



Department of Health and Human Services
 Public Health Service
 Food and Drug Administration
 Center for Biologics Evaluation and Research

Memorandum

DATE: OCTOBER 20, 2015

FROM: Diana Kouivaskaia, CMC reviewer, DVP

TO: The file STN **125563/0.0**

THROUGH: Steven Rubin, DVP

COPY: Robin Levis, DVP
 Sara Gagnetten, DVP
 Kelsy Hoffmann, RPM
 Katie Rivers, RPM

STN: **125563/0.0 and Amendments**

SPONSOR: MCM Vaccine Company

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) also referred to as PR5I)

SUBJECT: Review of poliovirus (Vero IPV) component of the PR5I ((b) (4) vaccine CMC

Reviewer’s notes and comments are in *Italic font*.

TABLE OF CONTENTS:

Executive summary..... 4

Conclusion 5

PR5I DRUG PRODUCT SUMMARY..... 5

FACILITIES AND EQUIPMENT 6

DRUG SUBSTANCE: Inactivated Vero Trivalent Poliovaccine Bulk..... 6

 Structure..... 6

 Specification of the IPV Trivalent Concentrate..... 7

 Overview of manufacture of PR5I IPV Trivalent Concentrate 8

Cell Banking and Viral Seed Lot System (Approved Under IPOL License)	8
CONTROL OF MATERIALS.....	10
ADVENTITIOUS AGENTS SAFETY EVALUATION FOR THE DRUG SUBSTANCE (3.2.A.2)	11
Summary of DS manufacturing process and controls.....	12
Controls of Critical Steps for Manufacturing Process of IPV Trivalent Concentrate	13
Intermediate products specifications.....	14
Intermediate products Stability.....	14
Comparison of (b) (4) methods used for quantitation of IPV DU-content in IPV (b) (4) products and Final Vaccine (b) (4) products.....	14
Control of Drug Substance.....	15
PROCESS VALIDATION AND/OR EVALUATION	16
From Cell culture to Monovalent.....	16
Additional Validation of the (b) (4) following Change of (b) (4) Support.....	16
Change Of (b) (4) Source from (b) (4) :	16
Validation of the Trivalent Concentrate	17
Batch Analyses (IPV Trivalent Concentrate)	17
DRUG PRODUCT:	19
Description and composition of the Drug Product	19
Excipients.....	19
Description of Manufacturing Process and Process Controls.....	20
Controls of critical steps and intermediates	21
Batch Analyses (3.2.P.5.4).....	21
Process validation and evaluation: Formulation of Final Bulk product	21
Development of D-antigen Potency Test for IPV in PR5I (Section 2.2.4.2.2).....	22
Manufacturing Process Changes between Phase III Consistency Lots and Commercial Launch	24
Container Closure System (3.2.P.2.4).....	24
Description of manufacturing process and process controls (3.2.P.3.3).....	24
Controls of critical steps and intermediates	25
Process validation and/or evaluation	25
STABILITY (3.2.P.8)	26
Stability Summary (3.2.P.8.1).....	26
Post-Approval Stability Protocol and Stability Commitment (3.2.P.8.2).....	27

Final Bulk product	28
Stability of PR5I Finished Product	28
Stability Amendment 125563/0.2	30
ANALYTICAL TESTS AND VALIDATION	30
D-Antigen Content (by (b) (4) Method) Performed on the (b) (4) (3.2.S.4.2)	32
D-Antigen Content (by (b) (4) Method) –(b) (4) Product.....	33
Rat Immunogenicity Assay – (b) (4) Product	38
Lot Release Protocol:	42
PR5I Final Bulk Lot Release specifications:	42
DRUG SUBSTANCE (vIPV) RELEASE	44
Component information	47
INFORMATION REQUESTS AND RESPONSES:	48
Information Request of April 10, 2015.....	48
Information Request of June 19, 2015.....	55
Information Request of October 16, 2015.	57

EXECUTIVE SUMMARY

The original BLA STN 125563/0 was submitted by MCM (a partnership between Sanofi Pasteur Inc. and Merck & Co.) for the (b) (4) vaccine (referred to as PR5I in this memo), which is 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 vaccine was developed under IND14496, initially submitted 20 September 2010. PR5I is a sterile, liquid, preservative-free suspension presented as a single dose (0.5 ml) vial for intramuscular injection.

The vaccine is manufactured using modified and/or existing bulk intermediates from vaccines licensed in the US by Sanofi Pasteur and Merck. **This review is focused on the inactivated poliovirus (IPV) component of the vaccine only.**

Module 3 of the submission contains a description of the Drug Substance (DS), Drug Product (DP) and Finished Product manufacturing process, characterization of the product, in-process and quality controls applied to the process, manufacturing process development and validation, analytical methods and validations, and specifications and justification of specifications.

The IPV DS for PR5I is obtained as the “IPV Trivalent Concentrate” (b) (4)

[Redacted]

- | [Redacted]
- | [Redacted]
- | [Redacted]
- | [Redacted]

(b) (4)

CONCLUSION

I recommend approval of the PR5I vaccine, pending company's response to information request of October 16, 2015. The review team decided to CR the BLA. The response to this information request will be reviewed when the sponsor addresses the comments in CBER's CR letter and review of the BLA is resumed.

