

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Viral Products**

Date: December 21, 2018

To: Rana Chattopadhyay, DVRPA
Girish Ramachandran, DVRPA
Kelsy Hoffman, DVRPA

From: Sara Gagneten, DVP

Through: Robin Levis, DVP

Subject: **BLA STN 125563**
Subject covered in this memo: CMC review of the drug product section of the BLA for updated information submitted after the Complete Response letter of 1 November, 2015

Applicant: MCM Vaccine Company (Sanofi Pasteur Ltd. and Merck, Sharp and Dohme Corp. partnership)

Product: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine [Proprietary name: Vaxelis]

Receipt date: 12 August 2014
Compete response (CR) date: 1 November 2015
Applicant's response to CR: 29 June 2018 (Amendment 36)
Action Date (2nd review cycle): 29 December 2018

Cross-references: BLAs For Further Manufacturing Use (FFMU) for drug substances included in Vaxelis:

- STN 125581: For hepatitis B surface antigen (HBsAg) Bulk Intermediate manufactured using the licensed process for Hepatitis B Vaccine (Recombinant) (Recombivax, BLA 101066) with the (b) (4) [redacted]. The adsorbed HBsAg drug substance is manufactured by Merck at the (b) (4) [redacted] site.
- STN 125580: For amorphous aluminum hydroxyphosphate sulfate adsorbed polyribosylribitol phosphate conjugated to meningococcal outer membrane protein complex (AAHS PRP-OMPC) bulk intermediate manufactured using the licensed process of Liquid PedvaxHIB, (BLA 103237), manufactured by Merck at the (b) (4) [redacted], USA site.

Recommendation: Approval - based on the CMC drug product information

Contents

1.	Executive Summary and Recommendation	2
1.1	Summary and Recommendation	2
1.2	Memo Notes	3
1.3	BLA Complete Response	3
2.	Abbreviations	4
3.	Review of Drug Product CMC Information	5
3.1	Description and Composition of the Drug Product (BLA section 3.2.P.1).....	5
3.2	Control of Drug Product (BLA section 3.2.P.5).....	8
3.2.1	Specifications	8
3.2.2	Characterization of Impurities	11
3.2.3	Lot Release Protocol (LRP)	12
4.0	Stability (BLA section 3.2.P.8)	12
4.1	Stability Data and Proposed Shelf Life	12
4.2	Stability Protocol for Routine Monitoring and Stability Commitment	12
5.0	Information Requests (IRs)	13
6.0	CMC Post Marketing Commitments (PMC)	13
6.1	PMCs Communicated During the First Review Cycle.....	13
6.2	PMCs Communicated During the Second Review Cycle	14

1. Executive Summary and Recommendation

1.1 Summary and Recommendation

MCM Vaccine Co. (Sanofi Pasteur Ltd. and Merck Corp.) submitted a Biologics License Application (BLA) for a combination vaccine with proper name: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine (DTaP-IPV-Hib-HepB). The proposed trade name is Vaxelis and is referred to as PR5I Vaccine in this document. The clinical development of this vaccine was performed under BB-IND 14496, initially submitted 20 September 2010.

This hexavalent combination vaccine was developed by Sanofi Pasteur Ltd. (SPL) and Merck Sharp and Dohme Corp. (Merck), a subsidiary of Merck Corp. PR5I Vaccine is manufactured using modified and/or existing bulk intermediates from vaccines licensed in the U.S. by SPL and Merck.

Vaxelis (PR5I Vaccine) is a sterile liquid preservative-free suspension presented as a single dose (0.5 mL) vial for intramuscular injection. Each 0.5 mL dose is formulated to contain 15 Lf diphtheria toxoid, 5 Lf tetanus toxoid, acellular pertussis antigens [20 mcg detoxified pertussis toxin (PT), 20 mcg filamentous hemagglutinin (FHA), 3 mcg pertactin (PRN), 5 mcg fimbriae types 2 and 3 (FIM)], and inactivated polioviruses [29 D-antigen units (DU) Type 1 (Mahoney), 7 DU Type 2 (MEF-1), 26 DU Type 3 (Saukett)], 3 mcg polyribosylribitol phosphate (PRP) of *Haemophilus influenzae* type b covalently bound to 50 mcg of outer membrane protein complex (OMPC) of *Neisseria meningitidis* serogroup B, and 10 mcg hepatitis B surface antigen.

