

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: October 23, 2015

To: Rana Chattopadhyay, DVRPA
Katie Rivers, DVRPA
Kelsy Hoffman, DVRPA

From: Sara Gagneten, DVP

Through: Robin Levis, DVP

Subject: **BLA STN 125563**
Subject: CMC review of drug product section of the BLA
Sponsor: 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 [(b) (4)]
Receipt date: 12 August 2015
Action date: 11 November 2015

Table of Contents

1. Executive Summary and Recommendation	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 Description of the Drug Product and Pharmaceutical Development (BLA section 3.2.P.2)	7
3.2.1 Active Components.....	7
3.2.2 Inactive Components	10
3.2.3 Overfill and Overages.....	11
3.2.4 Manufacturing Process Development	11
3.2.5 Container Closure System	16

3.2.6	Microbiological Attributes/Container Closure Integrity	22
3.3	Manufacture (BLA section 3.2.P.3)	23
3.3.1	Manufacturers	23
3.3.2	Batch Formula	23
3.3.3	Description of Manufacturing Process and Process Controls.....	25
3.3.4	Controls of Critical Steps and Intermediates	28
3.3.5	Process Validation.....	29
3.4	Control of Excipients (BLA section 3.2.P.4).....	38
3.4.1	Specifications of Pharmacopoeial Grade Excipients Contained in PR5I	38
3.4.2	Specifications of Non-Pharmacopoeial Grade Excipients Contained in PR5I	38
3.5	Control of Drug Product (BLA section 3.2.P.5).....	39
3.5.1	Specifications	39
3.5.2	Analytical Procedures	42
3.5.3	Validation of Analytical Procedures.....	43
3.5.4	Batch Analyses	45
3.5.5	Characterization of Impurities	46
3.5.6	Justification of Specifications.....	47
3.6	Reference Standards or Materials (BLA section 3.2.P.6)	48
3.7	Container Closure System (BLA section 3.2.P.7).....	48
3.7.1	Final Bulk Product	48
3.7.2	Filled Product (Primary Packaging)	48
3.8	Stability (BLA section 3.2.P.8)	48
3.8.1	Stability Data.....	48
3.8.2	Routine Stability Monitoring.....	51
4.0	Information Requests (IRs)	53
4.1	Information Request emailed on 17 February 2015.....	53
4.2	Information Request emailed on 20 March 2015.....	54
4.3	Information Request emailed on 10 April 2015.....	56
4.4	Information Request emailed on 17 April 2015.....	58
4.5	Information Request emailed on 19 June 2015.....	66
4.6	Information Request emailed on 27 July 2015	68

4.7	Information Request emailed on 2 September 2015	70
5.0	CMC Post Marketing Commitments	70
6.0	Administrative CMC-related Information	71

1. Executive Summary and Recommendation

MCM (Sanofi Pasteur Ltd./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 (b) (4) and is referred to as PR5I 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 is manufactured using modified and/or existing bulk intermediates from vaccines licensed in the U.S. by SPL and Merck.

PR5I is a sterile liquid preservative-free suspension presented as a single dose (0.5 mL) vial for intramuscular injection. Each 0.5 mL dose contains 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 PR5I 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.

This memo covers my review of the information in the drug product (DP) section of the BLA with the exception of information specific to each active component. Production, testing, transport and storage of the intermediate bulks used for formulation of PR5I as well as the information on the potency testing and validation of potency tests performed for release and stability of PR5I DP were performed by product reviewers as follows:

- Diphtheria and Tetanus: Michael Schmidt
- Pertussis: Juan Arciniega and Tod Merkel
- Haemophilus b conjugate: Wei Wang and Tina Roecklein
- Hepatitis B: Alla Kachko
- Poliovirus: Diana Kouivaskaia

Analytical tests were reviewed by the DBSQC and potency and safety tests by the product reviewers in DBPAP and DVP. Clinical assays used for evaluation of vaccine response were also reviewed by reviewers in DBPAP and DVP.

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.

Recommendation:

The CMC DP information submitted in the BLA for the (b) (4) consistency lots is adequate. However, data from (b) (4) 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 out of OOS results, while two additional lots failed to meet specification for stage 1 testing. Therefore, the review committee members and OVRR management agreed that additional information regarding these results will be required prior to the approval of this product.

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 influenza</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)	(b) (4)
IR	Information Request
IVRP	In Vitro Relative Potency (test used for HBsAg potency)
(b) (4)	(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 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 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
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 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)

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 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, Pentacel contains sucrose, Polysorbate 80, and 2-phenoxyethanol. The sponsor confirmed that sucrose and 2-phenoxyethanol are not used in the manufacturing process of PR5I. 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 is estimated at less than 0.0056%. The amount of (b) (4) was not provided but the sponsor 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.

(b) (4) is an impurity but was not identified as such. (b) (4)

3.2 Description of the Drug Product and Pharmaceutical Development (BLA section 3.2.P.2)

3.2.1 Active Components

A brief description of the drug substances used in the formulation of PR5I is presented below.

(b) (4)

3 Pages Determined to be Not-Releasable: (b)(4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

3.2.3 Overfill and Overages

Each unit dose vial is filled with a volume in slight excess of the volume that is to be withdrawn. The filled volume is controlled by measuring (b) (4). The acceptance criteria for fill (b) (4) in each vial are (b) (4) to allow the extraction of one dose of 0.5 mL.

3.2.4 Manufacturing Process Development

3.2.4.1 Process Development for Manufacture of the Drug Product through Phase III

The optimal formulation of PR5I was selected based on safety and immunogenicity data from Phase II studies. Due to volume constraints at the final bulk formulation stage, it was necessary to concentrate the HBsAg, PRP-OMPC and DTaP-associated components prior to formulating the FBP.

The key process development strategies included:

(b) (4)

The manufacturing of PR5I was transferred from the Sanofi Pasteur Inc. (USA) site to the Sanofi Pasteur Limited (SPL) (Toronto, Canada) site for Phase III clinical trial lots. PR5I FBP lots C3145, C3146, C3147 and C3886 were manufactured at commercial scale ((b) (4) [REDACTED]). The manufacturing process of these PR5I lots was validated as part of production consistency lots. PR5I FBP lots C3145, C3146 and C3147, were used to support Phase III clinical trials.

The major manufacturing changes through Phase III are as follows:

(b) (4) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

[Redacted text block]

3.2.4.2 Manufacturing Changes between Phase III Consistency Lots and Commercial Launch

(b) (4)

[Redacted text block]

2 Pages Determined to be Not-Releaseable: (b)(4)

(b) (4)

Storage and Transportation

The (b) (4) Filled Product and Labeled Filled Product are stored at 2°C to 8°C. PR5I FBP is proposed to be shipped to the US by (b) (4) (SOP 48SD-030, “International Shipments Packing Exceptions”) to be delivered to one of the PR5I distribution centers in the US.

3.2.5 Container Closure System

The two main materials used for the container closure systems (b) (4) glass for Filled Product) have been selected as they are inert materials that do not interact with aqueous suspensions, can be cleaned and sterilized and offer suitable protection to the product during transportation and storage. Furthermore, equivalent container closure systems (b) (4), glass, bromobutyl stopper), as described for PR5I, are used for other licensed SPL combination vaccines and were proven to be suitable for the purpose of formulation and storage of FBP and Filled Product. [See comment below in this section (3.2.5).]

3.2.5.1 Final Bulk Product

(b) (4)

(b) (4)

The composition of the product contact storage container materials used for PR5I FBP is provided in Table 5.

Table 5: Composition of the Product Contact Storage Container Materials Used for PR5I Final Bulk Product

(b) (4)

3.2.5.2 Filled Product

The container closure system consists of a 2-mL single-dose glass vial, rubber stopper and an aluminum seal with a plastic flip-off cap. PR5I may be stored in this container closure system at 2°C to 8°C from the time of filling in vials until the end of its shelf-life.

The composition of primary packaging materials used for PR5I Filled Product is provided in Table 6.

Table 6: Composition of Primary Packaging Materials Used for PR5I Filled Product

Packaging Component	2-mL Vial	Stopper (b) (4)	Aluminum seal with flip-off cap
Material Composition	(b) (4) borosilicate glass tubing	(b) (4) isobutyl rubber (not made with natural rubber latex)	Aluminum (seal) Polypropylene (cap)

As reported by the (b) (4) stopper manufacturer, the stopper materials of construction are:

(b) (4)

3.2.5.3 Extractable and Leachable Studies to Evaluate Volatile and Semi/Non-Volatile Compounds

The extractable and leachable information of the BLA was updated in the submission of 5 June 2015 (SN11) in response to the IR of 17 April 2015. The summary below corresponds to the extractables and leachables information provided in this amendment.

2 Pages Determined to be Not-Releaseable: (b)(4)

Toxicology Assessment

The risk to human safety of the leachables obtained during leachable simulation studies (i.e., (b) (4)) was assessed in a specific toxicological assessment. A review of available toxicity data for these leachables was conducted through a literature review using standard sources, including searches in databases of toxicity data and other scientific literature and/or human drug information. The literature search showed acceptable safety thresholds and/or supportive toxicity data for each leachable. The toxicological assessment showed that on a per dose basis, all the leachables obtained were found at levels below the respective acceptable safety thresholds and as such, they are considered unlikely to pose a risk to human safety.