PR5I DRUG PRODUCT SUMMARY

PR5I is proposed as a vaccine for active immunization against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to *Haemophilus influenzae* type b (Hib), for use as a three-dose series in children from 6 weeks through 4 years of age (up to the 5th birthday).

- Proposed Name of the Drug Product: (b) (4)
- Drug Product manufactured by: Sanofi Pasteur Limited, Toronto Ontario Canada
- Presentation: Suspension for intramuscular injection in a single-dose vial.

PR5I is a hexavalent combination vaccine; composition of the vaccine is presented in the Table below.

Table: Composition of PR5I vaccine

Component	Amount on a per unit basis (0.5 ml)	Function
Haemophilus b conjugate (PRP-OMPC)	3 µg PRP covalently bound to 50 µg of OMPC	Active substance (Haemophilus type b immunization)
Hepatitis B surface Antigen (HBsAg)	10 µg	Active substance (Hepatitis B)
5-Component Acellular Pertussis 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)
Diphtheria Toxoid Adsorbed	15 Lf	Active substance (Diphtheria immunization)
Tetanus Toxoid Adsorbed	5 Lf	Active substance (Tetanus)
vIPV: - Type 1 (Mahoney) - Type 2 (MEF-1) - Type 3 (Saukett)	29 D-antigen Units 7 D-antigen Units 26 D-antigen Units D-antigens content is calculated using the (b) (4) test method.	Active substance (Poliomyelitis immunization)

Aluminum	319 µg	Adjuvant
Water for injection	qs 0.5 ml	Diluent

FACILITIES AND EQUIPMENT

The IPV Trivalent Concentrate is manufactured at the Sanofi Pasteur (b) (4), (b) (4) in the following locations:

- Cell culture, Viral culture, Purification, Inactivation, and Transfer of Monovalent Bulk, Monovalent Bulk storage: Building (b) (4) or Building (b) (4) solely dedicated to the manufacture of IPV Monovalent Bulk Types 1, 2, or 3;
- IPV Trivalent Concentrate: Building (b) (4), dedicated to (b) (4) activities of all Sanofi Pasteur inactivated vaccines intended for international markets manufactured at (b) (4) site.

PR5I Final Vaccine is formulated and filled at the Canadian facility, Sanofi Pasteur Limited, Toronto, Ontario in the following location:

- Formulation of Final Bulk Product - Building (b) (4) filling, inspection, labeling, and packaging occur in Building (b) (4)

DRUG SUBSTANCE: INACTIVATED VERO TRIVALENT POLIOVACCINE BULK

STRUCTURE

(b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

12 Pages determined to be not releasable: (b)(4)

DRUG PRODUCT:

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

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

Active ingredients of the vaccine include Haemophilus b conjugate (PRP-OMPC), 5-Component Acellular Pertussis adsorbed antigens (Pertussis Toxoid (PT), Filamentous Hemagglutinin (FHA), Pertactin (PRN), Fimbriae types 2 and 3 (FIM)), Hepatitis B surface Antigen (HBsAg), Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed, vIPV (Type 1 (Mahoney), Type 2 (MEF-1), Type 3 (Saukett)), and Aluminum (adjuvant). Please refer to Table “Composition of PR5I vaccine”, Section PR5I drug product summary on Page 5 of this review for the antigens’ doses.

The vaccine may contain the following materials from the manufacturing process:

Table: Residual components (impurities) in the PR5I vaccine.

Residual Components	Amount per unit dose (0.5 ml)	IPV-related
Yeast Protein	≤ 0.1 µg (Maximum 1.0% relative to HBsAg protein)	(b) (4)
Bovine Serum Albumin	≤ 50 ng	(b) (4)
Thiocyanate	≤ 0.125 µg as ammonium thiocyanate	(b) (4)
Formaldehyde	(b) (4)	(b) (4)
Glutaraldehyde	≤ 50 ng	(b) (4)
Neomycin	< 5 ng	(b) (4)
Polymyxin B	< 25 ng	(b) (4)
Streptomycin	< 200 ng	(b) (4)
Polysorbate 80	≤ 0.0056%	(b) (4)

EXCIPIENTS

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

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

Table: Excipients in PR5I vaccine

Excipients	Ingredients	Function
Amorphous Aluminum Hydroxyphosphate Sulfate	(b) (4)	Adjuvant
		Adjuvant

Aluminum Phosphate (b) (4)	(b) (4)	
(b) (4) Phosphate Solution		(b) (4)
WFI	WFI	Diluent
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

A brief description of the manufacturing process steps (formulation of Final Bulk product, filling and primary packaging) is provided below (based on Figure 1: PR5I Manufacturing Flowchart; page 6 of 25 in Section 2.3.P.3 Manufacture of the submission).

QC release tests on Final Bulk product (FBP):

(b) (4)

Final Bulk Product manufacture includes the following steps:

(b) (4)

In-process controls at different steps include:

(b) (4)

Batch Size: Target batch size is (b) (4) Final Bulk Product batch of (b) (4) may be filled in a total of (b) (4) vials and may correspond to one or several Filled product batches.