The proposed indication for Vaxelis (PR5I Vaccine) is for active immunization for the prevention of diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive disease caused by *Haemophilus influenzae* type b. The vaccine is recommended for use as a three-dose series administered at 2, 4, and 6 months of age.

Recommendation: Based on the drug product information in the BLA, I recommend approval of this BLA.

1.2 Memo Notes

- This memo covers my review of the information in the drug product (DP) section of the BLA submitted after CBER's complete response letter of 1 November 2015. For an overview of information covering the DP manufacturing and release tests, please see my memo of 23 October 2015. Production, testing, transport and storage of the intermediate bulks used for formulation of PR5I Vaccine as well as the information on the potency testing and validation of potency tests performed for release and stability of PR5I Vaccine DP were performed by product reviewers for each active component as follows:
Diphtheria and Tetanus: Michael Schmidt
Pertussis: Juan Arciniega, Tod Merkel, Freyja Williams
Haemophilus b conjugate: Wei Wang, Tina Roecklein and Lisa Parsons
Hepatitis B: Alla Kachko
Polio: Diana Kouivaskaia

Analytical tests were reviewed by the DBSQC reviewers and bioassays for potency and safety by the product reviewers in DBPAP and DVP as well as reviewers in DBSQC. My approval recommendation for the DP release tests is based on the recommendations from the reviewers assigned to review the release tests for each active component.

- No manufacturing changes were introduced in the DP steps after 1 November 2015. Changes to the DP release specifications are summarized in this memo. For changes to the pertussis drug substance (DS) manufacturing and release tests and the IPV DS manufacturing and release tests please see memos from the assigned reviewer.
- In this memo, when references are made to sections in the BLA, they are identified as such. All other references relate to sections within this memo.

1.3 BLA Complete Response

The CMC DP information submitted in the BLA for the PR5I Vaccine consistency lots was found to be adequate in the first review cycle. However, data from (b) prospective commercial scale lots tested at

release and as part of the stability program revealed out of specification (OOS) results in the potency immunogenicity test for pertactin (PRN), a pertussis component. Three of these (b) (4) lots gave OOS results, while two additional lots failed to meet specification for stage 1 testing. Therefore, the review committee members and OVRM management agreed that additional information regarding these results was required prior to the approval of this product. A complete response (CR) letter was issued on 1 November 2015, which contained comments on (1) the OSS pertactin (PRN) potency assay data for multiple manufactured lots and (2) appropriate qualification for use of expired lots of PRP-OMCP as a reference standard.

MCM submitted a response to CBER's CR letter on 29 June 2018 (amendment 36) addressing both comments: the of out-of-specification (OOS) pertactin (PRN) potency assay data for multiple manufactured lots and proposed use of expired lot of PRP-OMCP as a reference standard. This submission initiated a new 6-month review clock with a resubmission action due date of 29 December 2018.

Regarding CR comment 1, MCM provided information supporting the age and weight of the mice used in the Acellular Pertussis Mouse Immunogenicity Assay as the cause for the OOS results observed for the pertactin antigen in PR5I Vaccine. In addition, they referenced STN# 125145/483, a prior approval supplement for an increase in the age and weight of the mice to be used in the assay when testing Quadracel and Pentacel. The criteria proposed in STN# 125145/483 will be adopted for the release testing of PR5I Vaccine.

The response to CBER Comment 1 was found to be acceptable by the assigned reviewers. The data provided or cross-referenced indicated that the OOS results for the pertactin potency were likely due to the use of immature mice. The implementation of the proposed criteria of (b) (4) for the potency test is appropriate. The assigned reviewers found that the data support approval of the product using the proposed criteria for the age and weight of the mice, and the release and stability limits currently applied to the pertussis components of Quadracel.

Regarding CR comment 2, pertaining to the reference lots used to test (b) (4), the applicant provided the procedures for the selection of PRP-OMPC reference lots for use in the assay, qualification of new lots and annual re-qualification of existing lots. The assigned reviewer found that the information submitted for the qualification and re-qualification of PRP-OMPC lots is acceptable.

