



Date: October 23, 2015

From: Wei Wang, Ph.D., OVRR/DBPAP/LBP

To: Files STN 125563/0

Through: Willie F. Vann, Ph.D., Chief LBP, OVRR/DBPAP

Subject: Chemistry, Manufacturing and Controls (CMC) Review for the *Haemophilus influenzae* b conjugate (PRP-OMPC) component of PR5I.

Products: (b) (4) (PR5I), Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, *Haemophilus* b Conjugate [Meningococcal Protein Conjugate] and Hepatitis B [Recombinant] Vaccine, BLA 125563/0

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

Applicant: MCM Vaccine Company

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1. Introduction

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

P- PRP-OMPC Bulk Intermediate, it is important to note that the actual drug component in PR5I is amorphous aluminum hydroxyphosphate sulfate adsorbed polyribosylribitol phosphate conjugated to meningococcal outer membrane protein complex (AAHS PRP-OMPC) Conjugate Bulk, a drug substance used in the manufacture of Liquid PedvaxHIB® (STN BL 103237) [*Haemophilus influenzae* type b Conjugate Vaccine (Meningococcal Protein Conjugate)] – Merck & Co., Inc.

R- Recombinant Hepatitis B Surface Antigen (HBsAg) Bulk Intermediate, an intermediate used in the manufacture of RECOMBIVAX HB® (STN BL 101066) [Hepatitis B Vaccine (Recombinant)] – Merck & Co., Inc.

5- 5-component Acellular Pertussis Adsorbed (Pertussis Toxoid, Filamentous Haemagglutinin, Pertactin, and Fimbriae Types 2 and 3), Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed Bulk Intermediates, intermediates used in the manufacture of licensed vaccines, including Pentacel® (STN BL 125145), Diphtheria and Tetanus Toxoids Adsorbed Vaccine (STN BL 103944), DAPTACEL® (STN BL 103666), Adacel® (STN BL 125111) and TENIVAC™ (STN BL 103171) – Sanofi Pasteur Limited.

I- Inactivated Poliovirus Types 1, 2, and 3 Bulk Intermediate, intermediates used in the manufacture of Poliovirus Vaccine Inactivated (vIPV), IPOL® (STN BL 103930) – Sanofi Pasteur SA.

The composition of the PR5I final drug product is shown in Table 1.

Table 1. Composition of PR5I Drug Product (0.5-mL Single Dose)

Component*	Amount on a per unit basis (0.5 mL)	Function
<i>Haemophilus b</i> 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 immunization)
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 immunization)
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)
Aluminum§	319 µg	Adjuvant
Water for injection	q.s. 0.5 mL	Diluent

*(b) (4)

Refer to 3.2.P.3.2 Batch Formula and 3.2.P.3.3 Description of Manufacturing Process for details.

† In each dose of PR5I, Haemophilus b conjugate is comprised of 3 µg of PRP- polyribosylribitol phosphate 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)).

2. Review Identifiers and Dates

Biologics License Application (BLA) Submission Tracking Numbers (STN): 125563/0 and 125580

Materials Reviewed: The following general module sections of the BLA were reviewed:

- ml Regional

- m2 Common Technical Document Summaries
- m3 Quality

The following amendments were reviewed:

Original BLA 125563/0

Amendment 125563/0.10

Amendment 125563/0.11

Amendment 125564/0.20

Original BLA 125580/0

Amendment 125580/0.1

Amendment 125580/0.3

Amendment 125580/0.4

Amendment 125580/0.8

Related INDs and BLAs: BB-IND 14996, , Merck PedVaxHIB BLA (STN 103237/0)

3. Executive Summary

This CMC Review memo covers the active ingredient component of *Haemophilus influenzae* type b conjugate vaccine (Meningococcal Protein Conjugate) and the (b) (4) (PR5I) final drug product. The drug substance, Amorphous Aluminum Hydroxyphosphate Sulfate Adsorbed Polyribosylribitol Phosphate conjugated to meningococcal Outer Membrane Protein Complex (AAHS PRP-OMPC) Conjugate bulk, is manufactured at Merck Sharp & Dohme Corp.'s (b) (4) , U.S. site. CBER agreed prior to submission of the PR5I BLA that Merck could cross-reference data from the original PedvaxHIB® BLA (STN 103237) and later supplements. In addition, CBER required that Merck submit a "For Further Manufacturing Use (FFMU) BLA (STN 125580) to support the use of the AAHS PRP-OMPC Conjugate Bulk intermediate used in manufacturing of the PR5I final drug product. Merck states that the drug substance (AAHS PRP-OMPC bulk intermediate) is manufactured using the same process and in the same manufacturing facility as their currently licensed vaccine PedvaxHIB® (BLA 103237). Based on the approval of the original PedvaxHIB BLA and my review of the current manufacturing data submitted in support of the AAHS PRP-OMPC bulk intermediate, I find the manufacturing of AAHS PRP-OMPC generally acceptable for formulation of PR5I. However, Merck has not completely addressed outstanding issues regarding the qualification and re-evaluation of reference lots used to test (b) (4) PRP-OMPC drug substance. These outstanding issues, under the FFMU BLA 125580, must be resolved prior to approval.

I also reviewed the Drug Product (DP) section of the BLA 125563/0. The BLA cross-references previous BLA supplements for PedVaxHIB to cover the manufacturing process for those stages of manufacturing that are identical between PR5I and PedVaxHIB. Therefore, the DP review is focused on final bulk formulation and final DP formulation. Several deficiencies were noted during my review of PR5I. These deficiencies broadly included issues such as shipping validation, Extractable and Leachable studies for the DP container closure system,

manufacturing process validation, justification of specifications, analytical methods validation, acceptability of reference standards, and stability. We issued Information Requests (IRs) to Sanofi regarding these deficiencies on April 17, 2015 and May 27, 2015. These deficiencies and Sanofi's responses are covered in detail elsewhere in the memo. Based on my review of the current manufacturing, I find the manufacturing of the PR5I final formulated bulk and final drug product generally acceptable. However, Merck has not completely addressed outstanding issues regarding the qualification of the reference lots used to test (b) (4) of PRP-OMPC component of the final drug product. These outstanding issues, under BLA 125563/0, must be resolved prior to approval.

