



MEMORANDUM

14 November 2017

To To the File for: STN 125428/0
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Subject BLA: HEPLISAV™ [Hepatitis B Vaccine (Recombinant)] Sterility & Bioburden
Review for (b) (4) Final Container Testing

Conclusion

Based on review of the qualification and validation reports for sterility, bioburden test, (b) (4) and microbial purity tests submitted in this BLA; and the response to CBER's Information Request (IR) received from Dynavax Technologies Corporation on August 1, 2012, I recommend approval for these tests performed in the production of drug product HEPLISAV™ (recombinant Hepatitis B Vaccine) (b) (4)

Background

Dynavax Technologies Corporation (Dynavax) submitted Biological License Application (BLA) for HEPLISAV™, recombinant Hepatitis B Vaccine on April 26, 2012, with the proposed indication to prevent infection caused by all known subtypes of Hepatitis B virus in adults 18 through 70 years of age. The immunization schedule consists of 2 doses given 1 month apart. HEPLISAV™ is a clear solution intended for intramuscular injection with a proposed expiration date period of 24 months.

HEPLISAV™ contains HBsAg and 1018 ISS Adjuvant.

Hepatitis B Surface Antigen (HBsAg)

The HBsAg drug substance is the active pharmaceutical ingredient of HEPLISAV™, which is produced in the yeast strain *Hansenula polymorpha* using recombinant technology. The manufacturing of HBsAg is (b) (4)

[Redacted content]

(b) (4)

1018 ISS Adjuvant

The 1018 ISS Adjuvant is a 22-mer immunostimulatory phosphorothioate oligonucleotide that is produced by (b) (4)

(b) (4)

Manufacturing Process for Drug Product HEPLISAV™

HEPLISAV™ is a recombinant Hepatitis B vaccine manufactured in (b) (4)

(b) (4)

(b) (4)

(b) (4)

The acceptance criteria for the bioburden test for the (b) (4) batch (b) (4). Once bioburden test specifications are met, the (b) (4). The final container HEPLISAV™ is tested for sterility before it is released.

Since the Division of Biological Standards and Quality Control (DBSQC) primarily reviews product test method qualification/validation protocol/report and test specifications, this memo will review the:

(b) (4)

- 4) HBsAg release sterility qualification;
- 5) (b) (4) bioburden qualification;
- 6) HEPLISAV™(b) (4) bioburden qualification;
- 7) HEPLISAV™ final container sterility qualification; and

- 8) bioburden and sterility validation of (b) (4) HEPLISAV™ batches, as provided in the documents submitted; and related information from Dynavax, received on 01 August, 2012, in response to CBER's IR.

Review

Hepatitis B Surface Antigen (HBsAg)

(b) (4)

[Redacted text block]

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

HEPLISAV™ Drug Product

B&F Qualification Test for Bioburden on (b) (4)

Dynavax performed B&F test to demonstrate the product does not inhibit bacterial and fungal growth. The test was performed on three conformance lots of HEPLISAV™ drug product (i.e., (b) (4)).

(b) (4)

[Redacted]

(b) (4)

B&F Qualification Test for Sterility on Final Container

B&F testing was used to demonstrate HEPLISAV™ final container does not inhibit bacterial and fungal growth. The test was performed on final containers from the same three conformance lots.

The test was performed as described under B&F Qualification Test for Sterility under ‘Hepatitis B Surface Antigen (HBsAg)’ review section except (b) (4) vials of HEPLISAV™ final container samples and (b) (4), respectively.

All tests were performed in (b) (4) vials each since Dynavax was having problems (b) (4) as indicated above for each microorganism.

All test organisms cultured in (b) (4) had visible growth that was comparable between the test samples and controls. The test was performed and compliant with (b) (4), and the recovery of each challenge organism demonstrated no product inhibition of growth.