2. Abbreviations

Active Vaccine Components

aP	Acellular Pertussis - The 5-Component Acellular Pertussis Adsorbed Antigens are: - PT Pertussis Toxoid - FHA Filamentous Haemagglutinin - PRN Pertactin - FIM Fimbriae Types 2 and 3
D	Diphtheria Toxoid Adsorbed
DTaP	Diphtheria Toxoid, Tetanus Toxoid, and 5-Component Acellular Pertussis Antigens
HBsAg	Hepatitis B surface antigen
PRP-OMPC	Haemophilus b conjugate: PRP, polyribosylribitol phosphate of <i>Haemophilus influenzae</i> type b; OMPC, outer membrane protein complex of <i>Neisseria meningitidis</i> serogroup B

T	Tetanus Toxoid Adsorbed
IPV	Trivalent Inactivated Poliomyelitis Vaccine vIPV (poliovirus propagated on Vero cells) mIPV (poliovirus propagated on MRC-5 cells)

Other Abbreviations

AAHS	Amorphous Aluminum Hydroxyphosphate Sulfate
APSS	Aseptic Process Simulation Study
COA	Certificate of Analysis
CR	Complete Response
DS	Drug Substance
DU	D-antigen Units (used to report poliovirus content)
DP	Drug Product
ELISA	Enzyme-Linked Immunosorbent Assay
FBP	Final Bulk Product
(b) (4)	
IR	Information Request
IVRP	In Vitro Relative Potency (test used for HBsAg potency)
(b) (4)	(test used for endotoxin content)
Lf	Flocculation Units (used to report diphtheria and tetanus toxoids content)
LPS	Lipopolysaccharide
LRP	Lot Release Protocol
OOS	Out of Specification
Ph. Eur.	European Pharmacopoeia
PMC	Post-marketing Commitment
SCT	Safety Concern Threshold
SOP	Standard Operating Procedure
SN	Submission Number (i.e., amendment)
SPL	Sanofi Pasteur Limited, Toronto, Canada
TSB	Tryptic Soy Broth
USP	United States Pharmacopoeia
USPHS	United States Public Health Services
WFI	Water for Injection

3. Review of Drug Product CMC Information

3.1 Description and Composition of the Drug Product (BLA section 3.2.P.1)

PR5I Vaccine is a sterile, preservative-free, uniform, cloudy, white to off-white suspension for intramuscular injection. PR5I Vaccine is presented as 0.5-mL single-dose suspension for injection, in a 2.0-mL (b) (4) glass vial with a stopper (not made with natural rubber latex) and aluminum seal.

The final formula selected for PR5I Vaccine for commercial purpose is the same as the formulation shown to be safe and immunogenic in the Phase III pivotal clinical trials.

The active components of PR5I Vaccine (0.5-mL single-dose) in comparison with previously approved vaccine components (Pentacel, PedvaxHIB, Recombivax and IPOL) are described in Table 1.

