




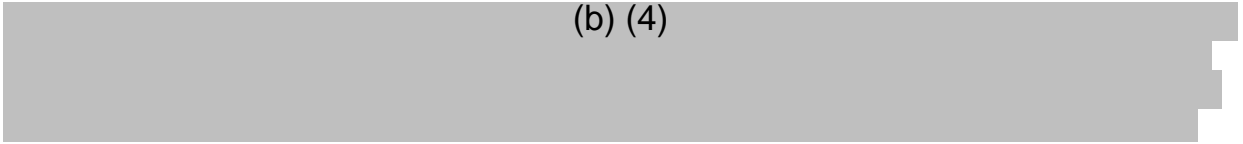


## MEMORANDUM

**Date:** November 16, 2016  
**From:** Brenda R. Baldwin, Ph.D., RRB3/DVRPA/OVRR/CBER  
**To:** The File  
**Through:** Elizabeth M. Sutkowski, Ph.D., RRB3/DVRPA/OVRR/CBER  
**STN:** 125428.0.42 and 0.56  
**Subject:** ADDENDUM to Adjuvant CMC Review dated May 10, 2013

(b) (4)











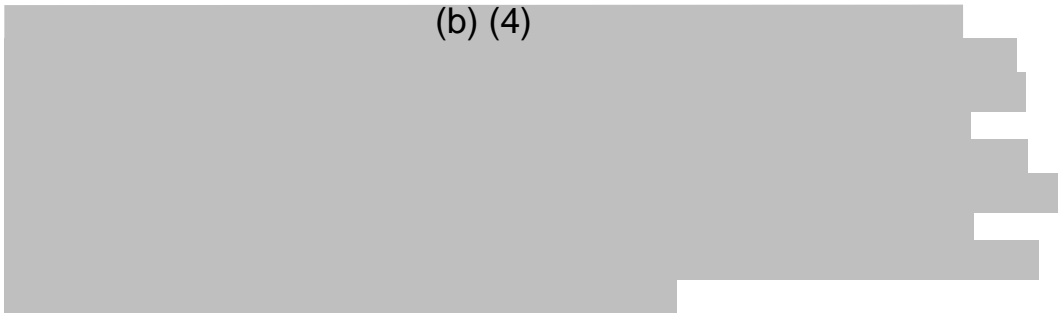


(b) (4)

53. In your November 20, 2012, response to the November 2, 2012, CBER Information Request regarding release tests for the final product, you proposed the release specification limit of NLT (b) (4) of 1018 ISS adjuvant by (b) (4) in the Hepatitis B Vaccine (Recombinant), Adjuvanted, and you stated that you do not agree to include the (b) (4) (b) (4). We note that the release test specification for the 1018 ISS adjuvant alone (b) (4) is NLT (b) (4). Please incorporate a release specification of NLT (b) (4) in the Hepatitis B Vaccine (Recombinant), Adjuvanted drug product or explain why you would need to have a lower limit for the (b) (4) in the final product than that for (b) (4) in the 1018 ISS adjuvant (b) (4). Regarding the (b) (4) test specification of "confirmed" we will allow it to remain; however, you will also need to state the (b) (4) as previously requested by CBER. Please provide the method validation protocol and report for the revised (b) (4) test method using the (b) (4) and revised (b) (4) of 1018 ISS adjuvant proposed for the release of the

Hepatitis B Vaccine (Recombinant), Adjuvanted drug product and include data from the analysis of several lots of drug product via the revised test to support your specification limits.