Cytotoxicity Studies

Compendial cytotoxicity tests were performed according to the procedure set forth in (b) (4)

[Redacted]

3.2.5.4 Stability Studies

Final Bulk Product Stability

(b) (4)

[Redacted]

Filled Product Stability

PR5I Filled Product stability studies were conducted on (b) (4) commercial-scale lots (b) (4)) stored in (b) (4) position in the 2.0-mL single-dose vial, (b) (4) stopper and aluminum seal with plastic flip-off cap at 2 to 8°C for up to 48 months. The results of the stability studies are supportive of the storage of PR5I Filled Product for 42 months (end of shelf-life) in the 2.0-mL single-dose vial, (b) (4) stopper and aluminum seal with plastic flip-off cap at 2°C to 8°C. [See section 3.8 *Stability Data* for the stability studies tests and results.]

Comments and Conclusion for Leachables and Stability Studies for Qualification of Container Closures

The updated leachables data submitted on 5 June 2015 (SN 11) in response to the IR of 17 April 2015 and updated stability data submitted on 12 September 2014 (SN 1) and 28 May 2015 (SN10) demonstrate that

(b) (4) for storage of FBP and the 2.0-mL single-dose glass vial with (b) (4) stopper for storage of PR5I are adequate container closure systems. The suitability of these container closure systems was also evaluated in container closure integrity studies described in section 3.2.6 *Microbiological Attributes/Container Closure Integrity*.

In the introduction of the *Container Closure System* section of the BLA, the sponsor indicated that equivalent container closure systems ((b) (4), glass, bromobutyl stopper), as described for PR5I, are used for other licensed SPL combination vaccines and were proven to be suitable for the purpose of storage of FBP and Filled Product. In the IR of 10 April 2015 we asked for further details on the licensed products that use the same (b) (4) and were filled in the same 2-mL glass containers with bromobutyl stoppers. In the response of 27 May 2015 (SN 9) the sponsor stated that Pentacel, Quadracel, Adacel and Tenivac are stored in the same containers ((b) (4) for FBP and 2-mL glass containers with bromobutyl stoppers at 2-8 °C for up to 36 months for Filled Product) as proposed for PR5I FBP and Filled Product. [See section 3.8 *Stability* and section 4 *Information Requests*, IR of 10 April 2015, Question 1 and IR of 17 April 2015, Question 15.]

3.2.6 Microbiological Attributes/Container Closure Integrity

Suitability of container closure is also reviewed by the assigned DMPQ reviewer.

(b) (4) for PR5I Final Bulk Product
(b) (4)

PR5I Vaccine, Unit Dose Vials – (b) (4) Study Using the (b) (4) Method

A (b) (4) study was performed to evaluate container closure integrity, based on the fact that the (b) (4) method has greater sensitivity in detecting possible leaks of the container closure system than the (b) (4) test. This study demonstrated the integrity of the 2.0-mL single-dose vial, (b) (4) stopper and aluminum seal with plastic flip-off cap container closure.

PR5I Vaccine, Unit Dose Vials – (b) (4) Study Using the (b) (4) Method

A container closure integrity test study was performed using the (b) (4) method to evaluate the container closure integrity in PR5I Filled Product. (b) (4) lots ((b) (4)) of PR5I Filled Product were used for the container closure integrity testing in May 2014. The container closure integrity test using (b) (4)

. The results for the CCIT for PR5I have met the acceptance criteria for all the lots tested.

Conclusion

The results of the (b) (4) studies in the (b) (4), the Container Closure (b) (4) Test at the Filled Product stage using the (b) (4) method and the Container Closure Integrity Test using the (b) (4) method, demonstrate that the container closure systems ((b) (4) and the 2.0-mL single-dose glass vial with (b) (4) stopper) are suitable for maintaining the sterility of the FBP and Filled Product.

3.3 Manufacture (BLA section 3.2.P.3)

3.3.1 Manufacturers

The DP is manufactured at the SPL facility located in Canada at
1755 Steeles Avenue West
Toronto, Ontario, M2R 3T4.

The operational responsibilities and manufacturing locations are shown in Table 8.

Table 8: Operations and Responsibilities of Sanofi Pasteur Limited

Operation	Responsibility	Building
Manufacturer of the PR5I FBP	Toronto – Canada	(b) (4)
Media Preparation (Phosphate Solution and Aluminum Phosphate Suspension)	Toronto – Canada	(b) (4)
Filling, labeling, packaging, release of PR5I in vials	Toronto – Canada	(b) (4)
Quality Control Testing, Stability Testing	Toronto – Canada	(b) (4)

3.3.2 Batch Formula

The preparation of the PR5I FBP begins with (b) (4)

(b) (4)

The PR5I FBP is then filled into vials, labeled and packaged.

(b) (4)

The amount of each component is such that the composition of the FBP is the same as the unit dose of PR5I described in section 3.1 *Description and Composition of the Drug Product*.

As an example, the concentration of each component in a single dose of PR5I and the concentration and quantity of the DS bulks used in the formulation of PR5I FBP for a typical (b) (4) batch size are described in Table 9. A (b) (4) batch may be filled to provide theoretically a total of approximately (b) (4) vials.

Table 9: Final Formula of PR5I (unit dose) and Final Bulk Product (b) (4)

(b) (4) (4)

(b) (4)

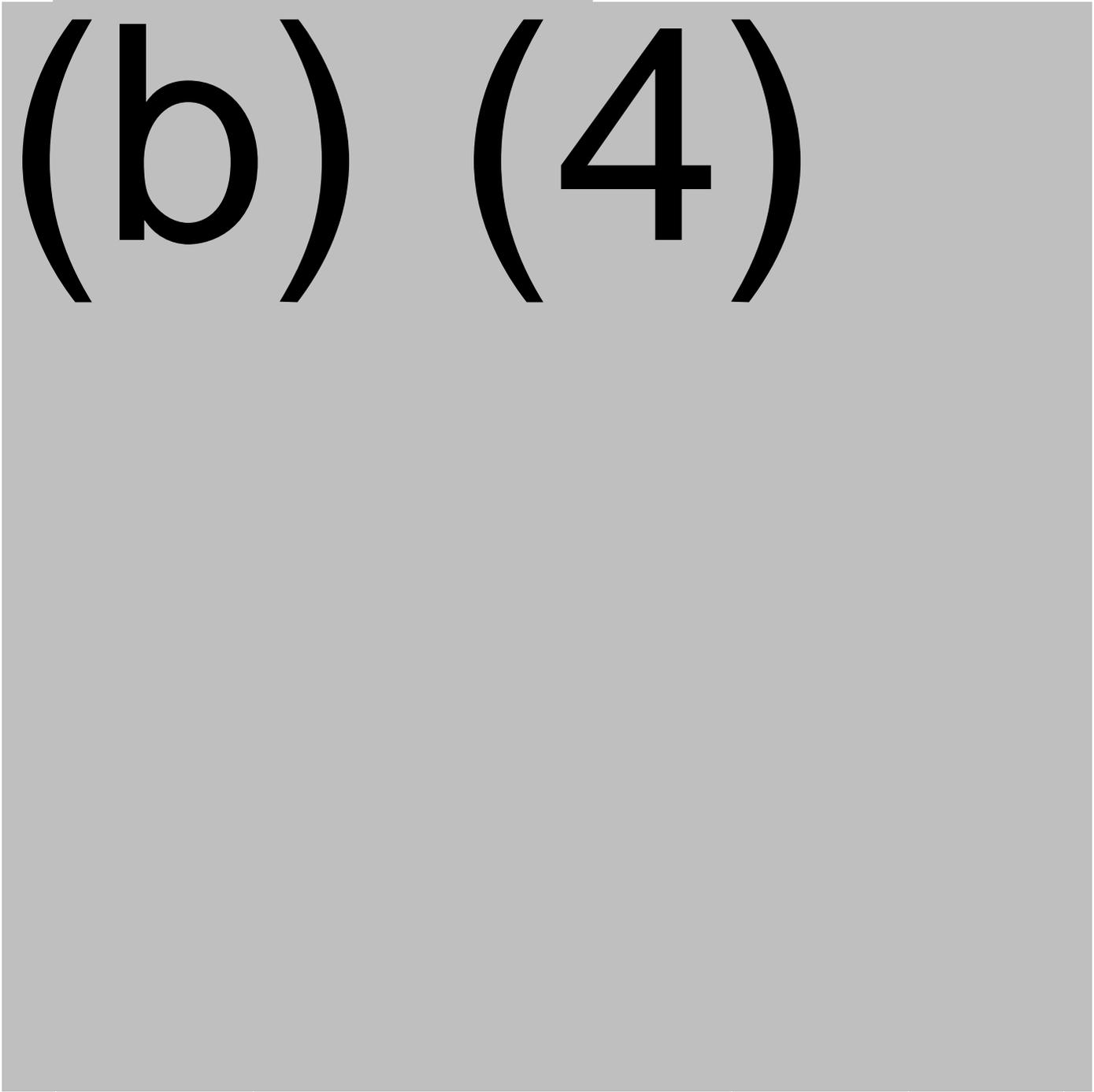
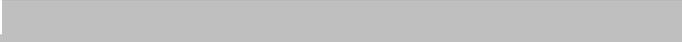
Overfill

Each unit dose vial is filled with a volume in slight excess of the volume that is to be withdrawn. The filled volume is controlled by measuring (b) (4). The acceptance criteria for (b) (4) in each vial are (b) (4)) to allow the extraction of one dose of 0.5 mL. The excess weight/volume is sufficient to permit withdrawal and administration of the labeled volume of 0.5 mL.