Table 1: Composition of PR5I Vaccine Drug Product and Licensed Vaccines

Component*	Amount on a per unit basis (0.5 mL)	Function	Reference	Components in licensed vaccines and content compared to PR5I Vaccine
Haemophilus b conjugate (PRP-OMPC)	3 µg PRP covalently bound to 50 µg of OMPC†	Active substance (Haemophilus type b immunization)	In-house	Liquid PedvaxHIB (Merck, West Point, PA): 7.5 µg PRP bound to 125 µg <i>N. meningitides</i> OMPC/0.5 mL New DS compared to Pentacel: In Pentacel 10 µg PRP bound to 24 µg tetanus toxoid (PRP-T)/0.5 mL
Hepatitis B surface Antigen (HBsAg)	10 µg	Active substance (Hepatitis B immunization)	In-house	Recombivax (Merck, (b) (4)): 5 µg/0.5 mL dose (pediatric dose) New component not in Pentacel
Component Acellular Pertussis (aP) Adsorbed Antigens: -Pertussis Toxoid (PT) -Filamentous Hemagglutinin (FHA) -Pertactin (PRN) -Fimbriae types 2 and 3 (FIM)	20 µg 20 µg 3 µg 5 µg	Active substance (Pertussis immunization)	In-house	Pentacel (SPL): Ap content same as Pentacel
Diphtheria Toxoid Adsorbed (D)	15 Lf	Active substance (Diphtheria immunization)	In-house	Pentacel (SPL): D content same as Pentacel
Tetanus Toxoid Adsorbed (T)	5 Lf	Active substance (Tetanus immunization)	In-house	Pentacel (SPL): T content same as Pentacel
Inactivated Vero Trivalent Poliomyelitis Vaccine (vIPV): - Type 1 (Mahoney) - Type 2 (MEF-1) - Type 3 (Saukett)	29 D-antigen Units‡ 7 D-antigen Units 26 D-antigen Units	Active substance (Poliomyelitis immunization)	(b) (4)	Pentacel (SPL): - vIPV in PR5I is propagated in Vero cells (same as IPOL) and mIPV in Pentacel is propagated in MRC5 cells - IPV DU content same as Pentacel, but reported using a different (b) (4) method. Pentacel (mIPV): 40, 8, 32 DU/0.5 mL IPOL (vIPV): 40, 8, 32 DU/0.5 mL
Aluminum§	319 µg	Adjuvant	In-house	Pentacel (SPL): -Contains 330 µg from aluminum phosphate -PR5I contains aluminum phosphate and amorphous aluminum hydroxyphosphate sulfate, a component of HBsAg and OMPC not contained in Pentacel
Water for injection (WFI)	q.s. 0.5 mL	Diluent	(b) (4)	

- * (b) (4)
- † In each dose of PR5I, Haemophilus b conjugate is comprised of 3 µg of PRP of *Haemophilus influenzae* type b covalently bound to 50 µg of OMPC-outer membrane protein complex of *Neisseria meningitidis* serogroup B.
- ‡ vIPV D-antigens Units are calculated using the (b) (4) test method.
- § Aluminum content in each dose is estimated at 319 µg (b) (4)

The Finished Product may contain residual amounts of materials used in the manufacturing process as listed in Table 2.

Table 2: Residual Components of PR5I Vaccine Drug Product

Residual Components	Amount per unit dose (0.5 mL)
Yeast Protein	≤ 0.1 µg (Maximum 1.0% relative to HBsAg protein)
Bovine Serum Albumin	≤ 50 ng
Thiocyanate	≤ 0.125 µg as ammonium thiocyanate
Formaldehyde	(b) (4)
Glutaraldehyde	≤ 50 ng
Neomycin	< 5 ng
Polymyxin B	< 25 ng
Streptomycin	< 200 ng
Polysorbate 80	< 0.0056%
(b) (4)	Content not provided*
(b) (4)	Content not provided*

*The content of (b) (4) was not provided but information on the assessment of their clearance was provided on 19 June 2015 (SN 18)

Internal Comments

The amount of each of the aluminum adjuvants contained in the vaccine [aluminum phosphate (AlPO4) and amorphous aluminum hydroxyphosphate sulfate (AAHS)] was provided on 20 April 2015 (SN 7). The amounts of these components in the PR5I Vaccine DP are 0.73 mg AlPO4/dose and 0.74 mg AAHS/dose. [See section 4 *Information Request*, IR of 20 March 2015, Question 2.]

Compared to PR5I Vaccine, Pentacel contains sucrose, Polysorbate 80, and 2-phenoxyethanol. The applicant confirmed that sucrose and 2-phenoxyethanol are not used in the manufacturing process of PR5I Vaccine. Polysorbate 80 (of (b) (4) origin) and (b) (4) are residual components from the manufacturing process for (b) (4) [See section 4 *Information Request*, IR of 20 March 2012, Question 3 and IR of 19 June 2015, Question 4.]

In the response to the IR of 19 June 2015 (SN 18) SPL indicated that a further assessment was conducted to determine whether there were other impurities from the manufacturing process that had not been included in the BLA and concluded that the only two impurities were Polysorbate 80 and (b) (4). The calculated amount of Polysorbate 80 in PR5I Vaccine is estimated at less than 0.0056%. The amount of (b) (4) was not provided but the applicant performed characterization studies demonstrating consistent elimination to a very low level. The characterization of impurities in the BLA

sections for the (b) (4) DP was updated to include this information. [See further details regarding DP impurities in section 3.2.2 *Characterization of Impurities.*]

3.2 Control of Drug Product (BLA section 3.2.P.5)

3.2.1 Specifications

The specifications applied for release and shelf-life of PR5I Vaccine (b) (4) Filled Product for commercial lots is provided in Table 3. The changes to acceptance criteria in response to CBER’s CR letter of 1 November 2015 and subsequent information requests are shown in strike-through and bold fonts.