4. Review

4.1. Drug Substance: PRP-OMPC, Merck, FFMU BLA 125580/0:

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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

(b) (4) [Redacted]

[Redacted]

[Redacted]

4.2. Drug Product (BLA 125563/0: PR5I)

4.2.1. Pharmaceutical Development

In the section 3.2.P.2.3, Sanofi stated the following manufacturing process changes that were made to the drug substrate PRP-OMPC conjugate between the Phase III Consistency Lots and Commercial Launch:

(b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

These changes are acceptable.

Container Closure System (CCS)

In section 3.2.P.2.4 of BLA 125563/0, Sanofi described the rationale for selection of the CCS for the Final Bulk Product and provided compatibility studies of the CCS used for the PR5I

vaccine final drug product (DP). The compatibility of the CCS used for PR5I was demonstrated through Extractable and Leachable Studies (E&L). We asked Sanofi to provide additional information on the E&L studies, such as: complete E&L study results, the rationale/justification for selecting specific compounds tested in the leachable study, and an assessment of any potential leachables released from the in-process equipment and containers used for vaccine production. All E&L questions were sent to Sanofi in an Information Request (IR) dated April 17, 2015. Please refer to the Drug Product Information Request section of this memo for complete details. There are no outstanding comments regarding E&L studies.

4.2.2. Manufacture - Process Validation and or Evaluation



Sanofi’s responses are acceptable and there are no outstanding questions.

4.2.3. Control of Drug Product

Specifications

In Section 3.2.P.5.1, Sanofi provided the specifications for release and shelf life specifications of PR5I Final Bulk Product, Release and Shelf-life Specifications for PR5I Filled Product (Unlabeled), and Release Specification for PR5I Labeled Filled Product. Release specifications for the labeled and filled product are in Table 1 below.

Table 11: 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

In an IR dated April 17, 2015, we requested that Sanofi clarify which method, (b) (4) methods (as listed in Table 11) would be used to test identity of HBsAg or PRP-OMPC. Refer to the Drug Product Information Request section of this memo for additional detail. Sanofi's responses are acceptable and there are no outstanding issues.

In addition, in separate IRs dated April 17, 2015 and July 27, 2015, we requested Sanofi add an Endotoxin test for release of PR5I (b) (4) Product. We also asked Sanofi to set the specification for the endotoxin to reflect manufacturing data. Please refer to the Drug Product Information Request section of this memo for complete details. Sanofi's response is acceptable and there are no outstanding issues.

4.2.4. Validation of Analytical Procedures

In Section 3.2.P.5.3, Sanofi provided the procedures for all analytical methods used for testing of the drug product, and described several analytical procedure related changes as described previously in this memo. These changes were considered acceptable. We issued multiple IR's to Sanofi regarding their analytical methods validations. These are summarized briefly as follows:

Validation of assay used for both (b) (4) PRP-OMPC (b) (4) Identity of PRP-OMPC for (b) (4) of labelled filled product - We requested information on (a) the assay specificity, (b) accuracy, (c) linearity, (d) precision, (e) the range of the assay, (f) robustness, (g) additional data to demonstrate suitability under actual conditions after the assay method was transferred from Merck to Sanofi, and (h) revalidate the assay or provide data for assay validation.

Validation of the assay for PRP content of the (b) (4) - We asked Sanofi to provide data for (a) assay specificity, (b) accuracy, (c) linearity, (d) precision, (e) the range of the assay, and (f) additional data to demonstrate suitability under actual conditions of use after the assay method transfer from Merck to Sanofi.

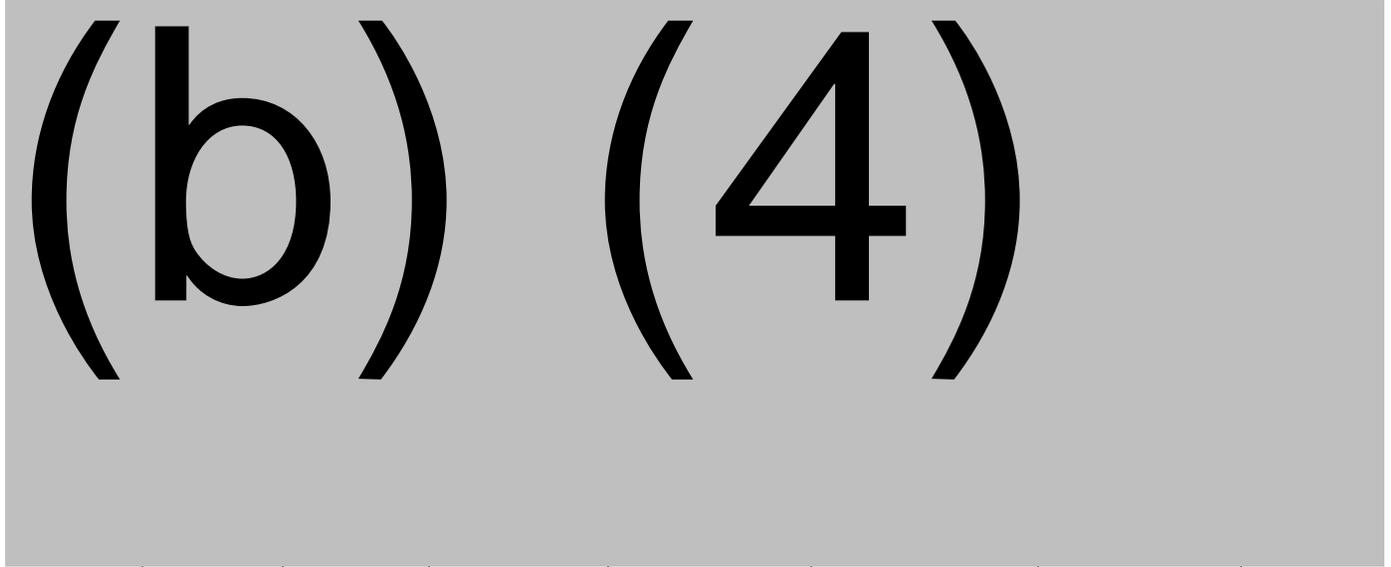
Validation of (b) (4) PRP-OMPC for the (b) (4) - We asked Sanofi to provide data for (a) assay specificity, (b) accuracy, (c) linearity, (d) precision, (e) the range of assay, and (f) additional data to demonstrate suitability under actual conditions after the assay method transfer from Merck to Sanofi.

