



CMC Review Memorandum

Date: December 14, 2018
To: The file STN 125563
From: Diana Kouivaskaia, OVRD/DVP, Product reviewer
Through: Steven Rubin, OVRD/DVP
Sara Gagneten, OVRD/DVP
Robin Levis, OVRD/DVP
Copy: Rana Chattopadhyay, OVRD/DVRPA, RPM
Applicant name: Sanofi Pasteur
STN: 125563/0.33; 125563/0.44 (responses to IR); 125563/0.54 (responses to IR); 125563/0.56 (responses to IR)
Product: PR5I (Vaxelis)
Subject: Quality amendment to approve changes related to reference standards used in Rat immunogenicity test and D-antigen content for IPV component and in the in vitro portion of the acellular pertussis mouse immunogenicity assay and review of responses to IR of 10/15/2018, 11/26/2018, and 12/04/2018
Action due date: December 29, 2018
Recommendation: Responses are acceptable.

Executive summary

This amendment was submitted to approve the following changes:

- a. (b) (4) 

This review is limited to the changes/data pertaining to the IPV component of the vaccine (change a, c, and d above).

Amendment 33 (dated April 23, 2018) - Review of CMC Changes

1. (b) (4) [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Comment to relay to the sponsor:

We do not agree with discontinuation of correction factor use. While at the time of reassessment of (b) (4) potency (date not stated), Type 1, 2, and 3 correction factors were close to (b) (4) the data shown in Figure 9 in document “Reference Standards or Materials Stability Data” (eCTD Section 3.2.P.6, Stability Data, pages 14 of 16) predict that the Type 1 and Type 3 potencies of (b) (4) will continue to decay. If your projections are correct, the correction factors will substantially deviate from (b) (4) in the near future, necessitating to reemploy correction factors. Please provide a plan for more frequent monitoring of (b) (4) potency in order to employ periodically adjusted correction factors. [See comment 1 under Information Requests.]

- *Extension of the reference vaccine shelf-life*

(b) (4)

[Redacted]

[Redacted]

[Redacted]

1 page determined to be not releasable: (b)(4)

- (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

3. Stability commitments

The company has committed to three stability commitments. Two of the stability studies have been completed.

- Accelerated stability commitment (stability studies Bio-12946 and Q_0521195)

The accelerated stability study included (b) (4) PR5I vaccine finished product lots:

- (b) (4) lots in (b) (4) presentation (b) (4)
- (b) (4) lots in vial presentation (b) (4)

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

- Complete stability data for Lot (b) (4) in vial presentation stored at 2-8°C

The results for 48 month stability time point for D-Ag content and up to 42 months for the immunogenicity test in rats were reviewed in the original application and were compliant. The only new stability data for IPV are for the Rat test for the 48-month time point. The results conform to the specification of (b) (4) for Types 1, 2, and 3, respectively).

Reviewer's comment:

Potency of the IPV component of the PR5I vaccine determined by two methods in the long-term stability studies was within the specification. The results are acceptable.

Amendment 44 (SN 46 dated October 26, 2018) – Responses to Information Request Issued on October 15, 2018

A request for information was communicated to the sponsor on October 15, 2018. The company submitted responses by email on October 24, 2018 (and as an amendment 125563/0.44, SN 46, on October 26, 2018). A review of the responses is below.

CBER Question 1a

With regard to the reference standard used in the rat immunogenicity test:

Based on the provided on your investigation into the OOS result for IPV Type 2 in the rat-based stability testing of DTaP-IPV-Hib vaccine, it appears that the potency of reference lot (b) (4) is decreasing over time, resulting in the likelihood of overestimating the relative potency of vaccine lots when tested in rats. Please comment.

Sponsor's Response:

(b) (4)

(b) (4)

Reviewer's comment:

Addressed in new comments #1 and 2 to be relayed to the sponsor (at the end of this review).

CBER Question 1b

Please provide stability data for D-antigen content of the reference lot (b) (4)

Sponsor's Response:

(b) (4)

(b) (4)

(b) (4)

CBER Question 2

With regard to the reference standards used in the D-antigen (b) (4)

- Please provide stability data for the reference lot (b) (4) stored at the Toronto site and used to determine IPV potency in the PR5I (b) (4) product.
- Please identify the location where lot (b) (4) was qualified (Toronto or MLE).