Table 3: Release Specification for PR5I Vaccine (b) (4) Shelf-life Specifications for Filled Product

Test	Method Reference	Release Acceptance Criteria (b) (4)	Shelf-life Acceptance Criteria (Filled Product)#
Sterility	(b) (4)	(b) (4)	Same as Release
(b) (4)	(b) (4)		Same as Release
Aluminum Content*	(b) (4)		NA [†]
Formaldehyde [‡]	In-house		NA
(b) (4)	In-house		NA
(b) (4)	In-house		(b) (4)
(b) (4)	In-house		(b) (4)
(b) (4)	In-house		Same as Release
HBsAg IVRP ^{‡***}	In-house		(b) (4)
PRP Content**	In-house		Same as Release
IPV Immunogenicity (Rat)	(b) (4)		Same as Release
			Same as Release
			Same as Release
D-antigen Content [§]	In-house		Same as Release
			Same as Release
		Same as Release	

Acellular Pertussis Immunogenicity (Mouse)	In-house	(b) (4)	Same as Release
(b) (4)	In-house		(b) (4)
(b) (4)	In-house		(b) (4)
Specific Toxicity*	(b) (4) USPHS		Same as Release
Diphtheria Potency	USPHS		Same as Release
Tetanus Potency	USPHS		Same as Release

* Test site changed from SP Inc. to SPL

** Test site changed from Merck to SPL

PR5I Filled Product stability acceptance criteria

† NA - Not Applicable

‡ HBsAg IVRP - *In Vitro* Relative Potency

§ IPV D-antigen Units (DU) are calculated using the (b) (4) test method

£ Formaldehyde - see PMC 1 under section 6.1 *PMCs Communicated During First Review Cycle* for information on this change

¥ (b) (4) method replaced the (b) (4) test for (b) (4) (see details below in this section)

The following specifications were revised during review of the BLA before the first action date:

(b) (4)

(b) (4)

Specific Toxicity - The acceptance criteria for diphtheria and tetanus toxicity were updated in SN 16 of 25 August 2015 as follows: (b) (4).” These revisions were made to align with the changes made to the Specific Toxicity acceptance criteria for other licensed combination vaccines submitted in a CBE-30 under STN BL 125145/339 and to address question 4 in the 18 June 2015 Information Request.

The following specifications were revised after the first action date:

Formaldehyde - The test for formaldehyde content was changed in response to CBER's IR of 17 April 2015 recommending that a quantitative test be developed and the acceptance criteria for the (b) (4) Product be revised to reflect the elimination of formaldehyde by the manufacturing process. Information to support implementation of the new (b) (4) method was provided in SN 32 of 18 April 2018. The acceptance criterion for residual formaldehyde was revised to (b) (4)

(b) (4)

The specifications applied for release and shelf-life of PR5I Vaccine Filled Product and Labeled Filled Product, are provided in Tables 4 and 5.

Table 4: Release and Shelf-life Specifications for PR5I Vaccine Filled Product (Unlabeled)

Test	Method Reference	Release Acceptance Criteria	Shelf-life Acceptance Criteria
Physical Appearance*	In-house	Uniform cloudy, white to off-white suspension	Same as Release
Sterility	(b) (4)	No microbiological growth	Same as Release
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	NA
Aluminum Content*	(b) (4)	(b) (4)	NA
Extractable Volume	(b) (4)	(b) (4)	NA
Pyrogen**	(b) (4)	Non-Pyrogenic	NA
General Safety Test – Modified*	In-house (Modified CFR 610.11)	(b) (4)	NA

* Test site changed from SP Inc. to SPL

** Test site changed from Merck to SPL

Table 5: Release Specification for PR5I Vaccine Labeled Filled Product

Test	Method Reference	Acceptance Criteria
Identity - (b) (4)	In-house	HBsAg and OMPC components detected
Alternate Identity Test*		
Identity - PRP-OMPC (b) (4)	In-house	PRP-OMPC Detected
Identity - HBsAg (b) (4)	In-house	HBsAg Detected

