

Date: July 5, 2017

From: Brenda R. Baldwin, Ph.D., RRB3/DVRPA/OVRR/CBER

To: The File

Through: Elizabeth M. Sutkowski, Ph.D., RRB3/DVRPA/OVRR/CBER

STN: 125428.0.74

Subject: ADDENDUM II to the Adjuvant CMC Initial Review dated May 10, 2013 and
ADDENDUM I dated November 16, 2016

46. In your response to item #51 in our Complete Response letter dated February 22, 2013, you indicated that the (b) (4) method was implemented to determine the purity and product-related impurities of the (b) (4) [REDACTED]. We were unable to find the (b) (4) results for the (b) (4) reference standard; please provide these results.

A stylized, abstract illustration of a city skyline. The composition features various geometric shapes, including rectangles, squares, and triangles, arranged to represent buildings and structures. The color palette is monochromatic, using different shades of gray on a white background. The style is minimalist and modern, with a focus on form and composition. The skyline is composed of several distinct elements: a large, dark gray rectangular block at the top left; a series of horizontal lines and shapes in the middle; and a more complex arrangement of shapes at the bottom, including a large, light gray rectangular block on the left and a series of smaller, darker gray shapes on the right. The overall effect is a clean, architectural representation of a cityscape.

UNII code designation for the CpG 1018 (an ingredient in Heplisav-B):

Even though the adjuvant quantity is determined by (b) (4) which should equate to UNII code (b) (4), UNII code H0E71D85ZS is the most appropriate for this substance because the fully protonated form (b) (4) cannot exist even though all the literature is currently associated with it. The UNII code that will be used for the CpG 1018 shall be H0E71D85ZS with a definition of DNA, D (P-THIO)(T-G-A-C-T-G-T-G-A-A-C-G-T-T-C-G-A-G-A-T-G-A), sodium salt

Executive Summary and Recommendation

Dynavax has submitted a Biologics License Application (BLA) for Heplisav-B, a Hepatitis B Vaccine (Recombinant), Adjuvanted with CpG 1018 (DNA, D(P-THIO)(T-G-A-C-T-G-T-G-A-A-C-G-T-T-C-G-A-G-A-T-G-A), sodium salt). The vaccine has been formulated to contain 20 micrograms (µg) HBsAg per 0.5 mL dose, in the presence of 3 mg of CpG 1018 Adjuvant in a (b) (4) to be administered intramuscularly. The proposed indication for Heplisav-B is for active immunization against infection caused by all known subtypes of Hepatitis B virus in adults 18 through 70 years of age. US development of this vaccine was conducted under INDs 12692 and 13332.

The CMC review on the antigen HBsAg, as well as the final drug product, Heplisav-B, of this original submission has been covered separately by Dr. Iryna Zubkova, DVP/OVRR.

The current review memo addendum (II) is focused on the CMC information provided for CpG 1018 Adjuvant only in amendment 74, Module 1 section 1.11.1. The initial review of CpG 1018 Adjuvant was completed on May 10, 2013 and review addendum I was completed on November 16, 2016.

All CMC (CpG 1018 Adjuvant) related outstanding issues have been resolved. This BLA is recommended for approval.