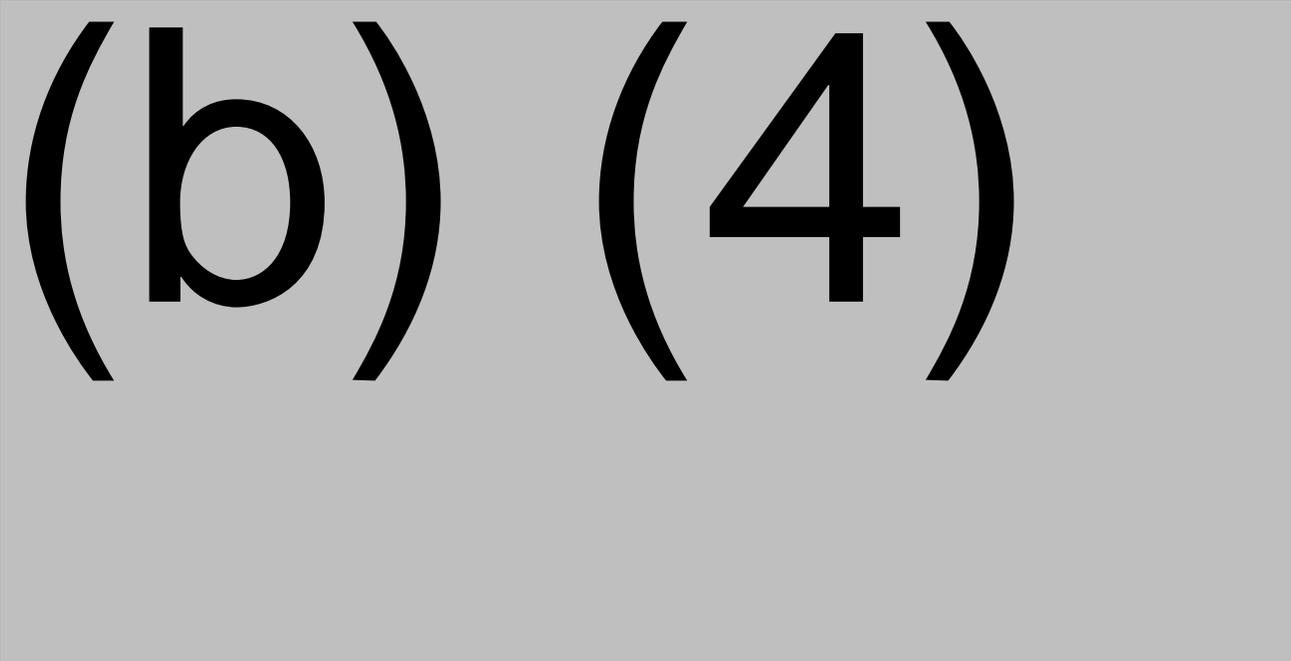
Sponsor's Response:

(b) (4)

Reviewer's comment:

(b) (4)

(b) (4)

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Information Request of November 26, 2018

An Information Request was relayed to the applicant on November 26, 2018. The company submitted responses in the Amendment 125563/0.54 on December 6, 2018. The responses are reviewed below.

Amendment 54 (SN 54 dated October 26, 2018) – Responses to Information Request Issued on November 26, 2018

CBER Question 1:

We do not agree with discontinuation of correction factor use. Although at the time of reassessment of (b) (4) potency (date not stated), Type 1, 2, and 3 correction factors were close to (b) (4), the data shown in Figure 9 in document “Reference Standards or Materials Stability Data” (eCTD Section 3.2.P.6, Stability Data, pages 14 of 16) predict that the Type 1 and Type 3 potencies of (b) (4) will continue to decay. If your projections are correct, the correction factors will substantially deviate from (b) (4) in the near future, necessitating to reemploy correction factors. Please provide a plan for more frequent monitoring of (b) (4) potency in order to employ periodically adjusted correction factors.

Sponsor's Response:

(b) (4)

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Reviewer's comment:

(b) (4)

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. The response is acceptable.

CBER Question 2a:

We note that the potency values determined for this material as reported in this submission for the Toronto site are different from the values determined for the same material at the MLE site as reported in STN 103930/5234. Please explain.

Sponsor's Response:

(b) (4)



CBER Question 2b:

Please provide the qualification report for reference lot (b) (4) . If the qualification study was not performed at the Toronto site, please provide data demonstrating acceptable performance of the reference material at the Toronto site. Such data should include a comparison of the D-antigen content of an appropriate number of production lots when tested using the current reference lot (b) (4) versus lot (b) (4)

Sponsor's Response:

(b) (4)




**Amendment 56 (SN 56 dated December 12, 2018) – Responses to Information Request
Issued on December 7, 2018**

CBER Question:

With regard to your response of December 6, 2018 to our Information Request of November 26, 2018, Question 2b, prior to implementation of reference standard lot (b) (4) , please provide

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

Sponsor's response:

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment:

The (b) (4) test, transferred from the MLE to the Toronto site, uses the same reference and critical reagents at both sites, and performance of the test is monitored using shared positive control. The new reference lot was initially calibrated and qualified at the MLE site against the current reference standard (b) (4) . Per CBER request to demonstrate that implementation of the new reference would not impact the results of the (b) (4) the company agreed to perform the comparability study at the Toronto site to qualify the reference before its implementation and submit the report as a CBE-30 supplement to the file. The response is acceptable.