* Alternate identity tests by (b) (4) will only be performed as a contingency in the event that the equipment for (b) (4) testing is not operational and could significantly delay performing the tests

** Test site changed from Merck to SPL

(b) (4)

General Safety Test - Exemption for General Safety Test is requested in the BLA, however the commercial launch lots will be tested until exemption is granted by CBER upon approval of the PR5I Vaccine BLA. During review of the BLA the regulation for the requirement of the General Safety Test was revoked. [See section 3.5.6 *Justification of Specifications.*]

Identity Testing of Active Components in (b) (4) Labeled Filled Product - For polio the D-Antigen (b) (4) is specific to each of the polio serotypes and serves as a test for potency and identity of each of the three serotypes. Similarly, the mouse immunogenicity assays for the diphtheria, tetanus and pertussis components also serve to confirm identity of these components in the (b) (4)

For commercial release, at the Labeled Filled Product stage, the identity testing strategy is to differentiate PR5I Vaccine from other products labeled on site. The identification test will test for the presence of HBsAg and PRP-OMPC components. These antigens are distinct and are present only in PR5I Vaccine, thereby, distinguishing the PR5I Vaccine from other labeled products manufactured at SPL.

The primary method used for identity testing will be the (b) (4) method. The alternate identity tests by (b) (4) will only be performed as a contingency in the event that the equipment for (b) (4) is not operational and could significantly delay performing the tests.

3.2.2 Characterization of Impurities

The impurities profile for the PR5I Vaccine FBP is a combined profile of the impurities from each of the DSs used in the formulation of PR5I Vaccine. No impurities are introduced in the final formulation of PR5I Vaccine.

The impurities listed for PR5I Vaccine are as follows: yeast protein, bovine serum albumin, thiocyanate, formaldehyde, glutaraldehyde, Neomycin, Polymyxin B, and Streptomycin. These impurities were also listed on the label. However, Polysorbate 80 and residual (b) (4) from the manufacturing process of the IPV component and most of the impurities from the manufacturing process of the DTaP and Hib components (listed below under “Internal Note”) were not listed as impurities in section 3.2.P.5.5. However, these impurities were provided in the DS modules for each component.

A complete list of impurities was requested in the IRs of 23 March 2015 and 19 June 2015. Although only partial information was provided for the DP detailed information was provided for each DS and was reviewed by the respective product reviewers. After internal consultations with DBPAP and DVP deputy directors, it was agreed that the impurities information provided in the BLA was acceptable to support product safety and quality.

Regarding the impurities cited in the Description section of the label, it was also agreed after internal consultation with the OVR associate Director for Policy and the assigned Clinical Reviewer that the list on the label was adequate.

Internal Note: The following are impurities from the bacterial DS components not listed in the DP section of the BLA:

From pertussis DS: (b) (4)

From diphtheria DS: (b) (4)

From tetanus DS: (b) (4)

From Hib (PRP-OMPC): (b) (4)

3.2.3 Lot Release Protocol (LRP)

After several revisions, the final blank lot release protocol template was submitted to CBER for review on 21 November 2018 (Amendment 49) and found to be acceptable. The updated blank LRP was reviewed by the product reviewers in DBPAP and DVP and feedback was provided to Karen Campbell of OCBQ/DBSQC.

CBER determined that samples of Vaxelis (PR5I Vaccine) lots to be released in the U.S. do not need to be tested at CBER for lot release and review of protocol at lot release will be sufficient. A Laboratory Quality Product Testing Plan was developed by CBER and will be used for routine lot release.

4.0 Stability (BLA section 3.2.P.8)

4.1 Stability Data and Proposed Shelf Life

The applicant provided updated stability data and a request for a shelf life extension to 48 months from the proposed 36 months in the initial BLA in Amendment 48 (SN 50, 20 November 2018). The stability results met the specifications shown in Tables 3 and 4 and support the proposed shelf life of PR5I Vaccine Finished Product in a 2.0-mL (b) (4) glass single-dose vial for 48 months at 2°C to 8°C.

The shelf life of PR5I Vaccine is 48 months from the date of Final Bulk Product formulation (Page 11) Finished Product does not exceed 48 months).

