shipping of HEPLISAV unlabeled vials from Rentschler to (b) (4) are through (b) (4) transportation.

Dynavax Response:

As summarized in Table 45-1 in the response to the CR item #45.a, and listed below, there is no change in the shipping configuration, no change in the target shipping temperatures and no change in the acceptance criteria evaluated in PD-2012-09 (shipping of HEPLISAV unlabeled vials from Rentschler to (b) (4) compared to the shipping of HEPLISAV unlabeled vials from Rentschler to (b) (4) through (b) (4) transportation.

Shipping Configuration: Identical configuration

(b) (4)		
		
		
		

Target Shipping Temperature: Identical ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$)

Acceptance Criteria: No Change

1. Maintaining acceptable product container integrity based on visual inspection: All shipments from Rentschler to (b) (4) will be visually inspected for damage during transportation.
 2. Maintaining acceptable product temperature based on the recording of the temperature logging devices: All shipments from Rentschler to (b) (4) will have temperature loggers on the (b) (4) to ensure temperature stayed within range ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) during transportation.
- c. You stated in page 3 of this assessment that the expected shipping time from Rentschler to (b) (4) is less than (b) (4) . However, it is unclear how you determined this shipping time since it appears that no shipment was sent to (b) (4) yet. Please clarify if you sent any shipment of unlabeled HEPLISAV Drug Product Rentschler to (b) (4) to corroborate that the expected shipping duration is less than (b) (4) . Alternative, please justify how you determined the shipping time to be less than (b) (4) .

Dynavax Response:

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Dynavax has not sent any shipment of unlabeled HEPLISAV Drug Product Rentschler to (b) (4). Dynavax determined the shipping duration to be less than (b) (4), based on expected shipping times from Europe (b) (4). It should be noted that long shipping durations are not considered high risk for product quality, since the shipment of unlabeled HEPLISAV Drug Product from Rentschler to (b) (4) is done via (b) (4) shipping containers (b) (4).

The shipments are also monitored via temperature loggers (b) (4) to ensure temperature stayed within range ($5^{\circ}\text{C} \pm 3^{\circ}\text{C}$) during the entire transportation duration. In addition, the (b) (4) have been qualified to maintain a temperature of $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ under 'worse case' temperature conditions.

- d. **Please corroborate if identity testing has been and will be conducted to the labeled drug product vials according to 21 CFR 610.14 and where this testing is conducted.**

Dynavax Response:

Dynavax has not performed identity testing of labeled drug product vials. However, Dynavax will perform identity testing of labeled drug product vials according to 21 CFR 610.14, for all commercial shipments, at the (b) (4) packaging and labeling sites.

Telecon Discussion Summary:

Regarding Response to the IR Question 2.a.

- a. DMPQ requested Dynavax to submit the Risk Assessment with supporting data to demonstrate if there is any difference between the (b) (4) transportation method of HEPLISAV Drug Product from Rentschler (Germany) to the labeling and packaging facilities in (b) (4) in support for IR question 2.a. Also, DMPQ asked when this assessment will be submitted. Dynavax indicated that this assessment will be submitted the week of May 03, 2017.
- b. DMPQ asked Dynavax if any product quality testing has been conducted on the shipped HEPLISAV Drug Product in support for the shipping validation study from Rentschler (Germany) to the labeling and packaging facility in the (b) (4). Dynavax responded that no product quality testing has been conducted on the shipped HEPLISAV Drug Product in support for this shipping validation study.

Regarding Response to the IR Question 2.c.

- a. DMPQ asked Dynavax if they had conducted any shipment simulation study of HEPLISAV Drug Product from Rentschler (Germany) to the labeling and packaging

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facilities in the (b) (4) to corroborate the shipping time for this Drug Product according to Assessment PD-2016-04. Dynavax responded that no shipment simulation study has been conducted to corroborate the shipping time according to Assessment PD-2016-04.

- b. CBER requested that Dynavax submit a table, which details the time frame of the shipment of HEPLISAV Drug product from Rentschler (Germany) to the labeling and packaging facilities in (b) (4). Dynavax indicated that this table will be provided the week of April 10, 2017.

CBER requested that Dynavax submit the responses received via email on March 31, 2017 as a formal amendment to BLA STN 125428/0.

Telecon concluded at 11:45AM EST.