Summary Validation of the (b) (4) Test for the Labeled Filled Product - We asked Sanofi to provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results.

Please refer to the Drug Product Information Request Section of this memo for further details on assay validation issues. There are outstanding issues related to the qualification and reevaluation of reference standard for PRP-OMPC (b) (4) assay that remain unresolved.

4.2.5. Batch Analyses

In section 3.2.P.5.4 of BLA 125563, Sanofi provided satisfactory batch analysis results that met all acceptance criteria for following lots of final drug product PR5I (Table 13).



4.2.6. Justification of Specifications

In Section 3.2.P.5.6, Sanofi described their justification of specifications for release of PR5I Final Bulk Product, Filled Product and Labeled Filled Product. We did not agree with the approach of setting up proposed acceptance criteria for (b) (4) PRP-OMPC, (b) (4) PRP-OMPC, PRP Content and (b) (4) Information requests related to specifications were issued on April 17, 2015 and May 27, 2015.

4.2.7. Reference Standards or Materials

In Section 3.2.P. 6, Sanofi provided information and data on the qualification and re-evaluation of several Reference Standards or Materials. Specifically with respect to this review Sanofi provided this information for the reference standards used in assays for (b) (4)



. Therefore, additional IR comments were issued on July 27, 2015. Sanofi's responses to the IR question regarding the dating extension of the PRP-OMPC conjugate lot reference standard was not sufficient, therefore a Complete Response comment

should be issued for this outstanding item. Please refer to the Drug Product Information Request section of this memo for further details.

4.2.8. Stability

4.2.8.1 Stability Summary and Conclusion

In Section 3.2.P.8.1, Sanofi provided the stability study plans and data for the PR5I Final Bulk Product and the PR5I Final Drug Product. Stability studies for the final bulk were performed to support storage of the bulk for (b) (4) containers. Stability studies for the final drug product were performed to support a 42 month expiry for product in 2.0-mL single-dose (b) (4) glass vials, with a (b) (4) stopper and a 13 mm aluminum seal with plastic flip-off cap. Both studies were performed at (b) (4). Stability data for both the final bulk and final drug product were not complete at the time of submission.

With respect to the study design, we issued an IR to Sanofi for the PR5I final bulk product on April 17, 2015 requesting that they provide a detailed comparison of the large scale containers used in routine manufacturing and the small scale containers used in stability studies, and to provide stability data using containers used in routine manufacturing. Sanofi's response to this IR was not sufficient. Therefore, an additional IR was issued on July 27, 2015. Sanofi's response is acceptable and no further action is required. Please refer to the Drug Product Information Request section of this memo for further details.

4.2.8.2 Post-Approval Stability Protocol and Stability Commitment

Section 3.2.P.8.2, Post-Approval Stability Protocol and Stability Commitment, contains Sanofi's commitments to complete stability studies of the PR5I final drug product and their commitment to perform on-going routine stability studies. In an information request dated April 17 2015, we requested that Sanofi provide an updated post approval stability protocol and commitment for the 42 month shelf life, and to revise section 3 of the Post-Approval Stability Protocol and Stability Commitment to provide detailed procedures on the post approval stability program. Sanofi's responses are acceptable. Please refer to the Drug Product Information Request section of this memo for further detail.

4.2.8.3 Stability Data

In Tables 2 to 5 of Section 3.2.P.8.3, Sanofi provided stability study results for PR5I Final Bulk Product lots (b) (4) stored in a (b) (4) container (b) (4). These data were acceptable.

Sanofi also provided stability data for the PR5I Finished Product lots (b) (4), stored at 2-8°C in section 3.2.P.8.3, Tables 6 to 9. These available stability results met acceptance criteria for the Hib related tests, for all lots through 36 months except for Lot (b) (4). The 30 month time-point for Lot (b) (4) was listed as pending for (b) (4) PRP-OMPC, PRP Content, and (b) (4) PRP-OMPC.

(Table 9 of Section 3.2.P.8.3). We requested that Sanofi submit these data for review in an IR dated April 17, 2015. Sanofi provided requested stability data. The stability data were acceptable and no further action is required.

4.2.9. Information Requests and Responses for Drug Product

Information Request Dated April 17, 2015 and Responses

We issued an Information Request (IR) on April 17, 2015. This IR included multiple questions on the final container product and a question on the bulk product. Sanofi Pasteur Limited (Sanofi) responded to these IR questions through two amendments. Amendment 10 (STN 125563/0.10), was submitted on May 28, 2015, and amendment 11 (STN 125563/0.11) was submitted on June 5, 2015). The IR comments, Sanofi's responses, and evaluation of the responses are listed below.

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.*
 - a. *Please include your results for both extractable and leachable studies in both µg/dose and ppm.*
 - b. *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) at the 15-month time-point and at a concentration of (b) (4) 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) (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 to Q2 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 1 and updated Section 3.2.P.2.4):

2a) Sanofi states that they have updated Section 3.2.P.2.4 Container Closure System with results of the new leachables studies obtained using PR5I Vaccine which include the toxicological assessment of the detected compounds.

