



CMC Review Memorandum

Date: November 29, 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: 125563/0.43 (Sequence Number 44)
Product: PR5I (Vaxelis)
Subject: Quality amendment submitted in response to CBER Information Request of 09/27/2018
Action due date: December 29, 2018
Recommendation: An Information Request pertaining to the material discussed in this amendment was issued on October 15, 2018

Review of the amendment

This amendment was submitted in response to the CBER information request dated 09/27/2018.

CBER Question 1:

Regarding the acceptance limits for the IPV components, we note that the proposed lower limits are lower when reporting potencies using the (b) (4) method than the corresponding limits for Pentacel using the (b) (4) method. Therefore, we request that the lower limits for the IPV components in PR5I be revised to reflect the lower limits for Pentacel as close as possible. One approach could be to apply conversion factors as you relayed previously (e.g., (b) (4), for poliovirus Types 1, 2, and 3, respectively), if applicable in this situation.

Sponsor's Response:

The company considers applying correction factors to the acceptance criteria not appropriate for the following reasons:

- (b) (4)

- (b) (4)

The company deems that vIPV product specific criteria should be maintained and referred to Amendment 125563/0.38 that contains results of stability monitoring of the clinical lots. The company also stated that it will re-evaluate the product acceptance criteria once data are collected from approximately (b) (4) PR5I vaccine lots.

Reviewer's comment:

Please see the comment below (after review of response to Question 2).

CBER Question 2:

In your response to Question 3 you indicated, "...the D-antigen contents indicated in the Product Information for PR5I US is based on the (b) (4) method (29, 7, 26 DU/dose) whereas the D-antigen content indicated in the Product Information for PR5I Europe (40, 8 and 32 DU/dose) is based on the method used for the (b) (4) method). However, the (b) (4) used for PR5I US and PR5I EU are identical and strictly formulated and tested for D-antigen content in the same way using the same acceptance criteria." We understand that the (b) (4) are tested using the (b) (4) method for PR5I released in the US and EU; however, the calculation method used on the PR5I (b) (4) Product (i.e., (b) (4) Filled Product released in the EU is not clear. Please clarify which D-antigen (b) (4) calculation method is used on the drug product steps ((b) (4) Filled Product, as applicable) for release of PR5I vaccine in the EU and provide the acceptance limits.

Sponsor's Response:

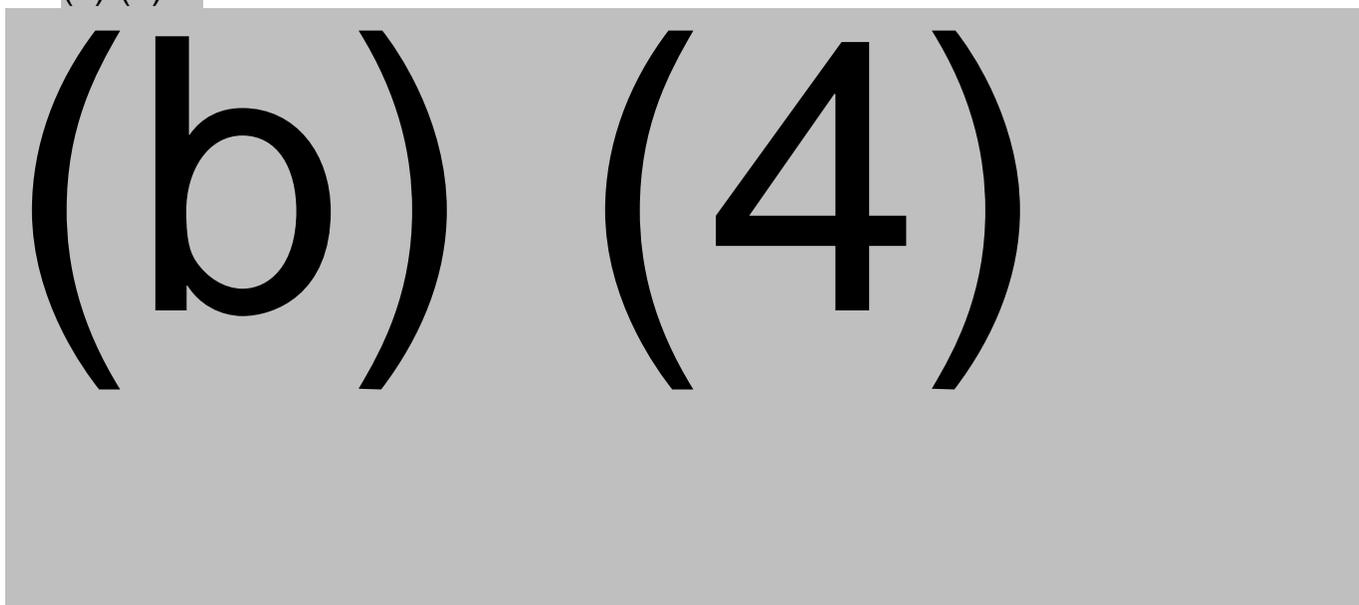
The company confirmed that the products for the two markets are tested using the same method at the (b) (4) for stability monitoring. The (b) (4) calculation method and acceptance criteria are the same for the two markets; however, the D-Ag content listed in the EU Product information is different for historical reasons to reflect previously used formulation target content based on the (b) (4) method. This is reflected in the footnote to the IPV potency of the Vaxelis EU label that states "or equivalent antigenic quantity determined by a suitable immunohistochemical method".

Comment to Relay to the Sponsor

The responses were discussed internally; the following comment was included in the IR emailed to the company 10/15/2018 (Question 6 of the IR).

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) 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 HB™ 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 Tables 1 and 2.

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



The content of Table 1 is redacted with a large grey box containing the text (b) (4) in large black font.

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



The content of Table 2 is redacted with a large grey box containing the text (b) (4) in large black font.

(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.

Note:

Response to the IR of 10/15/18 was submitted in the Amendment STN 125563/0.44, was reviewed and discussed, and another IR was emailed to the company on 11/01/18. The IR included request for a commitment (b) (4) within one year of approval of the BLA for PR5I (Vaxelis).

In the response (Amendment 0.47), the company committed (b) (4)

The response was found to be acceptable.

Please refer to the STN 125563/0.44 review memo for review of amendments 0.44 and 0.47.