Additional stability data for Final Bulk Product stored in containers used in routine manufacturing to support the proposed expiry of (b) (4) for PR5I Vaccine Final Bulk Product were provided as a post-marketing commitment. [See item 2 in section 6.1 *PMCs Communicated During the First Review Cycle.*]

4.2 Stability Protocol for Routine Monitoring and Stability Commitment

The applicant agreed to place (b) (4) commercial scale lots of PR5I Vaccine per year on the stability program, for at least three years. After data are accrued and reviewed for those (b) (4) lots, the results will be evaluated by CBER and the decision to test only one lot per year on the stability program may be made in consultation with CBER.

The samples for this stability program will be tested at time points (b) (4) 12, 24, 36 and 48 months (from the date of formulation) while stored at 2°C to 8°C. (b) (4)

5.0 Information Requests (IRs)

MCM's responses to IRs (issued after CBER's CR letter of 1 November 2015) pertaining to tests performed for release of FBP or Filled Product for each of the active components is summarized in the memos from the reviewers for each active component listed in section 1.

6.0 CMC Post Marketing Commitments (PMC)

6.1 PMCs Communicated During the First Review Cycle (fulfilled in the second review cycle)

During review of the BLA the applicant agreed to the PMCs listed below. Given the BLA was not approved in November 2015, the PMC-related information was submitted in amendments to the BLA. All comments identified as PMCs during the first review cycle were fulfilled as summarized below.

1. An IR was emailed on 17 April 2015 (Questions 20). The applicant submitted a response on 28 May 2015 (sequence # 10) as follows:

Question 20

Formaldehyde Content Test (b) (4) is based on the (b) (4). We requested that SPL establish a specification reflective of the capacity of the manufacturing process to remove formaldehyde and that the actual results of the test be reported in the certificates of analysis and lot release protocols for (b) (4) lots.

Response:

The applicant agreed to comply with CBER's request that a specification for the Formaldehyde Test is established, which is reflective of the capacity of the manufacturing process to remove formaldehyde, and that the actual result of the test is reported in the certificate of analysis and the lot release protocol. In order to implement a quantitative Formaldehyde Content assay, the test method will need to be revalidated. The company proposes to complete the revalidation of the test with an updated acceptance criterion as a post approval commitment. A supplement will be submitted to CBER with the updated method by August 2016. [See section 4 *Information Requests*, IR of 17 April 2015, Question 20.]

PMC Fulfilment Amendment 32 (18 April 2018)

The test for formaldehyde content was changed in response to CBER's IR of 17 April 2015 recommending that a quantitative test be developed and the acceptance criteria for the (b) (4) Product be revised to reflect the elimination of formaldehyde by the manufacturing process. Information to support implementation of the new (b) (4) method was provided and acceptance criterion for residual formaldehyde was revised to (b) (4)

2. An IR was emailed on 27 June 2015 (Question 1). The applicant submitted a response on 15 September 2015 as follows:

Question 1

You have stated in your response to Question 15c of the IR dated 17 April 2015 that stability studies of PR5I Vaccine Final Bulk Product using (b) (4) are not warranted. We do not concur with your response. Please provide stability data for Final Bulk Product stored in containers used in routine manufacturing to support your proposed expiry of (b) (4) for PR5I Vaccine Final Bulk Product. Alternatively, please commit to provide these data post approval.

Response

The applicant committed to perform (b) (4)

PMC Fulfilment Amendment 33 (23 April 2018)

A stability study was conducted under the stability protocol Q_0557093, which included (b) (4) PR5I Vaccine (b) (4) Product (b) (4) commercial manufacturing container. The purpose of the study was to demonstrate that the (b) (4) Product held in the (b) (4) container would yield results consistent with the (b) (4). The stability study for this (b) (4) was completed and results for up to (b) (4) were provided. The testing parameters and acceptance criteria for the (b) (4) product were the same as those for release. All results complied with the acceptance criteria over the study period with the exception of the (b) (4) test at the (b) (4) time-point. An investigation was conducted and the result concluded that the current (b) (4) test design is not robust for testing the complex PR5I Vaccine matrix and as such the company proposes to replace this test with the (b) (4) assay.