In Table 3 under Section 3.2.P.2.4, Sanofi provided results of extractable studies that were performed by the stopper manufacturer on the physical and chemical properties on the (b) (4) stopper. Sanofi indicated that Extractable Studies were carried out following the Compendial Standards (b) (4)

Sanofi stated that, from extractable studies provided by the stopper manufacturer to evaluate volatile and non-volatile compounds of the (b) (4) stopper, the most extractables were below the analytical detection limit, while some trace (b) (4) were detected at negligible levels in parts per billion (ppb).

In Table 5 under the revised 3.2.P.2.4 Container Closure System, Sanofi provided leachables simulation study data on the (b) (4) Stopper for Tdap-IPV Vaccine. Sanofi explained that, (b) (4)

PR5I Filled Product up to 48 months (2-8°C, single-dose vial with (b) (4) stopper) indicated that no adverse interaction between the container closure systems and the Drug Product during the storage.

2b) In addition to above mentioned extractable and leachable studies, in its response to Question 2a, in the revised Section 3.2.P.2.4, Sanofi also performed cytotoxicity studies following compendial standards (b) (4)) and concluded no evidence of cytotoxicity from container closure system. Sanofi states that the new PR5I leachables simulation studies used analytical techniques capable of detecting all listed potential compounds with the exception of (b) (4) .

2c) Sanofi stated that the leachable studies were designed and executed by following recommendations by the (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)

2d) Sanofi performed a leachables study using PR5I stability vial samples stored at 2°C to 8°C for 48 months (b) (4) position to confirm the end of shelf-life quantities of the observed leachable compounds. Sanofi detected (b) (4)) as potential leachables. Because each leachable compound was above the (b) (4)), Sanofi performed toxicological assessments through a literature review using standard sources, including searches in databases of toxicity data plus other scientific literature and/or human drug information. Sanofi stated 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.

2e) Sanofi stated that for PR5I Drug Product the two main materials used in production of the container closure systems are: (b) (4)

. Additional components used with the 2 mL borosilicate vials are: (b) (4) Bromobutyl rubber stoppers (not made with natural rubber latex); and polypropylene caps with aluminum flip-off seals.

2f, 2g and 2h) Based on new leachable studies data, Sanofi updated and replaced the Tdap-IPV leachable results with the results of the PR5I leachables studies which include the toxicological assessment of the detected compounds (see the responses to 2a and 2d).

These responses are acceptable.

3. *In Section 3.2.P.3.5, you provide process validation data for bulk intermediate (b) (4) of PRP-OMPC. The information provided is not sufficient.*

(b) (4)

Response to Q3 (STN 125563/0.10, submitted on May 28, 2015, Section 1.11.1 Amendment 1 and Section 3.2.P.3.5)

(b) (4)

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 is used to set product specifications. In addition, we request that only release data be used to calculate the specification.*

Response to Q4 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 2).

Sanofi stated that due to the relatively small amount of data available, the company commits to re-evaluating the release acceptance criterion once data are collected from approximately (b) (4) PR5I final vaccine lots, or earlier if warranted due to data trending. The statistical reviewer for this committee, Dr. Tsai-Lien Lin reviewed Sanofi's response to this IR. Based on her review we issued a second IR on May 27, 2015. Refer to this section for further details.

5. *In Section 3.2.P.5.6, you provide justification for a (b) (4) PRP-OMPC specification of (b) (4) at release. This value was set based on the 99/99 lower tolerance interval accounting for assay and lot-to-lot variability. 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 is used to set product specifications. In addition, please verify that only release data were used in the calculation of the release specification.*

Response to Q5 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 3)

Sanofi stated that due to the relatively small amount of data available, the company commits to re-evaluating the release acceptance criterion once data are collected from approximately (b) (4) PR5I final vaccine lots, or earlier if warranted due to data trending. The statistical reviewer for this committee, Dr. Tsai-Lien Lin reviewed Sanofi's response to this IR. Based on her review we issued a second IR on May 27, 2015. Refer to this section for further details.

- In Section 3.2.P.5.6, you provide justification for a (b) (4) PRP-OMPC release and stability specification of (b) (4). This value was set based on the 99/99 lower 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 is used to set product specifications. We also request that only release data be used to calculate the release specification. In addition, the data provided show a (b) (4) on stability. Therefore, we do not concur that the release and stability specification should be the same. Please set your release specification to ensure that a stability specification of (b) (4) can be met at expiry.*

Response to Q6 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 3)

Sanofi stated that due to the relatively small amount of data available, the company commits to re-evaluating the release acceptance criterion once data are collected from approximately (b) (4) PR5I final vaccine lots, or earlier if warranted due to data trending. The statistical reviewer for this committee, Dr. Tsai-Lien Lin reviewed Sanofi's response to this IR. Based on her review we issued a second IR on May 27, 2015. Refer to this section for further details.

- In Section 3.2.P.5.6, you provide justification for PRP Content release specification of (b) (4). You state that this value was set on assay variability (b) (4) variance about the 3 µg/dose target). You also state that a 95/99 tolerance interval accounting for assay and lot-to-lot variability was used to confirm that the proposed release specification limit is acceptable. 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 is used to set product specifications. We also request that only release data be used to calculate the release specification. Please provide the details on your calculation of the 95/99 tolerance interval including the data used in the calculation, the (b) (4), and the tolerance interval result.*

Response to Q7 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 3)

Sanofi stated that due to the relatively small amount of data available, the company commits to re-evaluating the release acceptance criterion once data are collected from approximately (b) (4) PR5I final vaccine lots, or earlier if warranted due to data trending. The statistical reviewer for this committee, Dr. Tsai-Lien Lin reviewed Sanofi's response to this IR. Based on her review we issued a second IR on May 27, 2015. Refer to this section for further details.

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 to Q8 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 2)

Sanofi stated that due to the relatively small amount of data available, the company commits to re-evaluating the release acceptance criterion once data are collected from approximately (b) (4) PR5I final vaccine lots, or earlier if warranted due to data trending. The statistical reviewer for this committee, Dr. Tsai-Lien Lin reviewed Sanofi's response to this IR. Based on her review we issued a second IR on May 27, 2015. Refer to this section for further details.

