



U.S. FOOD & DRUG
ADMINISTRATION

DATE: 16 November 2018

TO: File for: STN BL 125563/0 and STN BL 125580/0

FROM: Lisa Parsons, PhD, Chair (125580)/Reviewer (125563), Staff Fellow
LBP/DBPAP/OVRR/CBER

THROUGH: Willie Vann, PhD, Lab Chief
LBP/DBPAP/OVRR/CBER

PRODUCT: Vaxelis® (PR5I): Diphtheria and Tetanus Toxoids and Acellular
Pertussis Vaccine adsorbed, Inactivated Poliovirus, Haemophilus b
Conjugate [Meningococcal Protein Conjugate] and Hepatitis B
[Recombinant] Vaccine, BLA 125563/0.

Amorphous aluminum hydroxyphosphate sulfate adsorbed
polyribosylribitol phosphate conjugated to meningococcal outer
membrane protein complex (AAHS PRP-OMPC) bulk intermediate (an
intermediate used in the manufacture of Liquid PedvaxHIB®, BLA
103237), For Further Manufacturing Use (FFMU) BLA 125580/0

SUBJECT: Response to Complete Response letter dated 02 November 2015 and
submission of a validated formaldehyde test for the drug product

APPLICANT: MCM Vaccine Company

1. General Information

1.1. Submission Tracking Number (STN) # 125563/0, 125580/0

1.2. Submission received by CBER 29 June 2018

1.3. Review completed 16 November 2018

1.4. Material Reviewed 125563/0.32, 125563/0.36, 125563/0.42, 125580/0.10,
125580/0.11

1.5. Related Master File, INDs and BLAs: STN 103237 (PedvaxHIB), STN
101066 (Recombivax HB®), STN 125145 (Pentacel®), STN 103944 (Diphtheria
and Tetanus Toxoids Adsorbed), STN 103666 (Daptacel®), STN 125111
(ADACEL®), and STN 103171 (TENIVACTM), STN 103930 (IPOL®), IND 14496

2. Executive Summary

MCM Vaccine Company submitted Biologics License Application STN BLA 125563/0 for licensure of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus B Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine. The proprietary name is Vaxelis®. The Vaxelis® vaccine was jointly developed by Sanofi Pasteur Inc. (Sanofi) and Merck Sharp and Dohme, a subsidiary of Merck & Co., Inc. (Merck). The bulk intermediates are used in currently licensed vaccines PedvaxHIB®, Recombivax HB®, Pentacel®, Daptacel®, ADACEL®, TENIVAC™, and IPOL®. On 15 December 2015, a Complete Response (CR) letter was issued regarding the original filing of BLA 125563/0 (Vaxelis) and the AAHS PRP-OMPC bulk intermediate component filed for further manufacture under BLA 125580/0 after MCM Vaccine Company failed to adequately respond to two separate information requests (IRs). The questions pertained to how reference lots used to test (b) (4) of PRP-OMPC (b) (4) by (b) (4) " and "(b) (4) PRP-OMPC of drug product as determined by (b) (4) would be chosen and how the quality of these reference lots would be monitored over time. The applicant's responses to the CR questions, filed under BLA 125580/0.10 and BLA 126653/0.36, are reviewed here and found to be acceptable. In an IR dated 17 April 2015, CBER requested that the applicant establish a specification for formaldehyde reflective of their manufacturing capability. In response, the applicant submitted a validated formaldehyde test for the drug product under BLA 125563/0.32. They (b) (4) the acceptance criteria from (b) (4) and validated the test as a quantitative test instead of a limit test. Validation was acceptable. On 22 March 2018, Merck submitted 125580/0.11 CBE-30 submissions that had been approved for PedvaxHIB (BLA 103237) during the interim following the CR letter. An updated lot release protocol (LRP) was received 03 October 2018 including a table of the changes made to the LRP. The units for PRP-OMPC were changed from (b) (4) to µg/mL. Approval of AAHS PRP-OMPC bulk intermediate For Further Manufacturing Use (BLA 125580) and the Vaxelis vaccine (BLA 125563) is recommended.

3. Background

MCM Vaccine Company submitted Biologics License Application STN BLA 125563/0 for a hexavalent combination vaccine (Vaxelis) that was jointly developed by Sanofi Pasteur Limited (Sanofi) and Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (Merck). The Vaxelis vaccine (often referred to as PR5I by the applicant) is manufactured using bulk intermediates from currently licensed vaccines. The bulk components are either identical to those used in the parent licensed vaccines or they are modified for use in Vaxelis. The components of Vaxelis are:

- 1) AAHS PRP-OMPC Conjugate Bulk, a drug substance used in the manufacture of Liquid PedvaxHIB® (STN BL 103237) [*Haemophilus influenzae* type b Conjugate Vaccine (Meningococcal Protein Conjugate)]. This component is produced by Merck.

