



CMC Review Memorandum

Date: November 30, 2018
To: The file STN 125563
From: Diana Kouliavskaia, OVRD/DVP, Product reviewer
Through: Steven Rubin, OVRD/DVP
Sara Gagneten, OVRD/DVP
Robin Levis, OVRD/DVP
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Applicant name: SANOFI PASTEUR
STN: 125563/0.44 (Sequence Number 46) and 125563/0.47 (Sequence Number 49)
Product: PR5I (Vaxelis)
Subject: Quality amendments submitted in response to CBER Information Requests of 10/15/2018 and 11/1/2018
Action due date: December 29, 2018
Recommendation: **Request for a post-marketing commitment was issued on November 1, 2018. Response is acceptable.**

Summary

This amendment was submitted in response to the information request of October 15, 2018, that included comments pertaining to:

- Amendment 125563/0.33: Questions 1 and 2 were questions regarding reference standards used in the IPV potency assays. Please refer to the STN 125563/0.33 review memo.
- Amendment 125563/0.38: questions 3-5 were questions concerning statistical aspects of the assay and calculations and will be reviewed by the statistical reviewer.
- Amendment 125563/0.43: question 6, reviewed below.

Review of the amendment

The following question (Question 6 of the IR) was communicated to the company after review of the Amendment 125563/0.43:

We have reviewed your responses to question 1 regarding establishment of IPV potency acceptance criteria for PR5I release and stability. While we concur with your explanation for why application of correction factors obtained with vIPV is not appropriate, we do not concur that the currently proposed acceptance criteria for the minimum potency at release (b) (4) and (b) (4) D-antigen units for poliovirus types 1, 2, and 3, respectively) provides assurance that “PR5I is as immunogenic as the currently licensed component vaccine control(s) (i.e., PENTACEL™ and RECOMBIVAX HBTM in the US, and INFANRIX™ hexa in Europe)” as stated in the BLA. One approach to setting acceptance limits for PR5I could be to make them proportionally equivalent to those for Pentacel as shown in Table 1 and Table 2.

Table 1: Pentacel and PR5I minimum D-antigen specifications (per 0.5 mL dose) for release of (b) (4)