3.3.3 Description of Manufacturing Process and Process Controls

3.3.3.1 Formulation of Final Bulk Product and In-process Controls

(b) (4)



(b)

(4)

(b) (4)

3.3.3.3 Filling Process

Preparation and Sterilization of Primary Packaging Components

PR5I FBP is filled into a 2.0-mL (b) (4) glass vial with a stopper (not made with natural rubber latex) and aluminum seal with plastic flip-off cap. (b) (4)

Filled Product Process Description

(b) (4)

The FBP is filled into 2-mL glass vials and stoppered using an automated vial tunnel filling line. The seals are 13 mm one-piece aluminum seals with plastic flip-off caps and are applied to the vials using a capping machine. The sealed vials are inspected by the automatic vial inspection system and samples are taken for testing. The inspected unlabeled vials are stored at (b) (4) until released for labeling and secondary packaging. The filled vials are labeled and packed with or without a pre-formed blister tray into a cardboard carton containing a leaflet. The Finished Product is stored at 2 to 8°C until released to market.

In-process Controls during the Filled Product Manufacture

The following in-process controls are performed:

- (b) (4)

3.3.3.4 Storage and Transportation

(b) (4) Labeled Filled Product are stored at 2 to 8°C. The product is packaged in a corrugated cardboard shipper box identified with the product name, material number, lot number, and expiry date with bar codes. Each shipment is equipped with a temperature-monitoring device. The packaged product is shipped to the US by (b) (4) (SOP 48SD-030, “International Shipments Packing Exceptions”) and can be delivered to one of the PR5I distribution centers in the US.

3.3.4 Controls of Critical Steps and Intermediates

3.3.4.1 Description of Critical Steps

The steps identified as critical for the manufacturing process of the DP are presented below.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

3.3.4.2 Control of Critical Steps

Table 12 provides a summary of the controls in place to monitor the critical steps

(b) (4)

(b) (4)

3.3.4.3 In-process Material Tests Used in Lieu of Finished Product Tests

Table 13 provides the acceptance criteria, method/reference, and justification for the (b) (4) assay, an in process material test performed at the DTaP Bulk Concentrate (b) (4) stage.

(b) (4)

3.3.5 Process Validation

The overall process validation approach for the production of PR5I consists of process qualification and continuous process verification. The process evaluation and validation studies included:

- FBP formulation
- Filling process
- Mixing process
- (b) (4) of DS (vIPV bulk)
- (b) (4) of water for injection (WFI)
- (b) (4) DS (PRP-OMPC and HBsAg bulk intermediate)
- Aseptic process simulation of formulation and filling.

Further details on each validation are provided below.

(b) (4)

[Redacted]

[Redacted]

7 Pages Determined to be Not-Releaseable: (b)(4)

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Process Validation Conclusion (conclusion for section 3.3.5)

The results of the completed validation studies demonstrate that the manufacturing process can consistently yield DP of adequate quality.

All results of the release and validation specific tests met the specifications and acceptance criteria with the exception of IPV D-antigen content (b) (4) [Redacted] Test, and (b) (4) [Redacted]. [See summary of non-conformances in section 3.3.5.1 Formulation of (b) (4) Product.]

3.4 Control of Excipients (BLA section 3.2.P.4)

3.4.1 Specifications of Pharmacopoeial Grade Excipients Contained in PR5I

Water for Injection (WFI) is a pharmacopoeial grade excipient used as a diluent in the formulation of PR5I FBP.

3.4.2 Specifications of Non-Pharmacopoeial Grade Excipients Contained in PR5I

During the formulation of PR5I FBP, 5-Component Acellular Pertussis Adsorbed Antigen Concentrates (PT, FHA, PRN and FIM), Diphtheria Toxoid Adsorbed Concentrate and Tetanus Toxoid Adsorbed Concentrate are (b) (4).

The PRP-OMPC and HBsAg-containing drug substances consist of an antigen adsorbed onto the amorphous aluminum hydroxyphosphate sulfate adjuvant.

The (b) (4) of PR5I FBP may be (b) (4)

The non-pharmacopoeial grade excipients contained in PR5I are listed in Table 15.

Table 15: Non-pharmacopoeial Grade Excipients

Excipient	Excipient Function	Raw Materials Used for the Excipient	Test Method for the Raw
Amorphous aluminum hydroxyphosphate sulfate	Adjuvant	(b) (4)	(4)
Aluminum phosphate	Adjuvant	(b) (4)	(4)
(b) (4) Phosphate solution	Source of (b) (4)	(b) (4)	(4)
(b) (4)	(b) (4)	(b) (4)	(4)
(b) (4)	(b) (4)	(b) (4)	(4)

No excipients of human or animal origin are used in the DP manufacture of PR5I.

No novel excipients are used in the DP manufacture of PR5I. All the raw materials used for the preparation of the excipients are used during the manufacture of other licensed vaccines.

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

3.5.1 Specifications

The specifications applied for release and shelf-life of PR5I (b) (4) Filled Product for commercial lots is provided in Table 16.

Table 16: Release Specification for PR5I (b) (4) Product and Shelf-life Specifications for Filled Product

Test	Method Reference	Release Acceptance Criteria (FBP)	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)
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 indicating acceptance criteria

† NA – Not Applicable

‡ HBsAg IVRP - *In Vitro* Relative Potency

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

The following specifications were revised during the course of the review of the BLA:

(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 specification(s) applied for release and shelf-life of PR5I Filled Product and Labeled Filled Product, are provided in Tables 17 and 18.

Table 17: Release and Shelf-life Specifications for PR5I 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)	≥ 0.5 mL	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 18: Release Specification for PR5I 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

** 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 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 (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 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, thereby, distinguishing the PR5I product from other labeled products manufactured at SPL.

Comment

In the submission of 28 May 2015 (SN10) in response to an IR [see section 4 *Information Requests*, IR of 17 April 2015, Question 19], SPL clarified that 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.

3.5.2 Analytical Procedures

The (b) (4) analytical tests are performed in compliance with pharmacopoeial methods for sterility, (b) (4) and extractable volume.

A list of all other analytical procedures is provided in Table 19. Assay methods and validations were reviewed by reviewers in DVP and DBPAP for the active components and by DBSQC reviewers for inactive components, sterility tests and other physicochemical tests.

Table 19: Non-USP Analytical Tests

Test Name	Method Reference
Aluminum Content	(b) (4)
Formaldehyde	In-house
(b) (4)	In-house
HBsAg IVRP	In-house
PRP Content	In-house
IPV Immunogenicity (Rat)	(b) (4)
D-Antigen Content	In-house
Acellular Pertussis Immunogenicity (Mouse)	In-house
(b) (4)	In-house
Specific Toxicity	(b) (4) /USPHS
Diphtheria Potency	USPHS
Tetanus Potency	USPHS
Physical Appearance	In-house
Pyrogen (<i>in vivo</i>)	(b) (4)
General Safety Test - Modified	In-house (Modified CFR 610.11)

Comment

The procedures for retesting of samples for release (b) (4) Filled Product lots were provided on 20 April 2015 (SN 7) as follows:

- The following analytical procedures contain retesting provisions if the results do not meet the acceptance criteria: IPV Immunogenicity, Acellular Pertussis Immunogenicity, (b) (4) Diphtheria Potency, Tetanus Potency, Pyrogen, and the General Safety. If the acceptance criteria are not met after the retesting procedures are completed an investigation is performed following the SOP for

OOS test results. These tests also have validity criteria which are specific for each test. If the specified criteria are not met, the test may be repeated

- The following analytical procedures do not have retesting provisions if acceptance criteria are not met: Aluminum Content, Formaldehyde, (b) (4) PRP Content, HBsAg IVRP, D-Antigen Content and Specific Toxicity. However, these tests have validity criteria which allow for repeat testing if the validity criteria are not met.
- The tests which do not allow for retests and do not contain validity criteria include: Sterility, (b) (4) Physical Appearance, and Extractable Volume.

For all tests, if the results do not meet the acceptance criteria after the allowed retests have been completed (when permitted by the SOP), an investigation is performed following the SOP for OOS test results. [See section 4 *Information Request*, IR of 20 March 2015, Question 1.]

3.5.3 Validation of Analytical Procedures

Validation information for the analytical procedures for the release of PR5I (b) (4) Filled Product and Labeled Filled Products were provided. [Assay methods and validations were reviewed by reviewers in DVP and DBPAP for the active components and by DBSQC reviewers for inactive components and physicochemical tests.]

An overview of assay methods and validation approaches for selected assays is provided below.

HBsAg *In Vitro* Relative Potency (IVRP): This is an (b) (4) method used for the evaluation of HBsAg content in the (b) (4) and to monitor stability of Filled Product. A supplement (STN 101066/5656) for a modification of the assay to include a (b) (4) step was approved on August 17, 2015.

(b) (4)

PRP Content and (b) (4) PRP-OMPC: This is a (b) (4) assay for quantitation of (b) (4) PRP performed on the (b) (4) and to monitor stability of Labelled Filled Product.

IPV Rat Immunogenicity: This assay is used to measure the antibody levels in serum from rats inoculated with Poliovirus Vaccine Inactivated (IPOL) or poliovirus combination vaccines. The test is performed on the PR5I (b) (4) and to monitor stability of Labelled Filled Product. Two studies were performed to confirm that the IPV Rat Immunogenicity Assay is a suitable method for testing PR5I. One study was conducted to establish the suitability of the assay by examining performance parameters for Intermediate Precision and Robustness of the serum samples from rats immunized with poliovirus test vaccines (i.e., IPV, DTaP-IPV, DTaP-IPVHib).

The Rat Immunogenicity Assay is performed at the (b) (4) stage and it is based on the (b) (4) compendial method ((b) (4)). Since this is a compendial method, verification for suitability was performed by assessing intermediate precision and robustness. This study demonstrated that the various

sample matrices had no effect on precision and robustness, and that the assay is suitable to test samples for poliovirus-neutralizing antibodies from rats immunized with IPV combination vaccines.