CONTROLS OF CRITICAL STEPS AND INTERMEDIATES

The following tests are performed at critical steps:

(b) (4)

BATCH ANALYSES (3.2.P.5.4)

(b) (4) production consistency lots: (b) (4) of PR5I vaccine Drug product were manufactured at the Toronto, Canada facility (Building (b) (4) at the manufacturing scale and filled into vials. A summary of the lots is shown below.

Table: Production consistency lots of PR5I

(b) (4)

The test specifications and acceptance criteria for release of production consistency lots were as per Process Validation Study (PV08-004).

Certificates of analysis and compliance were provided for the consistency lots (b) (4) Product and are not shown in this memo. All lots had passing results in the IPV rat immunogenicity test. The D-antigen content results were presented for only one lot ((b) (4) and all results were within acceptance ranges. The D-antigen (b) (4) failed as a release test; therefore, the (b) (4) D-antigen method was developed and validated as discussed below. Please refer to the Section 3.2.P.3.5 Process Validation and Evaluation for details.

PROCESS VALIDATION AND EVALUATION: FORMULATION OF FINAL BULK PRODUCT

(b) (4)

2 Pages determined to be not releasable: (b)(4)

(b) (4)

MANUFACTURING PROCESS CHANGES BETWEEN PHASE III CONSISTENCY LOTS AND COMMERCIAL LAUNCH

Analytical Changes

(b) (4)

In the Amendment STN125563/0.15, submitted in response to CBER June 19, 2015 Information Request, the sponsor submitted a qualification report for a new reference (b) (4), that will be used in the Rat Immunogenicity test. For details on the references please refer to section 3.4.P.6 of the submission: Reference standards and Materials (summarized on Page 41 of this review). Identity tests: identity testing (using D-antigen (b) (4)) will be introduced at Sanofi Pasteur Limited for vIPV (b) (4) (3.2.P.2.3, Page 60/60).

CONTAINER CLOSURE SYSTEM (3.2.P.2.4)

Studies have been performed to support the use of container materials:

- Final Bulk product (b) (4)
- Filled product: filled in 2 ml single-dose glass (b) (4) borosilicate glass tubing vials with rubber stopper (bromobutyl rubber, not made with natural latex rubber).

DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS (3.2.P.3.3)

The Final Bulk Product manufacture consists of the following steps:

(b) (4)

(b) (4)

- PR5I vaccine Final Bulk product. Stored at (b) (4)
 - o QC release tests: (b) (4)

Filling and primary packaging of PR5I vaccine. Stored at 2-8 °C.

- o QC release tests: physical appearance, sterility, (b) (4) aluminum content, extractable volume, pyrogen, general safety test – modified (Exemption for General Safety Test is requested in the BLA, however the commercial launch lots will be tested until exemption granted by CBER upon approval of PR5I License, see 3.2.P.5.6 Justification of specifications).
- Labeling and secondary packaging.
 - o QC release tests: identity of HBsAg and PRP-OMPC components.
- Finished product. Stored at 2-8 °C.

The vIPV component is (b) (4)

CONTROLS OF CRITICAL STEPS AND INTERMEDIATES

(b) (4)

PROCESS VALIDATION AND/OR EVALUATION

The process validation studies were performed at the following stages and completed: Final Bulk Product formulation; filling process validation; (b) (4) process validation; (b) (4) Drug Substance vIPV; (b) (4) of WFI; (b) (4) of Drug Substance (PRP-OMPC and HBsAg); aseptic process simulation for formulation and filling.

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) (see section *Development of D-Antigen Potency Test for IPV in PR5I*, above in this memo), (b) (4) (b) (4) tests (see review memo from Juan Arciniega on test results for the Pertussis component).

STABILITY (3.2.P.8)

STABILITY SUMMARY (3.2.P.8.1)

(b) (4)

The proposed Shelf Life for the Finished Product was initially 36 months at 2°C to 8°C. The claimed shelf life (amendment STN125563/0.2 and STN125563/0.20) is 42 months from the date of FBP formulation ((b) (4) Finished Product does not exceed 42 months).

The proposed Shelf Life for the Final Bulk Product is (b) (4)

(b) (4) Finished Product at 2°C to 8°C is 42 months (from the date of Final Bulk Product formulation).

The stability studies included (b) (4) PR5I Final Bulk Product lots ((b) (4) and (b) (4) Finished Product lots (b) (4)), shown in the table below. All lots were manufactured at Sanofi Pasteur Toronto site.

Table: FBP lots and finished product lots placed on stability

Product Stage	Stability Protocol Number	Batch number	Batch Size	Date of Manufacture (Final Bulk Product formulation)	Date of Filling	Status	Objective
Final Bulk Product	(b) (4)						
Finished Product	B014063	(b) (4)				Completed	Initial stability study to support vaccine Shelf-life (42 months at 2°C to 8°C)
	B015684	(b) (4)				Completed	

* Batch size used for Final Bulk Product stability purposes

Final Bulk Product stability studies were conducted (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(b) (4)

Finished product stability studies were performed to support storage for 42 months at 2-8°C from the date of Final Bulk Product formulation in glass vials. The tests were performed at (b) (4) different sites. The samples were stored in (b) (4) orientation. The studies included (b) (4) lots (filled at Canada facility), manufactured at commercial scale; 0 time point was based on the date of Final Bulk Product formulation.