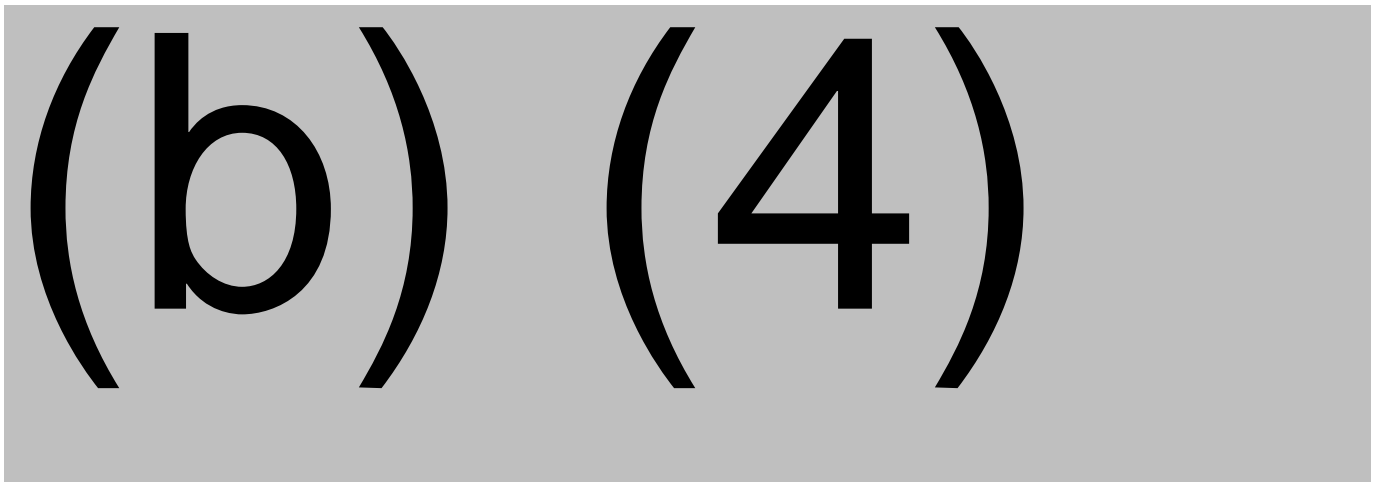
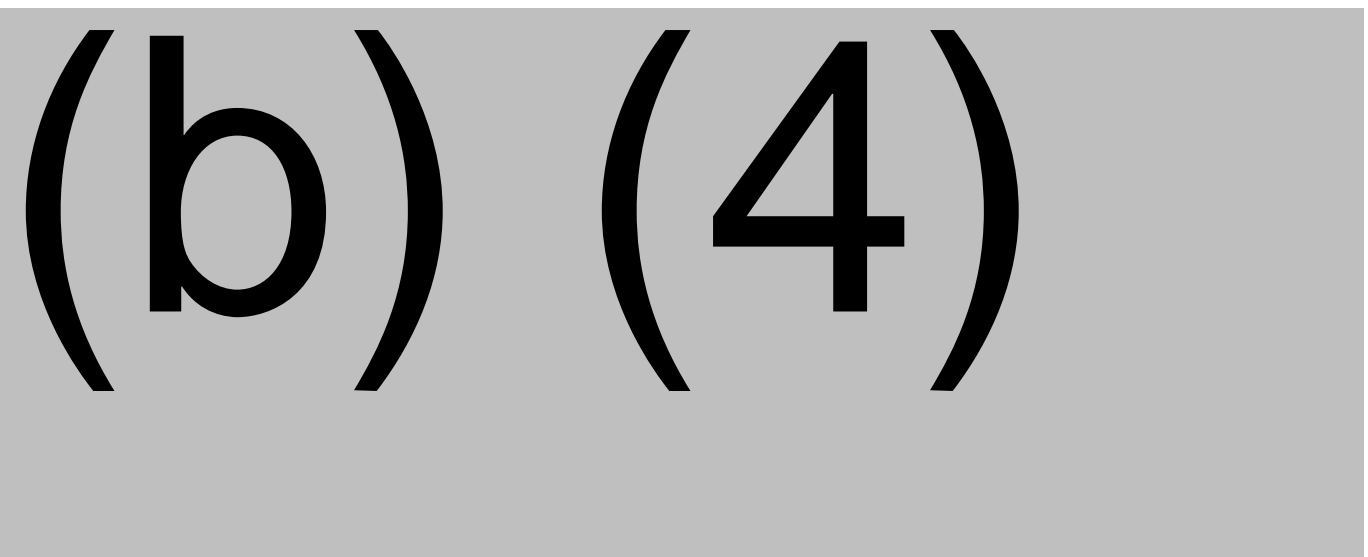
A large rectangular area is completely redacted with a solid gray background. In the center of this redacted area, the text "(b) (4)" is printed in a large, bold, black font, indicating that the table's content is withheld under FOIA exemption (b)(4).

Table 2: Pentacel and PR5I minimum D-antigen specifications (per 0.5 mL dose) for stability of final containers

A large rectangular area is completely redacted with a solid gray background. In the center of this redacted area, the text "(b) (4)" is printed in a large, bold, black font, indicating that the table's content is withheld under FOIA exemption (b)(4).

- (b) (4)

Although potency criteria should preferably be based on clinical experience with PR5I, we need to formulate an approach that is logical to assure that the potency of PR5I is equivalent to the potency of Pentacel. Therefore, we request that you revise the proposed potency lower limits for PR5I release and stability for the IPV Types 1, 2, and 3 components to reflect those of IPV in Pentacel as follows:

- (b) (4)

(b) (4)

- For stability monitoring of PR5I Filled Containers:

(b) (4)

Please revise all affected CMC sections of the BLA and update the blank LRP.