D-antigen (b) (4) This is a poliovirus type-specific D-antigen (b) (4) method performed for the evaluation of potency on (b) (4) to confirm the identity of poliovirus types 1, 2 and 3 in the (b) (4) and to monitor stability of Labelled Filled Product.

Acellular Pertussis Mouse Immunogenicity Assay: is used to evaluate the immunogenicity (potency) of fimbriae types 2 and 3 (FIM), pertactin (PRN), pertussis toxoid (PT) and filamentous haemagglutinin (FHA) in the (b) (4) to confirm that the vaccine induces antibody responses in mice to each of the acellular pertussis antigens and to monitor stability of Labelled Filled Product. This assay can also serve to confirm the identity of pertussis components in the (b) (4) The assay is conducted in (b) (4) phases; (b) (4)

(b) (4) As such, both phases of the assay were validated. (b) (4) the ELISA methods were validated for each of the four acellular pertussis antigens. [See the review memo of Dr. Juan Arciniega for details on assay OOS results and their resolution.]

(b) (4)

Specific Toxicity: This test is used to confirm the absence of residual tetanus or diphtheria toxin in the (b) (4) to monitor stability of Labelled Filled Product. This test is considered a pharmacopoeial qualitative test for impurities.

Diphtheria Potency: This test is performed according to the USPHS Potency Testing (Diphtheria Toxoid). The test is a compendial assay used to determine the potency (immunogenicity) and identity (or presence) of the diphtheria toxoid component in FBP. This test is also used to monitor stability of Labelled Filled Product. The test method involves (b) (4)

Tetanus Potency This test is performed according to USPHS Potency Testing (Tetanus Toxoid). The test is a compendial assay used to determine the potency (immunogenicity) and identity (presence) of the Tetanus Toxoid component (b) (4) . This test is also used to monitor stability of Filled Product. The test method involves (b) (4)

(b) (4)

(b) (4)

Comment

The site and validation status of several non-compendial tests performed for release and stability of PR5I was not clear; therefore, we asked the sponsor to identify the laboratory sites where these tests will be performed and the laboratory sites where validation of these tests was performed. [See section 4 *Information Requests*, IR of 18 June 2015, Question 5.]

3.5.4 Batch Analyses

The (b) (4) production consistency lots ((b) (4)) of PR5I were manufactured at the commercial manufacturing scale and filled into vials. The batch size, date of manufacture, use of batch, and manufacturing site for each of the DP lots is summarized in Table 20.

Table 20: Batch Description of Drug Product

Batch Number (Filled Product)	Batch Size (Final Bulk Product)	Batch Number (Final Bulk Product)	Date of Manufacture	Use of Batch	Manufacturing Site
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Phase III Clinical Study/ Production Consistency/ Stability	Toronto, Canada Building (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Phase III Clinical Study/ Production Consistency/ Stability	Toronto, Canada Building (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Phase III Clinical Study/ Production Consistency/ Stability	Toronto, Canada Building (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	Production Consistency/ Stability	Toronto, Canada Building (b) (4)

* DP lot (b) (4) was not used in the Phase III clinical trials or stability studies

† FBP lot (b) (4) was (b) (4) due to disruption in the filling process

Different DS batches from each active component were used to formulate the (b) (4) DP consistency batches shown in Table 21. For the PRN component batch (b) (4) was formulated with (b) (4) (used in (b) (4)).

(b) (4) (b) (4)

(b) (4)

Release data for the (b) (4) production consistency lots of the PR5I Labeled Filled Product, Filled Product, and FBP listed above were provided.

The release testing for commercial lots will differ from the testing performed on consistency lots. The major changes to test methods and release specifications that will be applied to commercial lots were described in sections 3.2.4 *Manufacturing Process Development* and 3.5.1 *Specifications*.

Results

All release results for production consistency lots of the PR5I (b) (4) Filled Product were within the defined acceptance criteria with the exception of the IPV D-antigen (b) (4) (b) (4) method) for PR5I FBP for lot (b) (4). Although this lot did not pass the D-antigen (b) (4) (b) (4) method), the quality of the DP was not affected as lot (b) (4) had passing results for the IPV Rat Immunogenicity Test. CBER had agreed (via CBER letter dated 16 March 2011 in response to IND 14496, Amendment #0002 submitted 07 February 2011) to replace the IPV D-antigen content (b) (4) (b) (4) method) with the IPV Rat Immunogenicity Test for release of the clinical trial lots. The investigation following the OOS result for lot (b) (4) determined that the IPV D-antigen (b) (4) (b) (4) method) lacks robustness. To address this issue, a globally harmonized IPV D-antigen (b) (4) (b) (4) method has been validated, and this assay is proposed as a release test for commercial lots along with the IPV Rat Immunogenicity Test. All four consistency lots of PR5I were tested by the new IPV D-antigen (b) (4) (b) (4) method during stability studies. [See section 3.2.4 *Manufacturing Process Development*.]

Lot Release Protocol

The lot release protocol template was included in the BLA. The assigned reviewers in DVP, DBPAP, and DBSQC reviewed the template and comments were compiled by DBSQC and emailed to the sponsor on June 18, 2015. The revisions to the lot release protocol (submitted on 6 and 16 October 2015, SN 23 and 25) are being reviewed by DBSQC, DVP and DBPAP.

3.5.5 Characterization of Impurities

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

The impurities listed for PR5I 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) (b) (4) from the manufacturing process of the IPV component and (b) (4) (b) (4) from the manufacturing process of (b) (4) (b) (4) were not listed as impurities.

Comment

See comment in section 3.1 *Description and Composition of the Drug Product* and Table 2: *Residual Components of PR5I Drug Product*.

3.5.6 Justification of Specifications

The justification for the specifications for the PR5I FBP, Filled Product and Labeled Filled Product are based on the experience with specifications for DTaP-IPV (Quadracel), DTaP-IPV-Hib (PediaceL) and Tdap-IPV (Adacel Polio) and on the manufacturing experience with developmental lots and clinical lots of PR5I.

Please see section 3.5.1 *Specifications* for details on the specifications for the FBP, Filled Product and Labeled Filled Product. The specifications for the release of PR5I (b) (4) shelf life of PR5I Filled Product are shown in Table 16 and the specifications for the Filled Product and Labeled Filled Product are shown in Tables 17 and 18. Justification on selected specifications is provided below.

Formaldehyde Justification for Specification in (b) (4)

A proper justification for the formaldehyde content of (b) (4) per dose was not provided.

Comment

(b) (4)

[See section 4 *Information Request* IR of 17 April 2015, Question 20)

Aluminum Justification for Specification in (b) (4)

The justification for aluminum content is based on the content of (b) (4)

Justification of Exemption of General Safety Test for PR5I Filled Product

A request for an exemption to the requirement to perform the General Safety Test on each commercial lot of Filled Product is based on SPL's and Merck's use of appropriate process controls and quality assurance practices throughout the manufacturing process and on the available PR5I General Safety Test results.

Conclusion: Based on the passing result of the General Safety Test performed on (b) (4) PR5I lots and on the process controls in place during the production and release of PR5I, the team agrees with the exemption of the GST. Additionally, during review of the BLA the regulation for the requirement of the General Safety Test was revoked (final rule effective 3 August 2015).

Identity by (b) (4) Specification of Labeled Filled Product

The (b) (4) Test is performed on PR5I Labeled Filled Product to confirm the identity of the product. For identity testing, the requirement is to differentiate PR5I from other products labeled on site. Therefore, the identity testing will involve the detection of PRP-OMPC and HBsAg antigen specific peptides. These two antigens are distinct and present only in PR5I and therefore this method distinguishes the PR5I product from other labeled products manufactured at SPL.

Alternate Identity Test by (b) (4) of Labeled Filled Product

The HBsAg (b) (4) Identity assay and the PRP-OMPC (b) (4) Identity assay both confirm the presence of HBsAg and PRP-OMPC, respectively. For identity testing, the requirement is to differentiate PR5I from other products labeled on site. Therefore, the identity testing will involve the detection of PRP-OMPC and HBsAg antigens. These two antigens are distinct and present only in PR5I Vaccine and therefore this method distinguishes the PR5I product 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. [See section 4 *Information Request*, IR of 17 April 2015, Question 19.]

Conclusion: Reviewers in DVP, DBPAP and DMPQ agree that testing for HBsAg and PRP-OMPC is sufficient to confirm the identity of the Labeled Filled Product and ensure adequate segregation or products.

3.6 Reference Standards or Materials (BLA section 3.2.P.6)

The reference standards used for quality testing of PR5I were reviewed by the assigned reviewers in DVP, DBPAP and DBSQC.

3.7 Container Closure System (BLA section 3.2.P.7)

3.7.1 Final Bulk Product

(b) (4)

[See further details on validation of the container closure systems in sections 3.2.5 *Container Closure Systems*, 3.2.6 *Microbiological Attributes* and 3.8 *Stability*.]

3.7.2 Filled Product (Primary Packaging)

The container closure system used for PR5I Filled Product consists of a single-dose glass vial, rubber stopper and an aluminum seal with a plastic flip-off cap.

[See further details on validation of the container closure systems in sections 3.2.5 *Container Closure Systems*, 3.2.6 *Microbiological Attributes* and 3.8 *Stability*.]