Test schedule (tests at SP Limited) for protocols B014063 (lots (b) (4)) and B015684 (lot (b) (4)) Rat immunogenicity test – 0, 6, 12, 24, 36, 42, 48 months; D-antigen content ((b) (4) method) – 3, 6, 12, 18, 24, 30, 36, 42, 48 months (the testing was initiated at later time points for different lots; the lots failed when tested using (b) (4) (b) (4) The stability tests also included (b) (4) Physical appearance, Specific toxicity, Container closure integrity, Sterility, and tests of other antigens.

Future lots of the vaccine will be tested using D-antigen (b) (4) method to assess D-antigen content at release and stability monitoring.

POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT (3.2.P.8.2)

ACCELERATED STABILITY STUDY

The sponsor intends to perform the following studies: (b) (4)

[REDACTED]

Time zero for the Finished Product studies was the date of formulation of the FBP. The first time point for this testing was after the (b) (4) method replaced the (b) (4) method. The tables below show results for the IPV component using the D-antigen ELISA and rat immunogenicity assays.

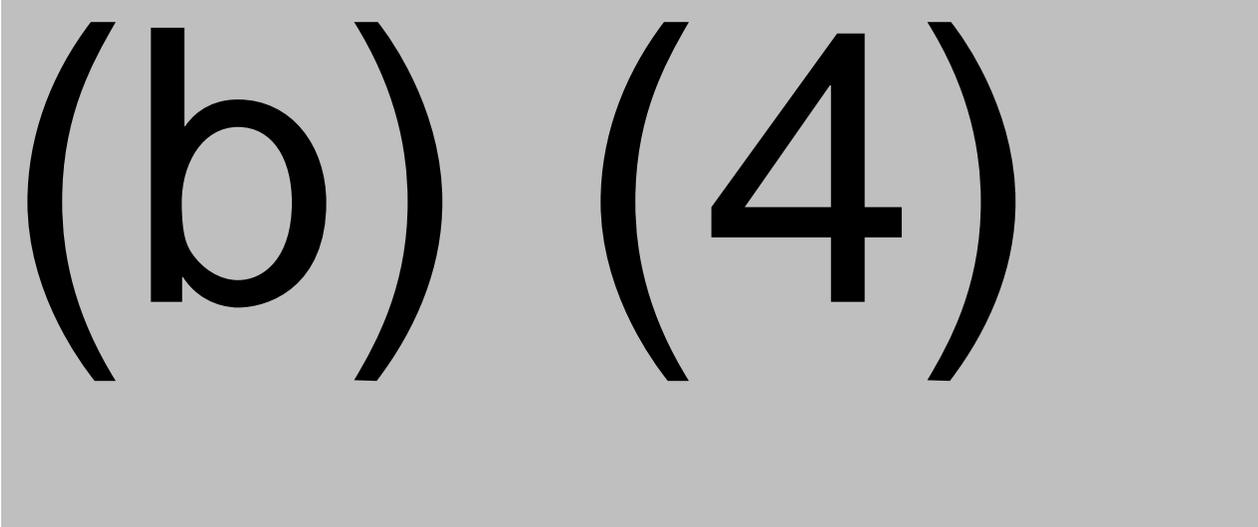


Table: Rat immunogenicity results, Lots (b) (4)

Lot #	Type	Acceptance	Relative potency, rat test						
			months						
			0	6	12	24	36	42	48
(b) (4)	Type 1	(b) (4)	1.8	0.8	1.4	1.5	0.8	0.9	0.9
	Type 2		0.8	0.6	1.8	0.9	2.1	1.2	0.7
	Type 3		1.3	1.2	1.3	1.0	2.9	1.6	0.8
(b) (4)	Type 1	(b) (4)	1.0	1.0	1.3	1.0	1.2	1.4	1.4
	Type 2		1.0	1.4	1.0	0.7	1.1	0.7	2.0
	Type 3		1.6	1.1	0.9	1.5	1.1	1.7	1.3
(b) (4)	Type 1	(b) (4)	0.7	0.8	0.6	0.7	1.4	1.2	0.7
	Type 2		0.7	0.7	1.0	0.7	0.9	1.5	0.8
	Type 3		0.6	0.7	0.6	0.7	1.6	1.6	0.9

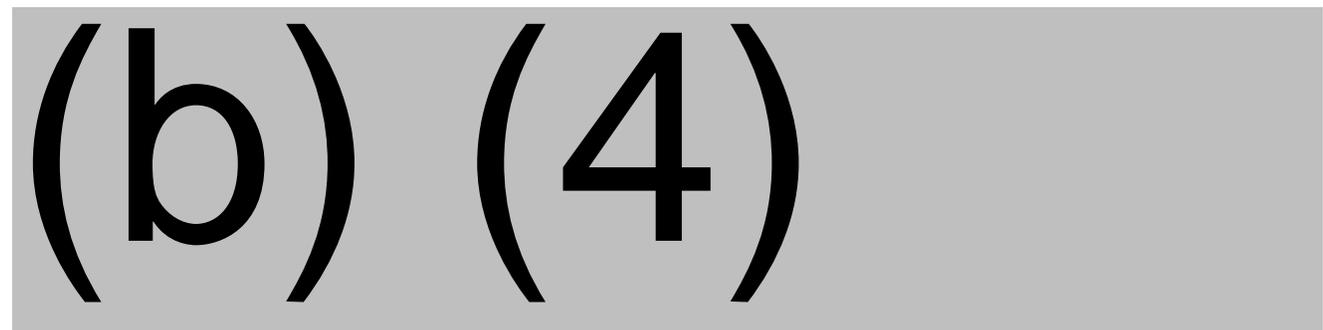


Table: Rat immunogenicity results, Lot (b) (4)