Sponsor's Response:

The company stated that to establish Pentacel D-antigen (b) (4) acceptance criteria, statistical data from (b) (4) were analyzed, and the results obtained from the statistical analysis were approximately (b) (4) than the mIPV target concentration of 40 DU/0.5 mL, 8 DU/0.5 mL and 32 DU/0.5 mL for Poliovirus Types 1, 2 and 3, respectively (the acceptance criteria for Pentacel are (b) (4) for Type 1, 2, and 3, measured by (b) (4) method).

The company emphasized that the D-antigen (b) (4) assays used to determine D-antigen content in vaccines containing IPV propagated on MRC-5 cells (mIPV) and Vero cells (vIPV) are different in terms of assay design, reference standards, and statistical model. Applying the acceptance criteria/target ratios used for the Pentacel vaccine to the PR5I vaccine is not appropriate. The company provided data from PR5I lots (including (b) (4) clinical lots) at release and on stability. For Poliovirus Type 1, the lots were trending very close to the acceptance limit proposed by CBER, and for Poliovirus Types 2 and 3, there were several data points, including from clinical lots that were below the acceptance limits proposed by CBER. All the PR5I U.S.

lots that have a D-antigen (b) (4) result for Type 2 and Type 3 below CBER's proposed acceptance criteria were tested in the Rat Immunogenicity assay and met acceptance criteria. The company also noted that the Rat Immunogenicity Assay is not performed for the PR5I lots marketed in Europe.

The company stated that all D-antigen (b) (4) data that are available to date are comparable between release and stability and considered the current acceptance criteria appropriate for both release and stability monitoring.

The current acceptance criteria for the D-antigen (b) (4) using the (b) (4) method for the PR5I (b) (4) product were first established (b) (4)

(b) (4)

Reviewer's comment:

The response was discussed internally. The proposal from the company to maintain current acceptance criteria for the vIPV content for release of (b) (4) Product was found acceptable for the following reasons:

- The vaccine is formulated to contain 29, 7, and 26 DU/ml of serotypes 1, 2, and 3 per dose, respectively. Based on the stability data provided by the company for (b) (4) lots of final vaccine, the IPV component is stable throughout the proposed shelf life of the product. In addition, the specifications used to assess stability are close for the PR5I and Pentacel (please refer to the Table 2 of this memo).
- The in-vivo potency test (rat immunogenicity test) will be performed on the (b) (4) product as a release test.
- The company committed (b) (4)
- Current acceptance criteria are harmonized across the vIPV-containing products, formulated to contain the same amounts of vIPV antigens. (b) (4)

Comment to relay to the sponsor:

The company's response to Question 6 and proposal to commit to (b) (4) as a post-licensure activity was discussed, and the following commitment request was issued to the sponsor on November 1, 2018:

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

Response:

The company submitted response in the Amendment 0.47 on November 19, 2018.

In the response, the company provided clinical data and addressed comparison of the D-antigen content of representative Pentacel and PR5I requested by CBER.

The clinical information provided in support of the release acceptance criteria appears to be duplicative of the information submitted in the original application (clinical lots C3145, C3146, C3147).

The company stated that due to the different D-Ag ((b) (4)) methods and reference standards used to formulate and test the two types of IPV DS (IPV manufactured with MRC-5 cells in Pentacel and Vero cells in PR5I), it is not expected that the two products have the same IPV content; both products have been shown to be immunogenic in the same clinical studies, and different acceptance criteria are justified.

As requested by CBER, the company commits to measure

((b) (4))

one year of approval.

The data will be submitted within

Recommendation:

The company committed ((b) (4))

. Although no specific information on comparability study was provided in the amendment, design of the study may be discussed after approval as CBER requested to submit this information within a year of approval. The response is acceptable.