3.8 Stability (BLA section 3.2.P.8)

3.8.1 Stability Data

The stability studies included (b) (4) PR5I FBP lots ((b) (4)) and (b) (4) Finished Product lots ((b) (4)). The stability study of the FBP was conducted (b) (4) containers (b) (4) . The assessment of the Finished Product shelf-life was conducted in 2.0-mL single-dose (b) (4) glass vials with (b) (4) stopper and 13 mm aluminum seal with plastic flip-off cap at 2 to 8°C.

On 12 September 2014 (SN 2) the sponsor submitted updated stability data to support a shelf life of 42 months for PR5I starting from the date of FBP formulation (b) (4) Finished Product does not exceed 42 months). Additional stability data for the 48-month time-point and updated specifications were submitted on 28 May 2015 (SN 10) and 15 September 2015 (SN 20).

3.8.1.1 PR5I Final Bulk Product

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.8.1.2 PR5I Finished Product

Stability studies were designed to support the shelf-life period of PR5I finished product in the 2.0-mL single-dose (b) (4) glass vial, (b) (4) stopper and 13 mm aluminum seal with plastic flip-off cap for a period of 42 months at 2 to 8°C from the date of FBP formulation. (b) (4)

Finished Product does not exceed 42 months. Study B014063 included the (b) (4) PR5I consistency lots ((b) (4)) and study B015684 included (b) (4). These lots were manufactured at commercial scale and their time (b) (4) was based on the date of FBP formulation. These lots were filled at SPL.

Samples for the purpose of stability were stored in the (b) (4) orientation at 2 to 8°C and each lot was tested at time (b) (4) (on the FBP lots) and after 3, 6, 9, 12, 18, 24, 30, 36, 42 and 48 months of storage (on Finished Product lots). The stability indicating parameters were those listed on Tables 16 and 17 in section 3.5.1 *Specifications*. Additional parameters included container closure integrity, and (b) (4). The stability specifications for the consistency lots were similar to those proposed for routine monitoring of commercial lots (listed on Table 22). The differences between the stability specifications of the consistency lots and those for routine monitoring reflect input provided during review of the BLA.

Summary of Stability Data Submitted on 28 May 2015 (SN10) and 15 September 2015 (SN 20)

Stability results were provided for up to 48 months for the (b) (4) clinical consistency lots ((b) (4)) and for (b) (4). The results met the acceptance criteria set at the time for release of PR5I Finished Product with the following exceptions:

- The (b) (4) which is a test for the European market, did not meet the acceptance criteria for lot (b) (4) at 36-month time-point and for lot (b) (4) at the 48-month time-point but passed at all other time-points for both lots.
- The results for the (b) (4) are as follows:
 - Lot (b) (4) passed at all time-points (0, 18, 36, 42, 48 months) with repeat tests at 36 and 48 months.
 - Lot (b) (4) passed at all time-points, except for an OOS result at 42 months.
 - Lot (b) (4) passed at all time-points with a repeat test at 42 months.

- Lot (b) (4) passed at all time-points with a repeat test at 36 months.
- The D-antigen (b) (4) Assay was not used until the (b) (4)-month time-point for lot (b) (4) from the (b) (4)-month time-point for lots (b) (4) and (b) (4) and from the (b) (4)-month time-point for lot (b) (4) as the company was in the process of replacing the (b) (4) method with the (b) (4) method. [See section 3.2.4 *Manufacturing Process Development* for details on the change from the D-Antigen (b) (4) method to the (b) (4) method.]

The (b) (4)

were performed as part of the development process of PR5I. (b) (4)

These tests will not be part of the routine monitoring of commercial lots.

Conclusion

The results for the stability-indicating parameters support the stability of PR5I Finished Product in the 2.0-mL (b) (4) glass single-dose vial, (b) (4) stopper and 13-mm aluminum seal with plastic flip-off cap for 42 months at 2 to 8°C.

3.8.2 Routine Stability Monitoring

Each year the PR5I vaccine is filled, at least (b) (4) lots of PR5I vaccine marketed presentation will be placed in the stability program for at least three years. The commitment to place (b) (4) lots rather than one in the stability program was updated on 15 September 2015, SN20. 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. PR5I FBP lots will not be placed in stability routinely.

The initiation date for the routine monitoring studies (i.e., stability time-point zero) is the date of formulation of the FBP. The proposed shelf-life of PR5I Vaccine is 42 months from the date of FBP formulation (b) (4) Finished Product does not exceed 42 months).

The samples for this stability program will be tested at time points 0, 12, 24 and 36 and 42 months (from the date of formulation) while stored at 2°C to 8°C. Refer to Table 22 for an outline of the annual stability study design.

Table 22: Stability Study Design for PR5I Finished Product

Test Parameters	Shelf-life Acceptance Criteria	Test Intervals*				
		Storage Conditions: 2°C to 8°C				
		0	12 m	24 m	36 m	42 m
Diphtheria Potency	≥ 2 units/mL Diphtheria antitoxin	x (b) (4)	x	x	x	x
Tetanus Potency	≥ 2 units/mL Tetanus antitoxin	x (b) (4)	x	x	x	x

Acellular Pertussis Potency	1st Stage ^{(b) (4)} animals): PT (GMU): (b) (4) Responders FHA (GMU): (b) (4) Responders PRN (GMU): (b) (4) Responders FIM (GMU) (b) (4) Responders 2nd Stage ^{(b) (4)} animals): PT (GMU): (b) (4) Responders FHA (GMU): (b) (4) Responders PRN (GMU): (b) (4) Responders FIM (GMU): (b) (4) Responders	x ^{(b) (4)}	x	x	x	x
IPV Potency						
D-antigen ^{(b) (4)}	Type 1: (b) (4)	x ^{(b) (4)}	x	x	x	x
	Type 2: (b) (4)	x ^{(b) (4)}	x	x	x	x
	Type 3: (b) (4)	x ^{(b) (4)}	x	x	x	x
Immunogenicity IPV (Rat)	Type 1: Relative potency ^{(b) (4)}	x ^{(b) (4)}	x	x	x	x
	Type 2: Relative potency ^{(b) (4)}	x ^{(b) (4)}	x	x	x	x
	Type 3: Relative potency ^{(b) (4)}	x ^{(b) (4)}	x	x	x	x
^{(b) (4)}	(b) (4)	x (FP)	x	x	x	x
Physical Appearance	Uniform, cloudy, white to off-white suspension	x (FP)	x	x	x	x
Sterility	No microbial growth	x (FP)	-	-	-	-
(b) (4)	(b) (4)	x ^{(b) (4)}	x	x	x	x
(b) (4)	(b) (4)	x ^{(b) (4)}	x	x	x	x
(b) (4)	(b) (4)	x ^{(b) (4)}	x	x	x	x
PRP Content	(b) (4)	x ^{(b) (4)}	x	x	x	x
HBsAg IVRP	(b) (4)	x ^{(b) (4)}	x	x	x	x
(b) (4)	(b) (4)	x ^{(b) (4)}	x	x	x	x
Specific Toxicity	(b) (4)	x ^{(b) (4)}	x	x	x	x
Container Closure Integrity	The container closure integrity is maintained if the response for the ^{(b) (4)} test samples is less than that of the positive control reference	-	x	x	x	x

* (b) (4)

† The zero month time-point testing results are a combination of (b) (4) Filled Product test results. The stage at which each test is performed is identified as (b) (4) Filled Product.

Conclusion

The proposed routine monitoring is acceptable. An IR was issued to request that acceptance criteria be included in the proposed stability protocols for routine monitoring of commercial lots and for protocols with updated acceptance criteria. An updated stability study protocol with acceptance criteria was submitted on 15 September 2015, SN 20. [See section 4 *Information Requests*, IR of 19 June 2015, Question 3 and IR of 2 September 2015.]

4.0 Information Requests (IRs)

The information in this section pertains to IRs for the DP, but does not include IRs pertaining to potency and safety tests performed for release of (b) (4) Filled Product for each of the active components.

The questions issued to the sponsor are presented below in bold. In the questions, all section references are to the sections in the BLA. A summary of the responses from the sponsor follows each question. In the responses, the sections that refer to the BLA are identified as such and all other references are to sections in this memo.

4.1 Information Request emailed on 17 February 2015

- **On 18 March 2015 (SN 5) the sponsor submitted responses to the two questions in the IR. Responses to both questions are summarized below.**

Questions 1

The following request pertains to Pentacel. Please provide:

- Blank certificates of analysis (COAs) for final formulated bulks and final containers of Pentacel (DTaP-IPV and Hib bulks and final containers and reconstituted product)**
- Stability protocol for Pentacel.**

Response 1a

The blank certificates of analysis for DTaP-IPV FBP, Filled Product and Labeled Filled Product were provided. Of note, there is not a blank certificate of analysis for the Pentacel reconstituted product as the tests performed at that stage are not conducted for release but rather for stability monitoring.

Response 1b

(b) (4) of DTaP-IPV Vaccine Finished Product, a component of DTaP-IPV//Hib Vaccine, is monitored per year as part of the company's routine stability monitoring program with storage at 2°C to 8°C and testing at 0, 12, 24, and (b) (4) months. The company also performs a routine stability study on the reconstituted product (DTaP-IPV Vaccine used to reconstitute PRP-T Vaccine to form DTaP-IPV/Hib Vaccine). The sample for this stability program is tested at time 0, 12, 24 and (b) (4) months while stored at 2°C to 8°C.

Conclusion: The COA and protocol for routine stability monitoring of Pentacel were requested for comparison with the testing proposed for PR5I. The response is adequate.

Question 2

We acknowledge that PR5I trade-name does not contain PRT-T, however, please provide the following information pertaining to ActHib:

- a. Blank certificates of analysis (COAs) for final formulated bulks and final containers of ActHIB.
- b. Stability protocol for Act-Hib

Response 2a

The blank certificate of analysis for Act-Hib FBP and Filled Product were provided.

