



MEMORANDUM

Date: 14 November, 2016

To: **Biologics License Application Submission Tracking Number # 125428/0**

From: Varsha Garnepudi
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

Through: William M. McCormick, Ph.D., Director,
DBSQC/OCBQ/CBER/FDA

Subject: **Review of Lot Release Protocol Templates for Drug Substance and Drug Product of Biologics License Application for Hepatitis B Vaccine (Recombinant), Adjuvanted**

CC: Marian Major, Chair, BLA Review Committee, DBPAP/OVRR
Katherine Berkousen, Lead RPM, DVRPA/ OVRR
Richard Daemer, RPM, DVRPA/OVRR

Applicant: Dynavax Technologies Corporation

Product: **Hepatitis B Vaccine (Recombinant), Adjuvanted**

1. General Information

1.1 CMC Review Identifiers and Dates

1.1.1 Biologics License Application (BLA) Submission Tracking Number (STN) #: 125428

1.1.2 Submission received by CBER: Apr 26, 2012

1.1.3 Review completed: Nov 3, 2016

1.1.4 Material Reviewed

Original BLA: The following general module sections of the BLA were reviewed: M3 CMC, Quality

2. Executive Summary: The Lot Release Protocol Template submitted in amendment 125428/0.68 on Oct 21, 2016 is acceptable for use.

3. Review

3.1 Documents Reviewed

1. Lot Release Protocol Template submitted in 3.2R Regional Information in amendment 125428/0.42 on 3/15/2016
2. Lot Release Protocol Template submitted in amendment 125428/0.57 on 8/19/2016
3. Lot Release Protocol Template submitted in amendment 125428/0.64 on 9/28/2016
4. Lot Release Protocol Template submitted in amendment 125428/0.68 on 10/21/2016

3.2 Review

Dynavax responses are in italics and CBER responses are bold.

A lot release protocol template was requested as item 10 in the Complete Response letter dated Feb 22, 2013.

A lot release protocol template was included in the CR letter response (amendment 125428/0.42) received Mar 15, 2016

The following comments were sent on July 26, 2016.

We continue to review your submission for STN 125428 and have the following IR regarding the Lot Release Protocol Template which was submitted in STN 125428/0.42 on 16-Mar-2016. Please revise and resubmit your LRP template within 3 weeks of receiving this request.

1. The header on each page must include:

Cc: 125428 /1883/FC page x of y

Lot Number:

Other information is not needed in the header and it should be listed below this information if it is included.

2. On pages 2, 4 and 6 of 6, please remove 'Sterile' from the sterility test specification. The specification should be 'no growth'.

3. On page 2 of 6, Purified Antigen, please add (b) (4) tests.

4. On page 4 of 6, please update the specification for HBsAg (b) (4).

Dynavax Response in amendment 125428/0.57:

As requested, please see the attached draft Lot Release Protocol with the Agency's suggested changes. Additionally, this draft has been prepared consistent with information discussed in Dynavax's response to the Agency's Information Request (IR) dated 07 July 2016.

1. The header on each page now includes:

Cc: 125428 / 1883 / FC

Lot Number:

Page X of Y

2. 'Sterile' was replaced by 'No growth' for the sterility test specification.

3. (b) (4) has been added as an HBsAg drug substance release test (refer to the response to the Agency's Information Request dated 07 July, Question 4).

(b) (4) have been added as in-process control tests and not as release tests (refer to the response to the Agency's Information Request dated 07 July, Question 5). Hence, these are not included in this draft Lot Release Protocol.

4. The specification for HBsAg (b) (4) in drug product was updated to (b) (4)

5. For 1018 identity, a numerical acceptance criterion has been added to the release specification (refer to the response to the Agency's Information Request dated 07 July, Question 8).

6. 1018 (b) (4) has been added as HEPLISAV release test (refer to the response to the Agency's Information Request dated 07 July, Question 9).

CBER Response: Dynavax has addressed all CBER comments adequately.

A subsequent draft LRP template was submitted in amendment 125428/0.64 on 9/28/2016.

The (b) (4) results were added in Response to question #6 in the CBER information request submitted Sept 16, 2016.

Regarding your proposal to perform testing of (b) (4) only as an in-process test and exclude it from the release testing. At this time we do not agree with this proposal. Please submit a revised list of release tests for HBsAg Bulk that includes testing for (b) (4) together with the release specification.

Dynavax Response:

(b) (4) is included as a release test for HBsAg bulk with the proposed release specification (Section 3.2.S.4.1).

In addition to other sections of the BLA, a Lot Release Protocol, draft version 3.0, to reflect the current specification is provided with this submission.

CBER agreed that (b) (4) does not need to be added as a release test and is not included in the LRP template submitted in amendment 125428/0.64.

CBER Response sent Oct 14, 2016:

In the lot release protocol template submitted in amendment 125428/0.64 on 9/28/2016, we note that the incorrect address is being used for the sample custodian. Please change this to:

Food and Drug Administration
Center for Biologics Evaluation and Research
Sample Custodian
10903 New Hampshire Avenue
WO75-G707
Silver Spring, MD 20993-0002

3.3 Conclusions

The Lot Release Protocol Template submitted in amendment 125428/0.68 on Oct 21, 2016 is acceptable for use.