Lot #	Type	Acceptance	Relative potency, rat test											
			months											
			0	6	12	18	24	30	36	42	48			

(b) (4)	Type 1		0.9	*	0.6	-	1.3	-	0.7	1.4	Pending
	Type 2	(b) (4)	1.3		0.7	-	1.5	-	1.5	1.1	Pending
	Type 3		1.0		1.0	-	0.6	-	1.1	1.0	Pending

* No result is available as repeat testing could not be performed prior to the next scheduled time-point.

STABILITY AMENDMENT 125563/0.2

Additional stability information was submitted as an amendment (STN125563/0.2). This amendment provided data supporting stability of the PR5I vaccine stored at 2-8°C for 42 months from the date of Final Bulk Product formulation ((b) (4) finished product storage time). The sponsor stated that all results obtained up to and including the 42-month time point (30 months for lot (b) (4) met the acceptance criteria set at the time for release of PR5I Finished product with some exceptions (OOS results for (b) (4) (b) (4) [for European market] for some time points and (b) (4) test for lot (b) (4) at 42 months). No IPV-related OOS results were reported. The sponsor claimed storage time for PR5I Finished Product for up to 42 months at 2°C to 8°C from the date of Final Bulk Product formulation ((b) (4) Finished Product does not exceed 42 months).

The (b) (4) method was (b) (4)

Likewise, there are no stability data for Finished Product lots from Time 0 to 9 months (lots (b) (4)) or for Time 0 for Finished Product lot (b) (4) . Nonetheless, all results for later time points, up to 42 months, were within specification for the (b) (4) , with some exceptions due to lack of testing on schedule. All clinical lots were therefore released based only on results obtained with the rat immunogenicity test.

Monovalent lots used to formulate clinical/stability lots of PR5I were manufactured before significant changes were made to the manufacturing process at the Sanofi Pasteur (b) (4) facility ((b) (4) (b) (4)). These changes were approved under STN103930/5163 and /5033, respectively. Future lots of the vaccine will be produced with Poliovirus Trivalent Concentrates manufactured with the changes.

A request for submission of the protocol for routine stability monitoring program that will be performed post-licensure is included at the end of this review.

ANALYTICAL TESTS AND VALIDATION

Two IPV potency tests at two locations are performed for QC and release of the (b) (4) DP.

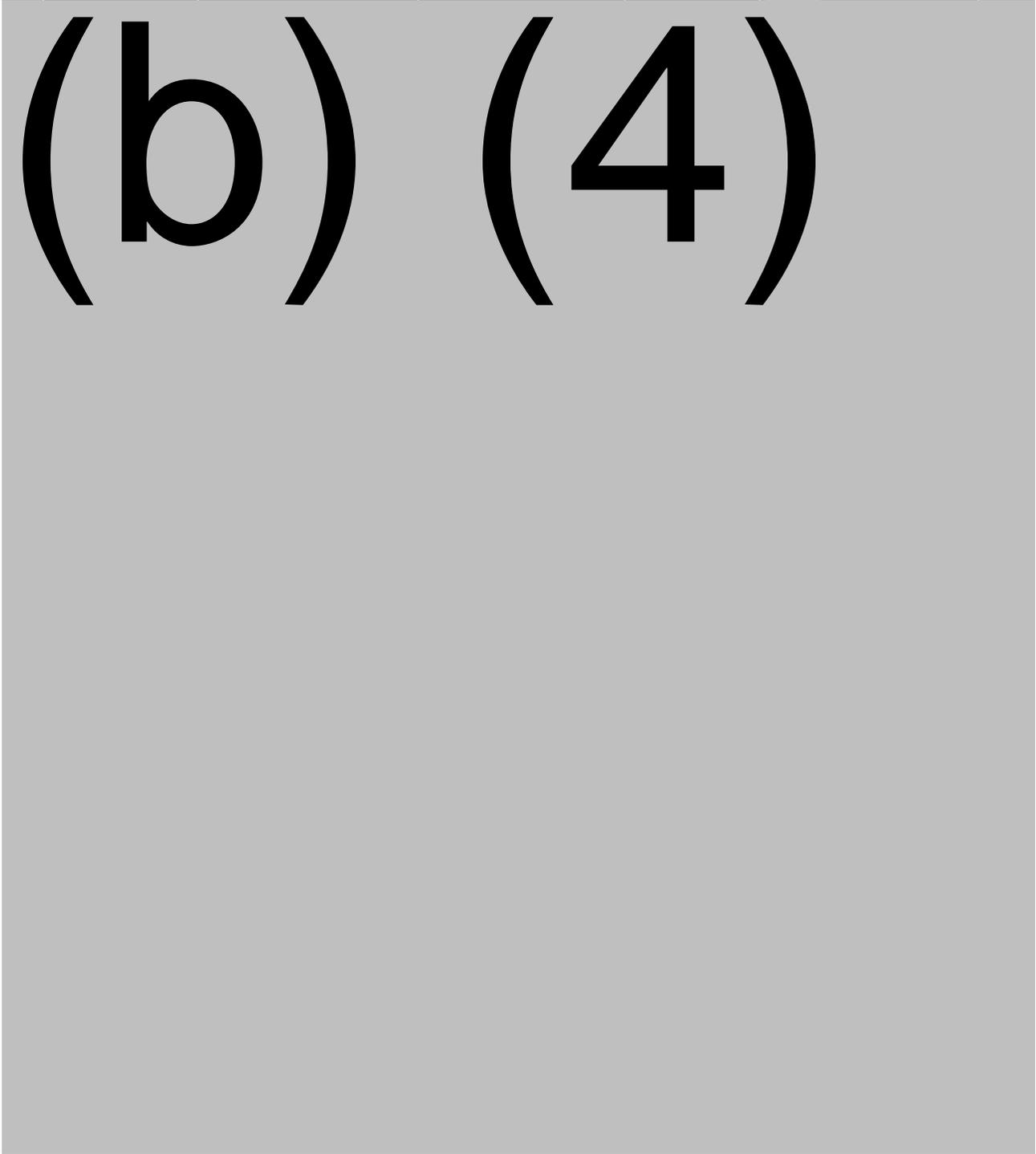
(b) (4)): D-antigen (b) (4) (b) (4) method; Rat immunogenicity test.