6.2 PMCs Communicated During the Second Review Cycle

During review of the second BLA review cycle the applicant agreed to the following post-approval commitments regarding the D-antigen (b) (4) Method:

1. An IR with a PMC request was emailed on 1 November 2018. The applicant submitted a response on 19 November 2018 (Sequence 49, Amendment 47) as follows:

The following is in reference to your 26 October 2018 (Sequence 46, Amendment 44) response to Question 6 of our information request dated 15 October 2018:

Please provide additional support that the currently proposed acceptance criteria for the poliovirus minimum potency at release ((b) (4) D-antigen units/dose for types 1, 2, and 3, respectively) for PR5I Vaccine is, as stated in the BLA, “as immunogenic as the currently licensed component vaccine control(s) (i.e., PENTACEL™ and RECOMBIVAX HB™ in the US, and INFANRIX™ hexa in Europe)”. One such approach would be to compare the D-Antigen content of representative Pentacel and PR5I lots tested in parallel in the same assay and calculated using the (b) (4) method. The number of lots tested should be adequate to allow statistical analyses and to support a potential adjustment of the release criteria for the IPV component of PR5I if necessary. Please commit to submit such supportive data within one year of approval of the BLA for PR5I (Vaxelis).

Response

The clinical results presented in this submission demonstrate that PR5I Vaccine, as tested by the current D-antigen (b) (4) Assay method, is as clinically immunogenic for IPV as the US licensed control vaccines.

As requested by CBER, the applicant committed to measure (b) (4)

. The applicant committed to submit these data within one year after approval.

- 2. An IR with a PMC request was emailed on 7 December 2018. The applicant submitted a response on 12 December 2018 (Sequence 57, Amendment 56) as follows:**

With regard to your response of December 6, 2018 to our Information Request of November 26, 2018, Question 2b, prior to implementation of reference standard lot (b) (4), please provide data on its qualification and calibration against the current reference standard. These data should be generated at the Toronto site since performance of the reference standard may be different when used in the (b) (4) at the MLE site (where it was initially qualified) as compared to its performance at the Toronto site where it will be used to assign potency for drug product release. Please include in your qualification report a comparison of results from an appropriate number of vaccine batches using both the current and new reference standards in parallel. Please commit to submit the qualification report prior to implementation of lot (b) (4) as a CBE-30 supplement.

Response

The applicant indicated that the (b) (4) test transferred from the MLE to the Toronto site, uses the same reference and critical reagents in both sites, and performance of the test is monitored using a shared positive control. The new reference lot was initially calibrated and qualified at the MLE site against the current reference standard (b) (4). Per CBER request to demonstrate that implementation of the new reference would not impact the results of the (b) (4) the company agreed to perform (b) (4)

During the finalization of the BLA review, OVRM management decided that the above PMCs regarding the D-antigen (b) (4) Line Method would not be included in the approval letter. Therefore, an IR with a PMC request was emailed on 19 December 2018. The applicant submitted a response on 20 December 2018 (SN59, Amendment 58). This IR is similar to the two PMCs listed above, but it includes recommendations on the reporting procedures to submit the final report as *Post-marketing Commitment – Final Study Report* or as a *Supplement Contains Post-marketing Commitment – Final Study Report*.

- 1. As requested by CBER on November 01, 2018, MCM committed on November 19, 2018, to measure the D-antigen content of prospective DTaP-IPV and VAXELIS lots tested in the same (b) (4) assay. As the D-antigen (b) (4) using the (b) (4) method is not validated for DTaP-IPV, these data are for characterization purposes. MCM committed to submit these data within one year after approval.**

Response

The applicant concurred with the above commitment.

- 2. In response to CBER Information Request, dated, December 07, 2018, you mentioned in your submission on December 12, 2018 to BLA (STN 125563/0) that the D-Antigen (b) (4) test for poliovirus 1, 2 and 3 transferred from the Marcy L'Etoile, France to the Toronto site, uses the same reference and critical reagents in both sites, and performance of the test is monitored using a shared positive control. The new reference lot was initially calibrated and qualified at the MLE site against the current reference standard (b) (4). Per our request to demonstrate that implementation of the new reference would not impact the results of the (b) (4) you committed to perform (b) (4)**

Response

The applicant concurred with the above commitment.

[End of Memo]