- 2) Recombinant Hepatitis B Surface Antigen (HBsAg) Bulk Intermediate, an intermediate used in the manufacture of RECOMBIVAX HB® (STN BL 101066) [Hepatitis B Vaccine (Recombinant)]. This component is produced by Merck.
- 3) 5-component Acellular Pertussis Adsorbed (Pertussis Toxoid, Filamentous Haemagglutinin, Pertactin, and Fimbriae Types 2 and 3), Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed Bulk Intermediates. The intermediates are used in the manufacture of licensed vaccines, including Pentacel® (STN BL 125145), Diphtheria and Tetanus Toxoids Adsorbed Vaccine (STN BL 103944), Daptacel® (STN BL 103666), ADACEL® (STN BL 125111) and TENIVAC™ (STN BL 103171). These components are produced by Sanofi.
- 4) Inactivated Poliovirus Types 1, 2, and 3 Bulk Intermediate, an intermediate used in the manufacture of Poliovirus Vaccine Inactivated (vIPV), IPOL® (STN BL 103930). This is produced by Sanofi.

On 15 December 2015, a CR letter was issued regarding the initial filing of BLA 125580/0 (AAHS PRP-OMPC bulk intermediate For Further Manufacturing Use (FFMU)) and BLA 125563/0 (Vaxelis Vaccine) after MCM Vaccine Company failed to adequately respond to two separate IRs regarding reference lots for assays testing the (b) (4). Further review of BLAs 125563 and 125580 was put on hold, however the applicant continued to make submissions. Submission history is as follows:

For 125580/0:

- Response to IR sent 17 April 2015 under BLA 125580/0.3 (pertains)
- Response to IR sent 27 July 2015 under BLA 125580/0.8 (pertains)
- Response to CR letter received 12 December 2016 under BLA 125580/0.10 (reviewed under 4.1)
- BLA 125580/0.11 - Update of CBE30 supplements approved for STN 103237 PedvaxHIB. 103237/5520 (b) (4) Manufacturing at (b) (4), 103237/5545 (Comparability protocol for (b) (4) expiry extension), 103237/5542 (Elimination of two non-critical attributes for PRP), 103237/5550 (Introduction of new material at (b) (4)), and 103237/5559 (b) (4)

PRP Working Cell Bank (WCB) Comparability protocol for Annual Report notification of new WCB lots.







For 125563/0:

- Response to IR sent 17 April 2015 under 125563/0.11 (pertains)
- Response to IR sent 27 July 2015 under 125563/0.20 (pertains)
- Response to CR letter received 29 June 2018 under 125563/0.36 (reviewed under 4.2)
- Fulfillment of commitment to include a validated formaldehyde test for the drug product as agreed upon under 125563/0.11. Submitted 18 April 2018 under 125563/0.32. (reviewed under 4.3)
- Response to IR sent 30 August 2018 (under 125563/0.42) requesting an updated Vaxelis Lot Release Protocol template (reviewed under 4.4)

4. Review

4.1 BLA 125580/0.10: Response to CR regarding Drug Substance PRP-OMPC

(b) (4)



(b) (4)

4.1.4 STN 125580/0.11: Per a communication with Rana Chattopadhyay Merck submitted STN 125580/0.11 on 22 March 2018 to include all Changes Being Effected in 30 Days (CBE-30) supplements that had been approved for PedvaxHIB STN 103237 since 03 December 2015. The submissions were included in a meeting backgrounder with intent to submit the documents as part of the first Annual Report for the FFMU BLA. However, to ensure that the dossier is up to date, the CBE-30 supplements were included in this amendment.

The following PedvaxHIB supplements were included:

103237/5520 ((b) (4) Manufacturing at (b) (4)
 103237/5545 (Comparability protocol for (b) (4) expiry extension),
 103237/5542 (Elimination of two non-critical attributes for PRP),
 103237/5550 (Introduction of new material at (b) (4)), and
 103237/5559 (b) (4)

In addition a comparability protocol to allow annual report notification of new PRP Working Cell Banks was included in 3.2.R.1.

These amendments are acceptable.

4.2 STN 125563/0.36: Response to CR regarding Drug Product Vaxelis

(b) (4) is used in the assay: (b) (4)
and Identity of PRP-OMPC Conjugate in PR5I Formulations as per SOP Q_0511566. The method measures the (b) (4)

(b) (4)

CR question from 15 December 2015:

2. In your September 15, 2015, response to Question 5 of our Information Request dated July 27, 2015, you state that lot (b) (4) was manufactured in (b) (4) (b) (4) for measuring (b) (4) PRP-OMPC of drug product” as determined by (b) (4). According to your procedures, this lot can be used as a reference for (b) (4). The approved hold time of lot (b) (4) when used in manufacturing is (b) (4); however, given the initial manufacturing date of (b) (4) lot (b) (4) will be (b) (4) at the end of the 4-year period specified for use of this lot as a reference. Please address the following:

- a. Please provide the procedures used to choose and qualify lots as reference standards. Please choose lots that are within their approved manufacturing hold time to be qualified as reference standards.
- b. Your procedures during qualification and during the annual re-evaluation do not include appropriate tests to determine that the quality of the conjugate has been maintained. Please perform additional testing during the qualification and annual re-evaluation to demonstrate that the reference conjugate is within specifications expected for the vaccine. Additional testing could include the normal release panel for PRP-OMPC or orthogonal methods to demonstrate that the conjugate is intact.
- c. Your re-evaluation procedures are based on trending of (b) (4). Please provide acceptance criteria for the (b) (4) to be used during the re-evaluation.