DP (b) (4) Product; Toronto, Canada): D-antigen (b) (4) method; Rat Immunogenicity Assay.

Detailed descriptions of the tests are provided.

The table below presents IPV potency assays used in the PR5I vaccine manufacturing process.

Table: IPV potency assays performed during PR5I manufacture at the (b) (4) and Toronto sites



D-ANTIGEN CONTENT (BY (b) (4) METHOD) PERFORMED ON THE (b) (4)
(b) (4)

The D-Antigen (b) (4) method is used to evaluate antigen content in the (b) (4)
(b) (4) and is performed at the MLE site.

The test is based on "Immunochemical Methods" (b) (4) .

ANALYTICAL PROCEDURE

(b) (4)

VALIDATION D-ANTIGEN (b) (4), (b) (4) METHOD (3.2.S.4.3)

(b) (4)

9 Pages determined to be not releasable: (b)(4)

(b) (4)

LOT RELEASE PROTOCOL:

There are two lot release protocols, one for the IPV Trivalent Concentrate shipped from Sanofi (b) (4) and one for the final PR5I Drug Product.

The lot release protocol for the IPV Trivalent Concentrate destined for PR5I is similar to that for IPOL with only minor formatting differences, and no testing differences, with exception of the (b) (4) " performed on the (b) (4) . In the currently approved LRP for IPOL, this test is performed on the (b) (4) , as well as on (b) (4) . The LRP for PR5I includes these tests, but additionally includes testing of (b) (4)

PR5I FINAL BULK LOT RELEASE SPECIFICATIONS:

(b) (4)

(b) (4)

RELEASE PROTOCOL SUMMARY

PR5I VACCINE

Licensed Name of Product: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, **Inactivated Poliovirus**, Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine (PR5I Vaccine)
Storage Temperature: +5°C +/-3°C

PR5I vaccine (IPV-relevant tests)

Inactivated Poliomyelities Vaccine

Concentrated Trivalent (vIPV) Lot No:

CBER Lot Release Date:

Label Strength (per 0.5ml)

Vero Inactivated Poliomyelities Type 1	29 D-antigen units
Vero Inactivated Poliomyelities Type 2	7 D-antigen units
Vero Inactivated Poliomyelities Type 3	26 D-antigen units

(b) (4)

2 Pages determined to be not releasable: (b)(4)

(b) (4)

Follow-up to the above comments:

The comments and revisions to the lot release protocol were managed by Karen Campbell at DBSQC and input on updated versions submitted to the BLA will be provided to her.

COMPONENT INFORMATION

I reviewed the IPV-related ingredients that are used in PR5I manufacturing process. IPV Drug Substance bulk is manufactured according to the IPOL license (STN103930). Raw materials and components used in the manufacture of IPV component of PR5I, including materials of animal origin, are identical to those used to manufacture IPOL, with no additional components, and therefore, are acceptable for the manufacture PR5I vaccine.

INFORMATION REQUESTS AND RESPONSES:

INFORMATION REQUEST OF APRIL 10, 2015

The following questions were communicated to the sponsor on April 10, 2015. The responses were submitted as Amendment STN125653/0.9 on May 27, 2015.

The Questions are numbered according to the numbering in the company's responses.