9. *In Section 3.2.P.5.3, you provide a summary of the validation for the assay that is used for both, (b) (4) PRP-OMPC for (b) (4) Product and Identity of PRP-OMPC for (b) (4) Labelled Filled Product. The information provided is not sufficient.*
 - a. *For specificity, please provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results. In addition, for the Identification specificity testing, a negative result was confirmed for the (b) (4) containing samples. Please specify what (b) (4) containing samples were tested. Please provide the results if (b) (4) was tested.*
 - b. *For accuracy, please provide data using a minimum of 9 determinations over a minimum of 3 concentrations covering the specified range of the assay using manufacturing samples.*
 - c. *For linearity, please provide data to include graphs, slope, y-intercept, and correlation coefficient to compare the linearity of the reference standard and manufacturing sample to cover a minimum of 5 concentrations.*

- d. *For precision, please provide data using a minimum of 9 determinations covering the specified range (3 concentrations, 3 replicates) using manufacturing samples. In addition, please provide data to show that there is no difference between analysts, plate readers, and coat times.*
- e. *The range of the assay was determined to be (b) (4) Please provide the data to support this determination.*
- f. *A robustness study was performed after the validation. Please provide the robustness data. Please note that any changes in SOP based on data from the robustness studies may require additional validation data to support performance of the assay when performed according to the SOP.*
- g. *The method transfer from Merck to Sanofi was verified by testing (b) (4) lots (b) (4) times in each lab. This does not provide sufficient data to verify a procedure's suitability under actual conditions of use for a specified drug substance or drug product. Please provide additional data for a minimum of 6 lots to show suitability under actual conditions. Please provide data on manufacturing samples with varying concentrations. Comparative studies should include evaluation of accuracy and precision with regard to assessment of inter-laboratory variability. For stability indicating assays, forced degradation samples or samples containing pertinent product-related impurities should also be analyzed at both sites.*
- h. *The method was changed substantively after the transfer to Sanofi. These changes include a change in reference standard, data analysis, analyte measured, (b) (4) Method verification was performed on samples covering the expected range of the manufacturing process and the range of the assay. We do not concur that method verification is sufficient. The changes in the method are substantial and the original validation is not adequate as can be seen above. Please revalidate the assay or provide data for the method validation.*

Response to Q9 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 3)

9a) Sanofi states that the specificity of the assay was assessed with (b) (4)

[Redacted]

9b) Sanofi states that accuracy was assessed with (b) (4) [Redacted]. Detailed results are provided in Table 4 of the response.

9c) Sanofi provided results for slope, y-intercept, and correlation coefficient over a range of (b) (4) as requested. These data are provided in Table 5 of the response

9d) Sanofi provided assay results of (b) (4)

to determine intermediate precision. Results are provided in Table 6 of the response.

9e) Sanofi indicated that the data to demonstrate assay accuracy in the response to 9b was also used to support assay range determination. CBER considers this response acceptable.

9f) Sanofi the robustness study and study results in the Tables 8 and 9 of the response and concluded that “there were no practically meaningful significant effects on (b) (4)”. Therefore, the assay is considered robust and no changes in the analytical procedure are necessary based on the data from the robustness study.

9g) Sanofi states that the analytical transfer study was conducted per (b) (4)

and the Feb 2014 (Draft) FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics.

Sanofi indicated that they are unaware of any published guidance regarding the specific minimum number of lots to be used during transfer studies.

9h) Sanofi disagreed that the method was changed substantially after transfer to Sanofi Pasteur.

All responses to Question 9 are acceptable.

10. *In Section 3.2.P.5.3, you provide a summary of the validation for PRP Content for (b) (4). The information provided is not sufficient.*

- a. *For specificity, please provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results.*
- b. *For accuracy, please provide data using a minimum of 9 determinations over a minimum of 3 concentrations covering the specified range of the assay using manufacturing samples.*
- c. *Precision was re-assessed in 2013. Please provide information on what samples were used in this study and how many determinations were made. Please provide data using a minimum of 9 determinations covering the specified range (3 concentrations, 3 replicates) using manufacturing samples.*
- d. *For linearity, please provide data to include graphs, slope, y-intercept, and correlation coefficient to compare the linearity of the reference standard and manufacturing sample to cover a minimum of 5 concentrations.*

- e. *The range was demonstrated to be (b) (4) . Please provide data to support this range.*
- f. *The method transfer from Merck to Sanofi was verified by testing (b) (4) lots (b) (4) times in each lab. This does not provide sufficient data to verify a procedure's suitability under actual conditions of use for a specified drug substance or drug product. Please provide additional data for a minimum of 6 lots to show suitability under actual conditions. Please provide data on manufacturing samples with varying concentrations. Comparative studies should include evaluation of accuracy and precision with regard to assessment of inter-laboratory variability. For stability indicating assays, forced degradation samples or samples containing pertinent product-related impurities should also be analyzed at both sites.*

Response to Q10 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 3)

10a) The Specificity for the PRP Content assay was confirmed by (b) (4)

10b) Sanofi provided satisfactory assay results of (b) (4) in the Table 12 of the response to demonstrate the accuracy of the assay.

10d) Sanofi provided the requested data in the Table 15 of STN 125563/0.11, Section 1.11.1 Amendment 3.

10e) Sanofi indicated that the data used to support the assay range is the same data used to establish accuracy, linearity, and precision, and was provided in Table 12 to Table 14 of STN 125563/0.11, Section 1.11.1 Amendment 3.

10f) Sanofi indicated that (b) (4) lots were used for the analytical transfer study from Merck to Sanofi in order to satisfy the required replicates per the statistical study design, and that the analytical transfer study was conducted based on following guidance:

(b) (4)

and the Feb 2014 (Draft) FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics.

Sanofi further stated that, besides the (b) (4)

(b) (4)

, Sanofi is not aware of any published guidance regarding the specific minimum number of lots to be used during transfer studies.