Response 2b

(b) (4) of Act-Hib Finished Product is monitored per year as part of the company's routine stability monitoring program with storage at 2°C to 8°C and testing at 0, 12, 24, and (b) (4) months.

Conclusion: The COA and protocol for routine stability monitoring of Act-Hib were requested for comparison with the testing proposed for the PRP-OMPC component of PR5I. The response is adequate.

4.2 Information Request emailed on 20 March 2015

- On 20 April 2015 (SN 7) the sponsor submitted responses to all ten questions in the IR. Questions 1 to 3 pertaining to the DP are summarized below.

Question 1

Regarding tests performed on (b) (4) final Filled Product:

- For each release test performed on (b) (4) Filled Product lots, please provide a description of procedures for the retesting of samples (and replacement of results if applicable). Given this information should be included in the standard operating procedure (SOP) for each test, you may submit the SOPs for all tests if more convenient.

Response 1

The analytical procedures which contain retesting provisions if the results do not meet the acceptance criteria were provided for the following tests: IPV immunogenicity, Acellular Pertussis Immunogenicity, (b) (4) Diphtheria Potency, Tetanus Potency, Pyrogen, and the General Safety, together with a brief description of the retesting provisions. If the acceptance criteria are not met after the retesting procedures are completed an investigation is performed following the SOP for OOS test results.

Other analytical procedures containing validity criteria which allow for repeat testing (but do not have provisions for retesting) include: Aluminum Content, Formaldehyde, (b) (4) PRP Content, HBsAg IVRP, D-Antigen Content and Specific Toxicity.

The tests which do not allow for retests and do not contain validity criteria include Sterility, (b) (4) Physical Appearance, and Extractable Volume. For all tests, if the results do not meet the acceptance criteria after the allowed retests have been completed (when permitted by the SOP), an investigation is performed following the SOP for OOS test results.

Conclusion: The response is acceptable.

Question 2

Please provide the calculated amount for each of the aluminum adjuvants contained in the vaccine (aluminum phosphate and amorphous aluminum hydroxyphosphate sulfate) and show how these amounts were calculated.

Response 2

(b) (4)

[REDACTED]

Conclusion: The response is acceptable. PR5I contains (b) (4) AlPO₄/dose and (b) (4) AAHS/dose

Question 3

Regarding the vaccine residual components:

- a. Please provide a brief description of the manufacturing step in which each of the following components is generated or used: yeast protein, bovine serum albumin, thiocyanate, formaldehyde, glutaraldehyde, neomycin, polymyxin B, streptomycin, and (b) (4)
- b. For all components, except formaldehyde and (b) (4) which are tested for release of (b) (4), please provide the calculated amounts and show how these amounts were calculated.
- c. Please provide information on any other residual components not included in the above list (comment #3a).
- d. Please confirm that (b) (4) and polysorbate 80 (contained in Pentacel) are not used in any of the (b) (4) manufacturing processes.

Response 3a

A brief description of the manufacturing step in which each of the residual components is generated or used in DS production was provided. The sponsor clarified that sucrose (which is present in Pentacel) is not listed as a residual component, as it is not generated or used in any parts of the manufacturing process for PR5I.

Response 3b

The calculated amount for each of the components listed in Question 3a and how each amount was calculated was provided. The maximum calculated amount per unit dose (0.5 mL) concurs with the amounts listed in the *Description* section of the (b) (4) label for residual components.

Response 3c

No additional residual components are used in the production of PR5I to those presented in Question 3a. The identified (b) (4) residuals include (1) those with sensitizing potential (e.g., yeast protein, Bovine Serum Albumin), (2) antibiotics (e.g., neomycin, polymyxin B, and streptomycin), (3) inactivation/detoxifying residuals (e.g., formaldehyde and glutaraldehyde), and (4) other process residuals associated with the (b) (4) manufacturing process (e.g., thiocyanate).

Response 3d

The sponsor confirmed that no (b) (4) is used in any of the manufacturing processes for the drug substances or the PR5I DP.

Polysorbate 80 ((b) (4) origin) is used in the manufacturing process for (b) (4). This (b) (4) origin Polysorbate 80 was approved on 03 April 2015 for Pentacel (STN BL 125145/321 Change in the source of Polysorbate 80 from (b) (4)).

Conclusion: The responses to questions 3.a and 3.b are acceptable. The response to questions 3.c contradicts 3.d because in the response to 3.d the sponsor confirmed that Polysorbate 80 is used in the manufacture of the (b) (4); however, in the response to 3.c the sponsor did not mention Polysorbate 80. As such it should be included in in Table 2: Residual Components of PR5I Drug Product [with amount per unit dose (0.5 mL)] as well as in the (b) (4) label.

As follow-up to the response to question 3.d submitted on 20 April 15, we asked the sponsor to include Polysorbate 80 and its amount per unit dose (0.5 mL) in Table 2: Residual Components of PR5I Drug Product. [See IR of 19 June 2015, Question 4]

4.3 Information Request emailed on 10 April 2015

- **On 27 May 2015 (SN 9) the sponsor submitted responses to all 6 questions in the IR. Responses to questions 1-3 pertaining to the DP are summarized below.**

Question 1

In sections 3.2.P.2.4 Container Closure System (page 3 of 14), you state that “equivalent container closure systems (b) (4), glass, bromobutyl stopper), as described for PR5I, are used for other licensed Sanofi Pasteur Limited combination vaccines and were proven to be suitable for the purpose of formulation of Final Bulk Product and storage of Final Bulk Product and Filled Product.” Please provide the names of the licensed vaccines that are stored in the same types of (b) (4) and filled in the same 2-mL glass containers with bromobutyl stoppers. For these licensed products, please include the duration and conditions of the hold times for each Final Bulk Product and approved shelf life for each Filled Product and specify if there are any differences in the preparation (e.g., wash and sterilization) of the primary packaging components (glass vials and stoppers) compared to Pentacel (DTaP-IPV component) or other licensed vaccines.

Response 1

The licensed vaccines for which the FBP is stored at (b) (4) in (b) (4) and the Filled Product is filled in 2-mL glass vials with (b) (4) bromobutyl stoppers and stored at 2°C to 8°C are shown in Table 23. There are no differences in the preparation (e.g., washing and sterilization) of the primary packaging components (vials and stoppers) of the vaccines listed in the table and PR5I.

Table 23: List of Licensed Vaccines Using the Same Container Closures for PR5I as for other SPL Products

Vaccine Name	Final Bulk Product Hold Time at (b) (4)	Vaccine Shelf-Life at 2 to 8 °C
DTaP-IPV component of DTaP-IPV/Hib (Pentacel®)	(b) (4) from the date of FBP formulation	36 months
DTaP-IPV (Quadracel™)		36 months
Tdap (Adacel®)		(b) (4) months
Td Adsorbed (TENIVAC™)		(b) (4) months
DTaP-IPV-Hib (PEDIACEL®)*		(b) (4) months

* This vaccine is not licensed in US but it is licensed in Canada and other countries.

Conclusion: The response is adequate and serves to further support the use of these container closure systems for PR5I especially for the storage of FBP for which the stability studies were conducted in a (b) (4) container made of the same construction material as the (b) (4) where the FBP will be stored for up to (b) (4) .

Question 2

Regarding the filling step, please confirm that the filling into the 2-mL glass vials is conducted by transferring Final Bulk Product directly from the (b) (4)

Response 2

(b) (4)

Conclusion: The response is adequate.

Question 3

In your amendment of September 12, 2014 you proposed a 42-month shelf life for (b) (4) and you included stability data for up to the 42-month time point for all stability indicating parameters. Please provide pending results for all stability tests performed at the 48-month time point.

Response 3

The sponsor noted that the updated stability data were compiled and would be provided as part of the response to the IR letter dated 17 April 2015. [See IR of 17 April 2015, Question 18 and IR of 2 September 2015.]

4.4 Information Request emailed on 17 April 2015

- On 28 May 2015 (sequence # 10) the sponsor submitted responses to questions 1, 3, 12, 15, 16, 17, 18, 19, 21, 22, and 23 of the 23 questions in the IR. Responses to questions pertaining to the DP are summarized below.

Question 12

In Section 3.2.P.5.3, you provide a summary of the validation for (b) (4) Identity Test for Labeled Filled Product. The information provided is not sufficient to support test specificity. Please provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results.

Response 12

The specificity of the method was demonstrated by (b) (4)

[Redacted]

[Redacted]

The method was validated for its intended purpose as an identity test for PR5I.

Conclusion: The response is adequate.

Question 15

In Section 3.2.P.8, you provide stability data for PR5I Final Bulk Product to support your proposed expiry of (b) (4). These studies were performed in (b) (4) used in routine manufacturing.

(b) (4)

[Redacted]

(b) (4)

[Redacted text block containing multiple paragraphs of information, all obscured by grey bars.]

Question 16

The stability information for the Filled Product in Section 3.2.P.8 was updated (amendment of September 12, 2014) with stability data for up-to the 48 month time-point and a request to extend the shelf life of PR5I from 36 to 42 months. However, the amendment did not include an updated

post-approval stability protocol and commitment for the 42-month shelf life. Please provide this information.

Response 16

The post-approval stability protocol was updated in section 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment* of the BLA to include the 42 month time-point. A revised version is provided with the response. This section of the BLA was also revised to include an updated *Accelerated Stability Study Protocol*.

Conclusion: The response is adequate.