(b) (4)



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In addition to the response to our questions in the CR, Dynavax changed quite a bit of the information in the BLA. The following are the changes (found in the reviewer's guide section 1.2 and additionally found while reviewing all the relevant information regarding the 1018 adjuvant in the amendment) for the 1018 adjuvant:

- (b) (4)
- 



- In our request dated 10/12/12 we asked for stability data from HEPLISAV lot(s) that contained adjuvant drug substance held in the (b) (4) and the HBsAg bulk drug substance held at (b) (4) (the proposed shelf life for both components). They responded that 2 lots would fit that scenario – (b) (4). I determined that (b) (4) meets the storage time as the CpG was held for (b) (4) and the HBsAg was held for (b) (4). **At the time of the CR they had 18 mos stability data for the Heplisav lot; however, in the CR response amendment the data for this lot was not provided. They need to provide this data or alternatively provide data from another lot that fits this scenario with the current formulation. Comment was sent on July 7, 2016 (see below).**
- Batch records for Heplisav now include sequencing via (b) (4) of 1018 adjuvant upon receipt at the Rentschler manufacturing facility (PI-000184 – (b) (4) test request and disposition sheet). In addition, they will test the 1018 for (b) (4).
- The Heplisav tests now include (b) (4) as requested. Tests and specifications for release and stability of Heplisav include:

Parameter	Test Method	Release Specification	Stability specification
Appearance		Color: (b) (4) Opalescence: (b) (4) Essentially free of visible particles	Color: (b) (4) Opalescence: (b) (4) Essentially free of visible particles
pH	(b) (4)		
HBsAg identity	(b) (4)	Confirmed	(b) (4)
HBsAg (b) (4)	(b) (4)		
HBsAg concentration	(b) (4)		
HBsAg (b) (4)	(b) (4)		
Potency	(b) (4)		
1018 identity	(b) (4)	Confirmed (b) (4)	(b) (4)
1018 (b) (4)	(b) (4)	(b) (4)	(b) (4)

		(b) (4)	
1018 content	(b) (4)		
Particle size (for (b) (4) aspect)	(b) (4)		
Particle contamination: subvisible particles/ particulate matter	(b) (4)		
Extractable volume	(b) (4)	NLT 0.5 ml	(b) (4)
Endotoxin	(b) (4)		(b) (4)
Sterility	(b) (4)	Sterile, no growth	(b) (4)
Container closure integrity	(b) (4)	NA	(b) (4)

**Comments sent on July 7, 2016:**

Dynavax was asked the following 1018 related questions by e-mail on **July 7, 2016**. They responded to each of the questions on August 19, 2016 (amendment 56). Below is the question, their response and my thoughts on their response.

2. You propose a shelf-life of 36 months for the Heplisav Drug Product stored at 5°C±3°C. Please provide 36 months stability data for the Heplisav Drug Product lots formulated with HBsAg bulk held for the proposed bulk shelf life of (b) (4) and with the 1018 ISS drug substance held in the (b) (4). These lots should be manufactured using the proposed commercial scale using the validated manufacturing process.

*Dynavax's response:* (b) (4) HEPLISAV lots (b) (4) were manufactured at the proposed commercial scale. In addition, (b) (4) HEPLISAV lots (b) (4) were manufactured to collect sequential stability data specifically intended to demonstrate stability of HEPLISAV when formulated with HBsAg and 1018 that had been held for the duration of their shelf life. They provide 36 month data for each of these lots, including (b) (4)

*FDA Reviewer comment:* This is still problematic because the only lot where each of the drug substances were held for the maximum time prior to combining is lot (b) (4)

which was manufactured at a (b) (4) process. Because of this issue, I propose along with the antigen reviewer to give Dynavax a (b) (4) shelf life for HBsAg DS, (b) (4) shelf life for 1018 in (b) (4) containers and a 36 month shelf life for Heplisav based on data from (b) (4) lots manufactured at full scale (b) (4). However, if they are going to use the (b) (4) containers for storage of 1018 DS, they will need to provide more data. They currently only have (b) (4) months data with one lot (b) (4) and (b) (4) months with one other lot (b) (4) using the (b) (4) containers. They have no stability data with the (b) (4). See comment below sent on September 14, 2016.

8. The rationale for not establishing a (b) (4) for the 1018 and instead proposing a (b) (4) is acceptable. Please include this as part of your Heplisav drug product release specifications.

Dynavax's response: The proposed acceptance criterion: Relative difference in (b) (4) (b) (4) between standard and test article not more than (b) (4). The release test specification has been revised.