Sanofi's responses to Question 10 are acceptable.

11. In Section 3.2.P.5.3, you provide a summary of the validation for (b) (4) PRP-OMPC for (b) (4) Product. The information provided is not sufficient.

- a. For specificity, please provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results.
- b. For accuracy, please provide data using a minimum of 9 determinations over a minimum of 3 concentrations covering the specified range of the assay using manufacturing samples.
- c. Precision was re-assessed in 2013. Please provide information on what samples were used in this study and how many determinations were made. Please provide data using a minimum of 9 determinations covering the specified range (3 concentrations, 3 replicates) using manufacturing samples.
- d. For linearity, please provide data to include graphs, slope, y-intercept, and correlation coefficient to compare the linearity of the reference standard and manufacturing sample to cover a minimum of 5 concentrations.
- e. The range was demonstrated to be (b) (4). Please provide data to support this range. Please confirm that this range supports the specification range of (b) (4).
- f. The method transfer from Merck to Sanofi was verified by testing (b) (4) lots (b) (4) times in each lab. This does not provide sufficient data to verify a procedure's suitability under actual conditions of use for a specified drug substance or drug product. Please provide additional data for a minimum of 6 lots to show suitability under actual conditions. Please provide data on manufacturing samples with varying concentrations. Comparative studies should include evaluation of accuracy and precision with regard to assessment of inter-laboratory variability. For stability indicating assays, forced degradation samples or samples containing pertinent product-related impurities should also be analyzed at both sites.

Response to Q11 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 3)

11a) The Specificity for (b) (4) PRP-OMPC – (b) (4) Product assay was confirmed by (b) (4)

(b) (4)

11b) Accuracy was assessed with (b) (4)

(b) (4). Sanofi provided satisfactory results in the Tables 18 and 19 in STN 125563/0.11, Section 1.11.1 Amendment 3.

11c) Sanofi showed that, in Section 3.2.P.5.3 PRP Content and (b) (4) PRPOMPC– (b) (4) Product, sub-section 3.1 Samples Used in Validation, (b) (4) (b) (4) from actual manufactured PR5I lots were used in precision re-assessing study. Sanofi provided data in Table 20, 21 and 24 to demonstrate the precision of the assay.

11d) Sanofi provided requested data in Table 22 and Figure 4 of STN 125563/0.11, Section 1.11.1 Amendment3.

11e) Sanofi indicated that Per ICH Q2(R1), the range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. Acceptable precision, accuracy, and linearity results for (b) (4) /dose PRP samples established the same range for (b) (4) PRP.

(b) (4)

11f) Sanofi indicated that the analytical transfer study was conducted based on following guidance:

- (b) (4) (b) (4) the Feb 2014 (Draft) FDA Guidance for Industry Analytical Procedures and Methods Validation for Drugs and Biologics.

Sanofi further stated that, besides the (b) (4) (b) (4), Sanofi is not aware of any published guidance regarding the specific minimum number of lots to be used during transfer studies.

Sanofi also stated that, due to the consistency of the manufacturing process, it was not possible to obtain data on manufacturing samples with a range of concentrations. Samples analyzed at both sites represented 100% target concentrations of all PR5I drug product components and therefore were representative of all product-related impurities.

Sanofi indicated that (b) (4) samples were not included in the transfer study, because (b) (4) samples themselves pose a risk to the method transfer study due to the potential for increased variability and decreased sample stability which may outweigh any added benefit to the transfer study's goal of evaluating the analytical procedure's performance at the receiving site.

Sanofi's responses to Question 11 are acceptable.

12. In Section 3.2.P.5.3, you provide a summary of the validation for (b) (4) 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 to Q12 (STN 125563/0.10, submitted on May 28, 2015, Section 1.11.1 Amendment 2)

Sanofi states that the specificity of the method is demonstrated by the positive detection of the PR5I specific (b) (4) in samples containing PR5I products and the negative detection in samples without the corresponding PR5I protein antigen. Sanofi provided satisfactory results (Table 2, of the Section 1.11.1 Amendment 2 in STN 125563/0.10) of specificity assessment for the (b) (4) Test for Labeled Filled Product.

13. In Section 3.2.P.6, you provide information on the qualification and re-evaluation of the reference standard used for (b) (4) PRP-OMPC and Identity of PRP-OMPC. The reference standard is an in-house PRP-OMPC Conjugate lot. The information provided is not sufficient.

- a. Please provide detailed procedures on how the reference standard is chosen or made.
- b. Please clarify who will be responsible for making and qualifying future reference standards. If Sanofi, please provide the procedures for making and qualifying future reference standards. If Merck, please provide procedures that Sanofi will perform to verify the qualification prior to use. Please note that since a Comparability Protocol was not submitted, we do not concur with your proposal to submit future reference standards in your Annual Report. Please withdraw this request.
- c. Please provide detailed procedures on how the reference standard will be re-evaluated for extension of dating. Please provide limits on the number of times a reference standard can be re-evaluated and expiry extended. If the procedure allows for extension beyond the approved hold time of the PRP-OMPC Conjugate lot, please describe how the expiry is assigned and how the reference standard is monitored to ensure that the reference standard does not deteriorate in quality beyond the expected shelf life of the Conjugate Lot.

Response to Q13 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 3)

13a) In Section 3.2.P.6 (STN 125563/0/11) Sanofi provided details of the qualification process to choose and qualify the reference standard for (b) (4) PRP-OMPC and Identity of PRP-OMPC, based on Merck's procedure for (b) (4) for (b) (4) and Identity of PRP-OMPC Conjugate in PR5I Formulations".

13b) Sanofi stated that per an agreement between Merck and Sanofi Pasteur, Merck will qualify and provide reference standard materials to Sanofi. Sanofi will not perform additional quality or suitability testing on received reference standards before routing usages.