(b) (4)

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(b) (4)

Information Requests

The reviewer observed the bioburden (b) (4) validation report (i.e., DYN-QCMic QBA061HELPSAV_MVR_v1.0) was not included in the BLA. It was also noted that sterility on (b) (4) was performed (b) (4) batches. Dynavax also mentioned in their Sterility Validation Report (DYN-QCMic QBA041HELPSAV_MVR_v1.0) that (b) (4) vials for release sterility test will be performed in a (b) (4)-fold determination', which was not clearly explained. As a result, an IR was sent to Dynavax on 12 July 2012 and their response was received 1 August 2012. Below are CBER IR questions, which are followed by Dyanvax's responses in italic font:

1. HEPLISAV Bioburden Validation Report, DYN-QCMic QBA061HEPLISAV_MVR_v1.0, for (b) (4) is missing. Please provide.

Dynavax's Response: The HEPLISAV Bioburden Validation Report

DYN_QCMic_QBA061HEPLISAV_MVR_v2.0 is now provided. Please note that although the report is titled (b) (4) of 'HEPLISAV' drug product," it describes the method validation for HEPLISAV (b) (4).

CBER finds the response acceptable. The validation report was reviewed and reported under "Bacteriostatic and Fungistatic (B&F) Qualification Test on (b) (4)" above.

2. According to document 3.2.P.3.3, Description of Manufacturing Process and Process Controls and Figure 3.2.P.3.3.8, Comparison of (b) (4) Process, during (b) (4) production process, bioburden test will be performed (b) (4) by release sterility on final containers. However in HEPLISAV drug product (b) (4) process validation report, bulk sterility results (b) (4) are missing and only release testing (final container sterility) under section 8, release, are provided. Please provide bulk sterility results, unless there is consideration of the new sterility testing rule for not providing the results.

Dynavax's Response: Bulk sterility testing was not performed for the (b) (4) scale process validation batches, hence bulk sterility data is not provided for the (b) (4) batches. However, bulk sterility testing was performed as part of the process (b) (4) strategy, and was implemented during the HEPLISAV Drug Product manufacturing process for the (b) (4) scale process validation batch (Lot (b) (4)). Per the recent FDA Amendments to Sterility Test Requirements for Biological Products (Federal Register Vol. 77, No. 86, 3 May 2012), bulk sterility testing will not be performed for future batches of HEPLISAV at either the (b) (4) scale.

CBER finds the response acceptable since bulk sterility test no longer a requirement as per 21 CFR 610.12 (Federal Register Vol. 77, No. 86, 3 May 2012).

3. Under section 2.4, Observations and Deviations, of HEPLISAV Sterility Validation Report, DYN-QCMic QBA041 HEPLISAV_MVR_v1.0, please clarify the statement "...recommended (b) (4) vials for release testing have to be tested in a (b) (4)-fold determination" and explain how this will be performed.

Dynavax's Response: HEPLISAV is tested for sterility according to (b) (4). Based on this (b) (4) guidance a total of (b) (4) vials of HEPLISAV are used for the sterility test. The test for sterility is carried out using (b) (4)

. As described in Section 2.4 of Validation Report DYN_QCMic_QBA041HEPLISAV_MVR_v1.0 which is summarized in Section 3.2.P.5.3.1.11 of the 26 April 2012 submission (SEQ 0000), (b) (4)

CBER reviewed Dynavax's clarified statement in their Sterility Validation Report, DYN-QCMic QBA041 HEPLISAV_MVR_v1.0 and finds the response acceptable since (b) (4) vials of HEPLISAV™ final container will be tested as per (b) (4)

Summary

After a thorough review, the reviewer concludes the sterility and bioburden tests for final drug product HEPLISAV™ recombinant Hepatitis B vaccine (b) (4) were performed in accordance with (b) (4) for sterility and (b) (4) for bioburden. Furthermore the (b) (4) purity tests were validated appropriately and demonstrated their suitability for intended purpose.