FDA Reviewer comment: Response is acceptable. The lot release protocol was also revised accordingly.

9. The request to remove the 1018 (b) (4) test from the release tests of Heplisav is not acceptable. This was also stated in an e-mail on September 26, 2012. Please include this test as a part of release and provide the revised Heplisav drug product testing plan to the BLA.

Dynavax's response: They will include the test as part of release and propose the acceptance criterion of NLT (b) (4). Dynavax suggests having a (b) (4) difference between the release acceptance criterion for purity of 1018 and the stability acceptance criterion for (b) (4) of 1018 in HEPLISAV due to differences in the test methods.

FDA Reviewer comment: Response is acceptable. The lot release protocol was also revised accordingly.

10. The reference material (b) (4) is to be requalified every (b) (4). It is not apparent that you have performed this requalification every (b) (4). Please provide this data.

Dynavax's response: Dynavax provided the data from Jan 2012, Aug 2012, Jul 2013, Feb 2015 and Mar 2016.

FDA Reviewer comment: The requalification results show that (b) (4) is stable with respect to (b) (4). They did not, however, provide data using the (b) (4) method as proposed and implemented to determine the purity and product-related impurities for the (b) (4) (refer to comment 51 in our Complete Response letter dated February 22, 2013). This test should be performed and data provided. This comment will need to be included in the CR letter to be issued (see below).

11. Please clarify if the (b) (4) test will be used for analysis of the 1018 adjuvant as information related to this test is still present in section 3.2.S.2.4 (page 29) and 3.2.S.2.4.3.4 (page 35).



Dynavax's response: (b) (4) will not be applied for testing of 1018. Section 3.2.S.2.4 has been revised.

FDA Reviewer comment: Response is acceptable.

12. You indicate that you do not intend to perform post-approval stability analysis of the 1018 Drug Substance (DS). (b) (4)

(b) (4)

(b) (4)

(b) (4)

13. Please indicate where the SOP for the 1018 ISS concentration by (b) (4) (QTM-000289) document can be found.

Dynavax's response: They provided SOP QTM-000298 in this amendment.

FDA Reviewer comment: Response is acceptable.

**Comment sent on September 14, 2016:**

2. Regarding the proposed shelf life of the two drug substances and the final drug product. At this time, we will allow a shelf life for the HBsAg drug substance of no longer than (b) (4), a shelf life for the 1018 adjuvant drug substance of no longer than (b) (4) (when stored in (b) (4) containers) and a Heplisav drug product shelf life of no longer than 36 months. We are (b) (4) your proposed shelf life due to insufficient data in support of a 36 month shelf-life for Drug Product manufactured from (b) (4) old HBsAg and (b) (4) old 1018 adjuvant produced at commercial scale. In addition, we are concerned about the loss of (b) (4) during accelerated stability studies of the (b) (4). Please note that the proposed shelf life for the 1018 adjuvant does not include 1018 stored in (b) (4) containers as the available data is limited and show that the (b) (4) is out-of-specification beginning at (b) (4). Until sufficient and satisfactory data is obtained, 1018 adjuvant stored in (b) (4) containers cannot be used for formulation of Heplisav drug product. Please acknowledge this communication and submit new stability protocols that incorporate these designated time periods.

Dynavax Response: *Dynavax acknowledges the assigned shelf-life for: 1018 adjuvant (b) (4) container): (b) (4) , HBsAg drug substance: (b) (4) , and HEPLISAV Drug Product: 36 months. Post approval stability studies for (b) (4) will monitor stability over (b) (4) . Post approval stability studies for HEPLISAV Drug Product will monitor stability over 36 months. As previously noted, Dynavax will not perform stability studies for 1018 adjuvant in (b) (4) containers. Dynavax acknowledges (b) (4) will only be introduced after approval from the Agency.*

FDA Reviewer comment: *Response is acceptable.*

**Comment to be communicated to Dynavax in the CR letter:**

1. 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 (b) (4) and product-related impurities of the (b) (4) . We were unable to find the (b) (4) results for the (b) (4) reference standard; please provide these results.