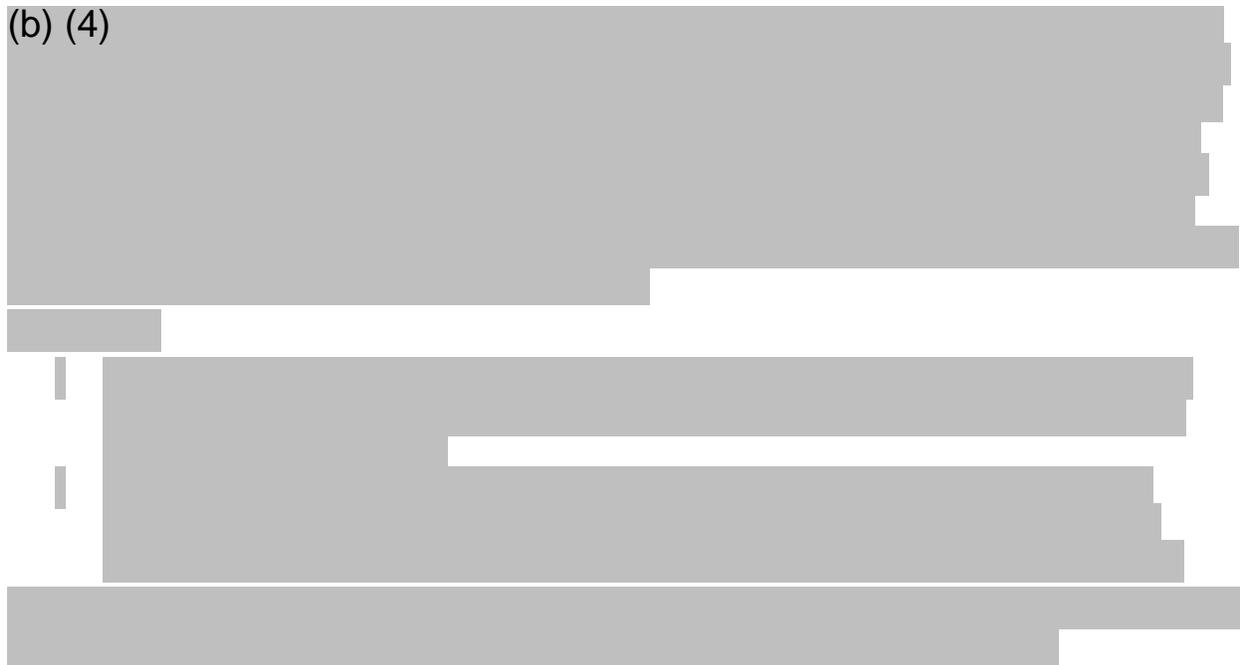
Question 4

With regard to D-antigen (b) (4) tests please provide the following information:

- 4a.** Describe procedures for monitoring the stability and performance of reference standards and controls used in the (b) (4) used to quantify D-antigen content in IPV (b) (4) Drug Product.

Response 4a:

(b) (4)



Comment: The response is acceptable.

- 4b.** Describe the D-antigen testing format at each manufacturing stage (i.e., number of samples tested, number of replicates, (b) (4) type).

Response 4b:

The sponsor provided the following summary for the tests:

(b) (4) method:

(b) (4)

method:

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

).

Request: The response is not acceptable. Please see comment 1 under Information Request of June 19, 2015.

- 4c.** Provide the SOP for the (b) (4) used to determine D-antigen content in PR5I vaccine (b) (4)

Response 4c:

The SOP is provided. I have reviewed the SOP.

Comment: (b) (4)

The response is acceptable.

- 4d.** With regard to the D-Antigen (b) (4) validation, your specificity assessment (Section 3.2.P.5.3_D-(b) (4) Product, Table 8, Page 8/19) involves comparing observed results to expected results. Define the basis for assigning values used as the “expected result” and clarify whether the same (b) (4) format (b) (4)) was used for all measurements.

Response 4d:

The sponsor replied that the expected values included in Table 8 section 3.2.P.5.3 Validation of Analytical Procedure is the (b) (4)

Comment: Please see comment for response 4e below.

- 4e.** With regard to the D-Antigen (b) (4) validation, it is not clear if a spike-recovery assessment was performed (i.e., (b) (4) a known amount of antigen in the PR5I matrix). If this was performed, please indicate where this information is presented. If it was not performed, please provide a rationale.

Response 4e:

(b) (4) results are presented in Tables 9-11, section 3.2.P.5.3 Validation of Analytical Procedure.

(b) (4)

Comment:

The results obtained by the (b) (4) for clinical lots of the vaccine (and in the stability program) confirmed that the assay is adequate for the intended purpose.

The response is acceptable.

- 4f. *We note that the D-antigen content measured by (b) (4) method is shown for the (b) (4) (b) (4) (b) (4) in Table 18 (3.2.P.5.6_Justification of specification, Page 32/49), and the results are higher for all three serotypes as compared to typical measurements shown for these lots in stability results. Please explain.*

Response 4f:

The data presented in the table include a correction factor applied for (b) (4). The test method SOP ((b) (4) Q_0235328) incorrectly applied the correction factor of “(b) (4) /0.9” to adsorbed products (intended to be used for products manufactured at the facility in France). The SOP has been updated to remove that requirement; all stability data have been verified. Table 18 has been updated and lists correct results (consistent with stability data).

Comment: The response is acceptable.