Question 17

In Section 3.2.P.8.2, you provide your post approval stability commitment to place (b) (4) of PR5I on stability each year it is filled. Please revise section 3 of the Post-Approval Stability Protocol and Stability Commitment to provide detailed procedures on the post approval stability program, specifically, the procedures for handling the (b) (4) testing on the Final Bulk Product and testing at the 12, 24, 36 and 42-month time-points on the Filled Product. We note that Table 4 shows part of this information for the time (b) (4) testing and in the related footnote. Please describe these procedures in the text.

Response 17

Subsection 3 in BLA section 3.2.P.8.2 *Post-Approval Stability Protocol and Stability Commitment* was update to include additional information on the procedures for the (b) (4) time-point and 12, 24, 36 and 42-month time points. (b) (4)

Conclusion: The response is adequate.

Question 18

In Section 3.2.P.8.3 of the 12 September 2014 amendment, you provide stability data for PR5I Filled Product to support your proposed expiry of 42 months at 2-8 °C. The 30-month time-point for Lot (b) (4) is listed as pending for (b) (4) PRP-OMPC, PRP Content, and (b) (4) PRP-OMPC. Please submit these data.

Response 18

Complete stability data up to and including the 48-month time-point were provided for lots (b) (4) . This response also addresses Question 3 of the IR of 10 April 2015. [Final stability data and stability commitment were submitted on 15 September 2015, SN20.]

Conclusion: The response is adequate.

Question 19

Section 3.2.P.5.1, Table 5 - Release Specification for PR5I Labeled Filled Product lists two alternative tests for identity of the HBsAg and OMPC components ((b) (4)). Please clarify when each method will be used. In addition, we note that no identity testing is proposed for the other vaccine components (DTaP and IPV), but that such testing was performed on consistency

lots (b) (4)). Please specify which tests are performed to confirm the identity of the DTaP and IPV components in the Final Drug Product or Labeled Filled Product and modify the specifications for the Final Drug Product or Filled Product and the Lot Release Protocol as applicable.

Response 19

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. BLA section 3.2.P.5.1 *Specifications* was updated to include a statement regarding the use of the alternate (b) (4) tests.

For commercial release of the Labeled Filled Product, the identity testing strategy is to differentiate PR5I from other products labeled on site. The identification test will test for the presence of HBsAg as well as the OMPC components. These antigens are distinct and present only in PR5I, thereby distinguishing the PR5I product from other labeled products manufactured at SPL. The differentiation identification strategy is consistent with the identification strategy for currently licensed products manufactured at SPL [e.g., Pentacel® (DTaP-IPV/Hib), DAPTACEL® (DTaP), Adacel® (Tdap), TENIVAC™ (Td)].

Conclusion: The response is adequate.

Question 22

In Section 3.2.P.5.4, you have provided a Certificate of Analysis for Final Bulk Product Lots (b) (4) . We note that you have provided (b) (4) data for each of these lots on a sample dispensed following the (b) (4) . We also note that this test was not listed in the Specification Table (Table 1 of Section 3.2.P.5.1). Please confirm that you are still performing this test for release. We request that this test be performed on all commercial lots and that the results are reported on the Lot Release Protocol.

Response 22

(b) (4)

[Redacted]

[Redacted]

Conclusion: See comment in response to Question 23.

Question 23

In Section 3.2.P.5.1, you provide a list of release specifications for PR5I Final Bulk Product, Filled Product, and Labeled Filled Product. We note that you plan on performing the Pyrogen test on

Filled Product. We request that you add an Endotoxin test for release of PR5I (b) (4) Product. Please set your endotoxin specification to reflect manufacturing data. The presence of both a Pyrogen test and an Endotoxin test will provide assurance for both safety and consistency of manufacture.

Response 23

Endotoxin testing using the (b) (4) method is performed at various stages during the manufacturing process to provide assurance of safety and manufacturing consistency as follows:

- (b) (4)

(b) (4)

(b) (4)

Conclusion: The in-process endotoxin testing of (b) (4) is adequate. However, on 27 June 2015 we sent a follow-up communication requesting that Filled Product be tested for endotoxin prior to release for additional assurance of product safety. [See IR of 27 June 2015, Question 4]

- **On 5 June 2015 (SN 11) the sponsor submitted responses to questions 2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14 and 20, in the IR of 17 April 2015 that had not been addressed in the 28 May 2015 amendment. Responses to questions pertaining to the DP are summarized below.**

Question 2

In Section 3.2.P.2.4, you provide extractable-leachable data on studies performed on the (b) (4) stopper that will be used in the final container. The information provided is not sufficient.

- Please include your results for both extractable and leachable studies in both µg/dose and ppm.**
- You have included a list of potential extractable compounds that were provided by the stopper manufacturer. You have also included lists of potential extractable compounds for**

each of the three extractable studies performed. Please provide your rationale for the selection of the specific compounds tested in the leachable study that was conducted during storage of vaccine in the final containers. Please provide your justification for why all the compounds listed as potential extractables by the stopper manufacturer and from your three extractable studies were not included in the leachable study. Please provide a detailed assessment as to why (b) (4) was not evaluated during your leachable study.

- c. Please provide details on the procedures used in your evaluation of leachables including test methods and validation.
- d. Please provide the complete data for the leachable study to include all time points (0, 15, and 36 months). Please provide an assessment if any trends are noted.
- e. Please provide an assessment about any potential leachables released from the in- process equipment and containers used for vaccine production.
- f. You have only provided a toxicological assessment on (b) (4). Please provide a risk assessment of the impact of leachables on product quality and safety including potential interaction of leachables with vaccine components as well as a safety assessment based on (b) (4) impurity limits or established thresholds of toxicological concern for parenteral drug products for all leachables.
- g. You state that (b) (4) was detected in the Tdap-IPV Vaccine at a concentration of (b) (4) µg/dose at the 15-month time-point and at a concentration of (b) (4) µg/dose at the 36-month time-point. Please provide the concentration of (b) (4) at the time zero time-point. Please provide your investigation into what specific compound the (b) (4) is from and your assessment of any potential reaction of the (b) (4) containing compound with your product. Please provide your assessment that the (b) (4) is not resulting in the (b) (4) reacting with product to have a detrimental effect on product quality.
- h. You have performed the leachable study on a different combination vaccine. We do not concur with this approach. Please commit to provide leachable data on PR5I for the proposed shelf-life post approval.

Response 2

Since the submission of the BLA for PR5I, SPL performed new leachables studies using the PR5I vial presentation, to complement the previously provided historical studies using Tdap-IPV. BLA section 3.2.P.2.4 Container Closure System was updated to replace the historical study results obtained using Tdap-IPV Vaccine with the results of the new leachables studies obtained using PR5I Vaccine which include the toxicological assessment of the detected compounds. Both, the historical studies and the new studies concluded that all potential leachables were below the acceptable safety threshold and unlikely to pose a risk to human safety. The responses provided below refer to the new leachable studies using PR5I vial presentation.

Response 2a

The leachables simulation study data in the revised BLA section 3.2.P.2.4 *Container Closure System*, Table 5 to Table 11 of the submission, include the laboratory results as well as the amount per dose of PR5I Vaccine, expressed in ppm, ppb and µg/dose.

Response 2b

The new PR5I leachables simulation studies used analytical techniques capable of detecting all listed potential compounds with the exception of (b) (4). These two components were addressed in the revised BLA section 3.2.P.2.4 *Container Closure System*, subsection 3.1.3.

Response 2c

The company designed and executed the leachable studies based on recommendations by the (b) (4) and the approach was described as follows. The initial phase of the leachables assessment was (b) (4)

The next phase was the leachables stability study which (b) (4)

Based on the toxicological assessment for the leachable simulation study no test method validation is required based on recommendation by the (b) (4) (mentioned above).

Response 2d

As stated in response 2c, the company commits to complete leachable stability studies throughout the shelf-life of PR5I in the vial presentation, where leachables will be monitored for any trends. The company provided a Leachable Study using PR5I samples that are 48 months (b) (4) in the revised 3.2.P.2.4 *Container Closure System* section of the BLA.

Response 2e

For PR5I DP the two main materials used for the container closure systems are (b) (4) for the FBP (b) (4) and glass vial for the Filled Product. These materials were selected as they are inert material that do not interact with aqueous suspensions (such as PR5I), can be cleaned and sterilized and offer suitable protection to the product transportation and storage. There are no other containers (b) (4) glass vials used for PR5I formulation and filling.

Responses 2f and 2g

Since the submission of the BLA for PR5I, the sponsor performed new leachable studies on the PR5I vial presentation which include the analysis of (b) (4) BLA section 3.2.P.2.4 *Container Closure System* was updated to replace the Tdap-IPV leachable results with the results of the PR5I leachables studies which include the toxicological assessment of the detected compounds.

Response 2h

Please see introductory paragraph in response to Question 2 and the response to Question 2d.

Conclusion: The responses to questions 2a to 2h are adequate.

Question 4

In Section 3.2.P.5.6, you provide justification for a (b) (4) specification of (b) (4). The proposed acceptance criterion is based on the 2-sided 99/99 tolerance interval accounting for assay and lot-to-lot variability calculated using the release and stability monitoring data. We do not concur with your proposal. We request that the specifications be set using the tolerance intervals with 99% coverage and 95% confidence, which is the level of confidence usually accepted when tolerance intervals are used to set product specifications. In addition, we request that only release data be used to calculate the specification.