Sanofi clarified that any the re-evaluation date extensions of the reference standards will be reported in the annual report, however, in the absence of an approved comparability protocol, implementation of new reference material lots would be submitted as a PAS to this BLA.

13c) In Section 3.2.P.6 (STN 125563/0.11) Sanofi provided details of the re-evaluation process to extend reference standard dating. Sanofi did not specify limits on the number of times a reference standard can be re-evaluated, but intent to evaluate the acceptability of the reference material on a continuing basis, and to extend the re-evaluation dates based on acceptable performance of the reference material.

Sanofi's responses to 13a and 13b are acceptable. The response to 13c was not acceptable. Therefore, an additional IR comment was issued on July 27, 2015. Refer to this IR for additional details.

14. In Section 3.2.P.6, you provide information on the qualification and of the reference standard used for PRP Content and (b) (4) PRP-OMPC. The reference standard is prepared from at least (b) (4) lots of PRP (b) (4) The information provided is not sufficient.

- a. Please clarify who will be responsible for making and qualifying future reference standards. If Sanofi, please provide the procedures for making and qualifying future reference standards. If Merck, please provide procedures that Sanofi will perform to verify the qualification prior to use. Please note that since a Comparability Protocol was not submitted, we do not concur with your proposal to submit future reference standards in your Annual Report. Please withdraw this request.*
- b. Please provide limits on the number of times a reference standard can be re-evaluated and extended. If the procedure allows for extension beyond the approved hold time of the PRP lot, please describe how the expiry is assigned and how the reference standard is monitored to ensure that the reference standard does not deteriorate in quality beyond the expected shelf life of the PRP Lot.*

Response to Q14 (STN 125563/0.11, submitted on June 5, 2015, Section 1.11.1 Amendment 3)

14a) Sanofi stated that Merck will qualify and provide reference standard materials to Sanofi. In its response to Q13b, Sanofi stated that the re-evaluation date extensions of the reference standards will be reported in the annual report, however, in the absence of an approved comparability protocol, implementation of new reference material lots would be submitted as a PAS to this BLA.

14b) Sanofi did not specify limits on the number of times a reference standard can be re-evaluated, but indicated that will continually monitor the validity criteria parameters for the reference standards during routine testing to evaluate the stability and continued suitability of the reference standards for use in each test.

Sanofi's response to 14a is acceptable. Sanofi's response to 14b was not acceptable. Therefore an addition IR was issued on July 27, 2015. Refer to this IR for further details.

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) containers that are representative of the (b) (4) containers used in routine manufacturing.

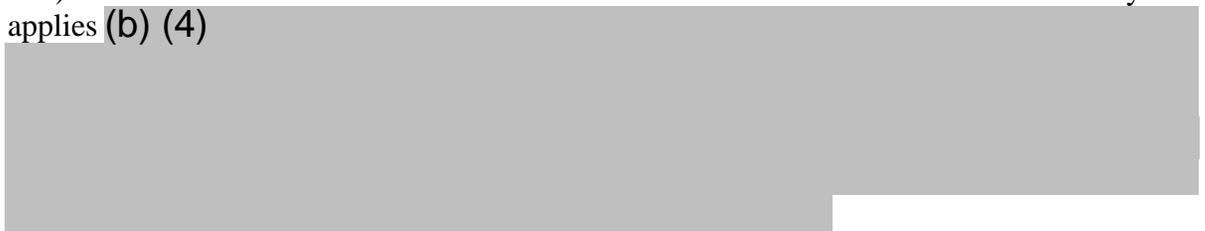
(b) (4)



Response to Q15 (STN 125563/0.10, submitted on May 28, 2015, Section 1.11.1 Amendment 2)

15a) Sanofi provided details on the container closure system in the updated Table 2 of Section 3.2.P.8.1 and in this amendment.

15b) Sanofi stated that the information in Table 2 of 3.2.P.7 Container Closure System applies (b) (4)



15c) (b) (4)

Sanofi's responses to Question 15 are acceptable.

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 to Q16 (STN 125563/0.10, submitted on May 28, 2015, Section 1.11.1 Amendment 2)

Sanofi updated the stability protocols in section 3.2.P.8.2 in amendment 10.

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 (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.

Sanofi's response to Question 17 is acceptable.

Response to Q17 (STN 125563/0.10, submitted on May 28, 2015, Section 1.11.1 Amendment 2)

Sanofi updated the section 3.2.P.8.2 of amendment 10.

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 to Q18 (STN 125563/0.10, submitted on May 28, 2015, Section 1.11.1 Amendment 2). Sanofi provided satisfactory 30-month stability data for (b) (4) PRP-OMPC, PRP Content, and (b) (4) PRP-OMPC in the Table 9 of Section 3.2.P.8.3 in amendment 20 dated September 15, 2015.

Sanofi's response to this question and updated stability data provided later are acceptable.

19. Section 3.2.P.5.1, Table 5 - Release Specification for PR5I Labelled 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 to Q19 (STN 125563/0.10, submitted on May 28, 2015, Section 1.11.1 Amendment 1)

Sanofi stated that the primary method used for identity testing will be the (b) (4)) method, whereas the alternate identity tests by (b) (4) will only be performed in the event that the equipment for (b) (4) is not operational and could significantly delay performing the tests.

Sanofi's response to question 19 is acceptable.

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 to Q23 (STN 125563/0.10, submitted on May 28, 2015, Section 1.11.1 Amendment 1)

Sanofi stated that because endotoxin is tested by (b) (4) method at various stages of manufacturing of PR5I. Endotoxin may be pyrogenic, and importantly, because pyrogen testing is conducted on the PR5I Filled Product, endotoxin testing will not be necessary on the PR5I (b) (4) Product.

Information Request Dated July 27, 2015

CBER considered many responses to the April 17, 2015 acceptable as discussed above. We issued an additional information request on July 27, 2015, for the following remaining issues:

Sanofi submitted a response to these IR's in Amendment 20 (STN 125562/0.20, submitted on September 5, 2015)

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 1: Sanofi stated that “the company commits to perform a post-approval bulk stability study (b) (4). The stability data will be submitted to CBER once available”. This response is acceptable.