4.2.1 Response to question 2.a:

The applicant stated the procedures for choosing and qualifying lots of the PRP-OMPC Reference Standard (RS) used in the (b) (4) for (b) (4) PRP-OMPC and Identity PRP-OMPC methods are described in Sanofi Pasteur document Q_0563840, Protocol for the Qualification of Critical Reagents in (b) (4) and Identity of PRP-OMPC Conjugate in PR5I Formulations SOPQ_0511566, and in 3.2.P.6 Reference Standards or Materials. (b) (4)

This response is acceptable.

4.2.2 Response to question 2.b:

(b) (4)

This response is acceptable.

4.2.3 Response to question 2.c:

The PRP-OMPC reference standard is used in the (b) (4) method to determine a (b) (4)

product. In response to the CR, the PRP-OMPC reference standard re-evaluation procedures now consist of a statistical evaluation of the historical performance of the reference standard in the (b) (4) as well as an evaluation of the reference standard using the (b) (4) described in the response to 2b. (b) (4)

This response is acceptable.

4.3 Fulfillment of commitment to include a validated formaldehyde test for the drug product Vixelis, BLA 125563/0.32

On 17 April 2015, CBER sent an IR question regarding the formaldehyde test as follows:

Question 20

In section 3.2.P.5.2 Analytical Procedures - Formaldehyde Content – (b) (4) Product, you state that “The result is reported as (b) (4) to the value defined as the specification limit.” In section 3.2.P.5.6 – Justification of Specifications, you state that “The acceptance criterion for the Formaldehyde Content Test (b) (4) is based on the (b) (4)”. We request that you establish a specification reflective of the capacity of the manufacturing process to remove formaldehyde and that you report the actual results of the test in the certificates of analysis and lot release protocols for (b) (4) Product lots. As necessary, please modify this test method and validation to serve the purpose of a quantitative procedure.

In response, the applicant made a commitment to include a validated formaldehyde test for the drug product in STN 125563/0.11 on 05 June 2015. On 18 April 2018 they submitted amendment 125563/0.32 in which they proposed to (b) (4) the acceptance criterion from (b) (4) and proposed to change the test method from a limit test to a quantitative test. To support their proposal, they validated the quantitative test by showing it meets criteria for accuracy, linearity, precision, range, and limit of quantitation and showed the quantitative test is robust and comparable to the limit test method.

Vaxelis was not tested but was not expected to be different since the matrix had no effect. All comparisons had less than (b) (4) CV

Sections 3.2.P.5.1 *Specifications*, 3.2.P.5.2 *Analytical procedures*, 3.2.P.5.3 *Validation of analytical procedures*, 3.2.P.5.6 *Justification of Specifications*, and 3.2.P.6 *Reference Standards or Materials* were provided in support of the change.

The new limit and the validation for the formaldehyde test are acceptable.

I verified that the quantitative results for formaldehyde were reported in the latest batch analysis (batches (b) (4)) under section 3.2.P.5.4 *Batch Analyses*. The applicant had not yet updated the acceptance criteria for formaldehyde in the batch analysis document, but the value was reported as (b) (4) rather than (b) (4) as for previous batches. In the proposed lot release protocol (STN 125563/0.42) there is a line for the formaldehyde results which the applicant notes (under the relevant table) has not been changed to the correct value of (b) (4) due to software limitations. An IR was sent by DBSQC 1 November 2018 asking them to correct the value. The applicant reiterated 8 November 2018 in STN 125563/0.46 that they could not due to software limitations. DBSQC says this is acceptable.

4.4 STN 125563/0.42: Updated Lot Release protocol for Vaxelis

An updated Lot Release protocol for Vaxelis was filed in response to an IR sent 30 August 2018. I reviewed the update to the PRP-OMPC section of the submission. The concentration under *Formulation of PR5I* (b) (4) is now expressed in µg/mL and not (b) (4) and matches the acceptance criteria of (b) (4) under 3.2.P.5.1-*Specifications*.

5. Recommendation

The firm responded to, and adequately addressed the concerns raised in the CR sent on 15 December 2015. The new acceptability criteria for the formaldehyde content is well under the initial limits. The units and concentration of PRP in the (b) (4) Test Summary of PR5I in the LRP match those under the section on specifications. I recommend approval of AAHS PRP-OMPC bulk intermediate For Further Manufacturing Use (BLA 125580) and the Vaxelis vaccine (BLA 125563).