Response 4

(b) (4)



Conclusion: The response is adequate. However, members of the review team requested that the (b) (4) stability specification be the same as the release specification because of a lack of data showing an (b) (4) values during storage of Filled Product. [See IR of 27 June 2015, Question 2]

Question 8

In Section 3.2.P.5.6, you provide justification for the (b) (4) release specification of (b) (4). This specification is based on a 99/99 tolerance interval. A tolerance interval with 95% confidence and 99% coverage is normally accepted provided the number of lots is not too small. Since you have only (b) (4) data points ((b) (4) final lots), using a tolerance interval approach would result in an unacceptably (b) (4). Therefore, we request that you set the (b) (4).

Response 8

(b) (4)



with an acceptance criterion of (b) (4). Sections 3.2.P.5.1 *Specifications* and 3.2.P.5.6 *Justification of Specifications* of the BLA were updated to reflect this change.

Due to the relatively small amount of data available, the company commits (b) (4)

Conclusion: The response is adequate.

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.

Response 20

The company agrees to comply with CBER’s request that a specification for the Formaldehyde test be established such that it is reflective of the capacity of the manufacturing process to remove formaldehyde, and that the actual result of the test be reported in the COA 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 provided to CBER with the updated method by August 2016.

Conclusion: The response is adequate.

Follow-up Action Required: We will need to follow-up on the submission of this information when the CR comments are addressed or as a PMC after the BLA is approved.

4.5 Information Request emailed on 19 June 2015

- On 21 August 2015 (SN 15) the sponsor submitted responses to questions 1 to 3 and 5 of the IR. Questions 3 and 5 pertaining to the DP are summarized below.

Questions 3

The following comment pertains to the stability information provided on 28 May 2015 (SN10):

- **The stability protocol for routine commercial monitoring of the PR5I vaccine provided in Section 3.2.P.8.2 - Post-approval Stability Protocol and Stability Commitment, Table 4 does not include the acceptance criteria for the stability tests. Please include the acceptance criteria for each test in Table 4.**

Response 3

The sponsor clarified that they would be updating Table 4 of BLA section 3.2.P.8.2 *Post-approval Stability Protocol and Stability Commitment* to reflect the acceptance criteria for each of the stability

tests. The revised section will be submitted with the response to the IR letter dated 27 July 2015 which requested further changes to the stability specifications.

Conclusion: The information requested in question 3 was submitted on 15 September 2015 (SN20) in response to the IR of 2 September 2015.

Question 5

The following comment pertains to the validation of quality control tests:

- For all non-compendial tests performed for PR5I Final Bulk Product and Filled Product release and stability please identify the following:
 - a. The laboratory sites where these tests will be performed.
 - b. The laboratory sites where validation of these tests was performed

Response 5a

All tests (compendial and non-compendial) to be performed for commercial release and/or stability of PR5I FBP and Filled Product will be conducted at SPL, Toronto, Canada.

Response 5b

The validation sites for all non-compendial tests performed for PR5I (b) (4) Filled Product for release and/or stability were provided. Method transfers to SPL were conducted for the following tests (performed on the (b) (4) which were validated at Merck & Co. Inc.:

- (b) (4)
- HBsAg IVRP
- (b) (4)
- (b) (4)
- PRP Content

A method transfer to SPL was performed for the container closure integrity test ((b) (4) method) which was validated at Sanofi Pasteur Inc. In the original BLA, section 3.2.P.2.5 *Microbiological Attributes* inadvertently stated that Sanofi Pasteur SA was the site of method validation for the container closure integrity test ((b) (4) method). The correct validation site for the test is Sanofi Pasteur Inc.

Conclusion: The response is adequate.

- On 1 September 2015 (SN 18) the sponsor submitted a response to question 4 of the IR of 19 June 2015.

Question 4

The following comment pertains to the impurities in the PR5I vaccine:

- We note that (b) (4) and Polysorbate 80 were not included in the list of impurities for the PR5I vaccine (Section 3.2.P.5.5 - Characterization of Impurities, Table 1) and were not mentioned in the response to Question 3 in your submission of 20 April 2015 (SN 7). Please update Table 1 to include these and any other impurities from the manufacturing process. For the (b) (4) and Polysorbate 80 please clarify if the amounts of these residual components are tested on the Drug Substance. Please provide the amounts of these impurities in the Final Bulk Product and show how these amounts are calculated.

Response 4

SPL conducted a further assessment 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 (b) (4). The calculated amount of Polysorbate 80 in PR5I is estimated at less than 0.0056%. The amount of (b) (4) was not provided but the sponsor performed characterization studies demonstrating consistent elimination to a very low level. The characterization of impurities in the (b) (4) DP section of the BLA was updated to include this information as well as the calculated amount of Polysorbate 80.

(b) (4)

Conclusion: The response is adequate. During future review of the BLA (when MCM responds to CBER's CR letter) we should ask the sponsor to include (b) (4) in Table 1 (BLA section 3.2.P.5.5 *Characterization of Impurities*).

4.6 Information Request emailed on 27 July 2015

- On 15 September 2015 (SN 20) the sponsor submitted responses to all questions in the IR. Questions 1, 2, and 4 pertaining to the DP are summarized below.

Question 1

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

Response 1

SPL committed to perform a post-approval bulk stability study on (b) (4). The stability data will be submitted to CBER when available.

Conclusion: The response is adequate.

Follow-up Action Required: We will need to follow-up on the submission of this information when the CR comments are addressed or as a PMC after the BLA is approved.

Question 2

In your response to Question 4 of the IR dated 17 April 2015, you propose a (b) (4) specification of (b) (4) for release and (b) (4) for stability. You propose two sets of specifications based on an (b) (4) trending that you have observed over time. The stability data presented do not support an (b) (4) trending for (b) (4). Your proposed stability specification is based on statistical analysis of (b) (4) test results from stability monitoring up to and including the 42-month time-point. We do not

concur with your proposed stability specification. Please revise your stability specification for (b) (4) to be the same as that proposed for your release specification.

Response 2

SPL re-assessed the (b) (4) specifications based on a data set consisting of (b) (4) results at release from (b) (4) PR5I (b) (4) lots and their respective filled presentations lots (vials (b) (4)). For the analysis, the suggested 95/99 tolerance interval was applied. The (b) (4) was calculated to be (b) (4) and the standard deviation was determined to be (b) (4) with a proposed acceptance criterion of (b) (4) for release and for stability monitoring.

Conclusion: The response is adequate.

Question 4

In your response to Question 23 of the IR dated 17 April 2015, you state that it is the company's position that (b) (4) testing is not required on the PR5I (b) (4) since (b) (4) testing is performed at various stages of manufacturing and pyrogen testing is conducted on the PR5I Filled Product. We note that you reference the PR5I End of Phase 2 / Pre-Phase 3 CMC Meeting of 28 March 2007 in which we recommended that you evaluate pyrogenicity at release and expiry and endotoxin content at intermediate time-points. Please note that these recommendations were in response to your proposed Phase III release and stability testing plan. The pyrogen test and endotoxin test will both provide assurance of safety and consistency of manufacture since (b) (4) is known to be associated with the (b) (4) component of your vaccine. Therefore, we ask that you please add an endotoxin test for both release and stability testing of PR5I Filled Product and include an endotoxin specification to reflect manufacturing data. Alternatively, please commit to add this test post approval.

Response 4

(b) (4)



Conclusion: The response is adequate.

4.7 Information Request emailed on 2 September 2015

- On 15 September 2015 (SN 20) the sponsor submitted responses to the question in the IR as summarized below.

Question

The release and stability monitoring acceptance criteria for several tests have been revised during the course of the review of the application. Therefore, we request that you revise section 3.2.P.5.1 *Specifications* to include a summary of all specification changes and update the table in this section as appropriate. Similarly, please updated section 3.2.P.8.2 *Post-approval Stability Protocol and Stability Commitment* to include updated acceptance criteria in Table 4, as requested in our email of June 19, 2015, comment 3.

Response

BLA sections 3.2.P.5.1 *Specifications* and 3.2.P.8.2 *Post-approval Stability Protocol and Stability Commitment* were updated as requested to include all the changes that were revised during the review process. These changes were incorporated in the relevant sections of this memo.

Conclusion: The response is adequate.

5.0 CMC Post Marketing Commitments

During review of the BLA the sponsor agreed to the PMCs listed below. Given the BLA will not be approved the PMC-related information may be submitted in future amendments when the CR comments are addressed.

- 1. An IR was emailed on 17 April 2015 (Questions 20). The sponsor 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:

SPL 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.]

2. An IR was emailed on 27 June 2015 (Question 1). The sponsor 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 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 Final Bulk Product. Alternatively, please commit to provide these data post approval.

Response

The company committed to perform (b) (4)

6.0 Administrative CMC-related Information

Unique Ingredient Identifier (UNII) Codes

The UNII codes for the viral components were confirmed. The UNII codes for the PR5I ingredients were emailed to the sponsor on 19 March 2015.

Components Table

The components tables for the PR5I DP prepared by the CBER IOD will be reviewed when the amendment addressing the CBER CR comments is submitted by the sponsor.

Lot Release Protocol (LRP)

Comments on the LRP for the testing of the viral components were provided by product reviewers to Karen Campbell of OCBQ/DBSQC. An IR for the PR5I LRP was emailed to the sponsor on 18 June 2015 and responses and revisions to the LRP were submitted on 6 and 16 October 2015.

Labeling

I reviewed the *Description* and *How Supplied* Sections of the package insert and provided comments to the labeling review group. These comments included input from Juan Arciniega for the pertussis component and Steven Rubin for the poliovirus component.

Product Exclusivity

A request for product exclusivity was included in the original BLA submission. To assist on the exclusivity determination a product exclusivity memo was drafted by Katie Rivers, DVRPA, and Sara Gagneten to assist with the exclusivity determination.