- 4g. *Define criteria for sample validity in the (b) (4) and for re-testing.*

Response 4g:

Sample validity criteria:

(b) (4)

Comment: The sponsor provided criteria for assay validity: acceptance range for reference standard Lots (b) (4), and acceptance range of validity control Lot (b) (4) the three polio serotypes (control limits (b) (4) Sample validity criteria (acceptable difference between triplicate data generated for the same sample and all tested samples) were not provided.

Request: The response is not acceptable. A request to provide sample validity criteria is included in the comment to the response to question 4b above. Please see comment 1 under Information Request of June 19, 2015.

4h. Provide the name and site of the laboratory where the D-Antigen (b) (4) was validated and the name and site where the assays will be performed to determine DU-content in PR5I vaccine.

Response 4h:

The (b) (4) was validated and performed at Sanofi Pasteur Limited, Toronto, in QC Immunochemistry department.

Comment: The response is acceptable.

Question 5

With regard to Lot release specifications, a (b) (4) that marginally fails the specification for purity with DU-antigen content measured by the (b) (4) method (e.g., intended for IPOL) might pass the same specification if the (b) (4) method is used (as for PR5I IPV (b) (4)). Please comment.

Response 5

(b) (4)

(b) (4)

The response is acceptable.

Question 6

With regard to the Rat Immunogenicity assay performed on PR5I (b) (4) Product please provide the following information:

6a. Provide Qualification report Q_0294513 Report for the qualification of Pediacel Lot (b) (4)

Response 6a:

The report was provided.

Comment: The response is acceptable.

6b. DTaP-IPV-Hib reference vaccine lot (b) (4) was used in performing the IPV Rat Immunogenicity Assay for lots (b) (4) for release and stability monitoring. Please provide qualification data for this lot and identify the method used to measure D-antigen content.

Response 6b:

Qualification report Q_0262381(Document C016413) was provided. D-antigen content was determined using the (b) (4).

Comment: The response is acceptable.

6c. The certificate of analysis for reference Lot (b) (4) stated a (b) (4) year re-test date from the date of manufacture. The planned re-test date was 09/10/2014. Please provide these results and identify the method used to measure D-antigen content.

Response 6c:

Reference vaccine lot (b) (4) was not used beyond its re-test date and has been replaced with a new reference vaccine lot (b) (4) (implemented in October 2014). The qualification report was provided: Q_0530200.

The qualified reference Lot (b) (4) has expired; the company is seeking approval for replacement of Lot (b) (4) with Lot (b) (4)

Review of the report:

The report Q_0530200 summarizes results of a qualification study for the new reference Lot (b) (4) (DTaP-IPV-Hib Lot (b) (4) used in the rat immunogenicity assay (SOP Q_0235209 and Q_0234899). (b) (4)

(b) (4)

Table 13: Relative Potency and Correction Factor for Pediacel Reference Vaccine Lots

(b) (4)

Table 14: Summary Statistics, Relative Potency Estimates and Correction Factor for Pediacel Sample and Reference vaccine lots

(b) (4)

Request: The response is not acceptable. Please see comment 2 under Information Request of June 19, 2015.

INFORMATION REQUEST OF JUNE 19, 2015

The following questions were communicated to the sponsor on June 19, 2015. The responses were submitted as Amendment STN125653/0.15 on August 21, 2015.

The following comments pertain to the D-Antigen (b) (4) and Rat Immunogenicity Test information submitted on 27 May 2015 (SN 9):

Question 1

With regard to (b) (4) D-antigen (b) (4) used at the (b) (4) Product stage:

- a) Provide data demonstrating the adequacy of using only a single sample (tested in triplicate) of the PR5I (b) (4) product to determine its D-antigen content.

Response: D-antigen (b) (4) was validated to test a single sample in triplicate. All validation parameters were found to be within acceptance criteria.

- b) Please identify any validity criteria imposed on triplicate values observed from each sample tested (e.g., coefficient of variation, standard deviation, range, etc.).

Response: No validity criteria are imposed on the triplicate values observed for each sample. When testing for D-antigen content in Vero IPV containing products, assessment of the sample result is done based on (b) (4) data from (b) (4).

Comment (b) (4)

Comment relayed to the sponsor on October 16, 2015: (b) (4)

(b) (4), we recommend that you establish such a criterion to provide additional assurance of assay performance and precision of the reported result. Please see comment under Information Request of October 16, 2015.

Question 2

With regard to the Rat Immunogenicity test, please provide the D-antigen content results for the reference vaccine lot (b) (4) and provide details showing how the correction factors (CF) were calculated and established.

Response:

Reference vaccine lot (b) (4) is a portion of routinely manufactured lot of DTaP-IPV-Hib vaccine Lot (b) (4) Results for the D-antigen content are presented below:

(b) (4)

Comment: I accept this explanation and concur with use of these conversion factors.

INFORMATION REQUEST OF OCTOBER 16, 2015.

The following request was sent to the sponsor:

Although you indicate that the (b) (4) was validated to provide a reliable result based on testing of the single sample in triplicate without imposing rules for inter-replicate values, we recommend that you establish such a criterion to provide additional assurance of assay performance and precision of the reported result. We acknowledge that additional data will be required to establish the requested criterion. Please commit to providing this information as soon as possible.

Response is pending.