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: Sanofi stated that “The proposed acceptance criteria for the (b) (4) test will be applied at release and stability monitoring”. This response is acceptable.

3. *In your response to Question 3c of the IR dated 17 April 2015, you state that the data provided in Table 1 in conjunction with the satisfactory batch release results support the (b) (4) conditions for PRP-OMPC Bulk. We do not concur. You are proposing a (b) (4) for the PRP-OMPC bulk (b) (4). The data provided support a (b) (4). Please provide data using the current manufacturing process to support the entire range of the proposed (b) (4) time. Alternatively, please commit to provide these data post approval.*

Response 3: Sanofi stated that “(b) (4) studies performed by Merck indicate that (b) (4). This response is acceptable.

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) Product 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 LPS is known to be associated with the OMPC 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: Sanofi indicated that endotoxin testing using the (b) (4) method is performed at (b) (4)

This response is acceptable.

5. *In your response to Question 13c of the IR dated 17 April 2015, you state that the reference standard used for (b) (4) PRP-OMPC and Identity of PRPOMPC will be re-evaluated for extension of dating by evaluating the (b) (4) for any potential trends. You have not provided comments to all of our concerns raised in Question 13c. Please provide detailed procedures on how the reference standard will be re-evaluated for extension of dating. Please provide limits on the number of times a reference standard can be re-evaluated and expiry extended. Since your procedure allows for extension of dating beyond the approved hold time of the PRP-OMPC Conjugate lot, please describe how the reference standard is monitored to ensure that it does not deteriorate in quality beyond the expected shelf life of the Conjugate lot.*

Response 5: Sanofi stated that lot (b) (4) was manufactured in (b) (4) (b) (4) for measuring (b) (4) PRP-OMPC of drug product as determined by (b) (4). According to your procedures, this lot can be used as a reference for (b) (4). The approved hold time of lot (b) (4) when used in manufacturing is (b) (4); however, lot (b) (4) can be used up to (b) (4) when used as a reference.

The following concerns remain:

- a. You have not provided procedures on how lots will be chosen to qualify as reference standards. Please provide these procedures.
- b. Your procedures during qualification and during the annual re-evaluation do not include appropriate tests to determine that the quality of the conjugate has been maintained. Please provide additional testing during the qualification and annual re-evaluation to demonstrate that the reference conjugate is within specifications expected for the vaccine.

- c. Your re-evaluation procedures are based on trending of the (b) (4) . Please provide acceptance criteria for the re-evaluation.
6. *In your response to Question 14b of the IR dated 17 April 2015, you provide your procedure on how the reference standard used for PRP Content and (b) (4) PRP-OMPC will be re-evaluated for extension of dating. You have not provided comments to all of our concerns raised in Question 14c. Please provide limits on the number of times a reference standard can be re-evaluated and expiry extended. Since your procedure allows for extension of dating beyond the approved hold time of the PRP lot, please describe how the reference standard is monitored to ensure that it does not deteriorate in quality beyond the expected shelf life of the PRP lot.*

Response 6: Sanofi indicated that “there is currently no limitation imposed for the number of re-evaluations for the PRP Content reference standard. This reference standard (b) (4)

This response is acceptable.

7. *In your responses to Questions 4, 5, 6, 7, and 8 of the IR dated 17 April 2015, you have committed to re-evaluate the specification limits for (b) (4) PRPOMPC, (b) (4) PRP-OMPC, PRP Content, and (b) (4) respectively, once data are collected from approximately (b) (4) PR5I vaccine lots, or earlier if warranted due to data trending. Please confirm that you plan to re-evaluate your specifications by using the tolerance intervals with 99% coverage and 95% confidence.*

Response 7: Sanofi stated that “the company proposes to re-evaluate the release specification limits for (b) (4) of PRP-OMPC, (b) (4) of PRP-OMPC, PRP Content, and (b) (4) by using appropriate statistical methods once data are collected from approximately (b) (4) PR5I Vaccine lots, or earlier if warranted due to data trending. The company will re-evaluate the specifications by using the tolerance intervals with 99% coverage and 95% confidence or other appropriate statistical method based on the distribution of the data. The updated acceptance criteria for these tests will be submitted in a supplement to CBER with the supporting data and analysis”. This response is acceptable.

Component Information Table

I reviewed the components that are used to manufacture PRP-OMPC Bulk Intermediate (from Liquid PedvaxHIB® BLA 103237) in the PR5I vaccine and no discrepancies were identified. The raw materials and all other ingredients including all components of animal origin are identical to the components used in the manufacture of the Liquid PedvaxHIB® (BLA 103237), therefore, are free of adventitious agents and acceptable for use in the production of PR5I.

5. Recommendation

After the complete reviewing of submissions STNs 125580/0, 125563/0 and related amendments, I recommend grant approval to these BLAs, pending satisfactorily resolution of the following deficiencies:

BLA 125580/0

(b) (4)



BLA 125563/0

In your response to Question 5 of the IR dated 27 July 2015, you state that lot (b) (4) was manufactured in (b) (4) for measuring (b) (4) PRP-OMPC of drug product as determined by (b) (4). According to your procedures, this lot can be used as a reference for (b) (4). The approved hold time of lot (b) (4) when used in manufacturing is (b) (4); however, lot (b) (4) can be used up to (b) (4) when used as a reference. The data provided do not support the proposed hold time of your reference.

- a. You have not provided procedures on how lots will be chosen to qualify as reference standards. Please provide these procedures.
- b. Your procedures during qualification and during the annual re-evaluation do not include appropriate tests to determine that the quality of the conjugate has been maintained. Please provide additional testing during the qualification and annual re-evaluation to demonstrate that the reference conjugate is within specifications expected for the vaccine.
- c. Your re-evaluation procedures are based on trending of the (b) (4). Please provide acceptance criteria for the re-evaluation.