



CMC Review Memorandum

Date: November 29, 2018
To: The file STN 125563
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Applicant name: Sanofi Pasteur
STN: 125563/0.38 (Sequence Number 39)
Product: PR5I (Vaxelis)
Subject: Quality amendment submitted in response to a CBER Information Request dated June 14, 2018 concerning IND 14496/0.123
Action due date: December 29, 2018
Recommendation: Information Requests pertaining to the material discussed in this submission were issued on September 27, 2018 and October 15, 2018

Summary

This amendment contains information regarding the IPV D-Antigen content in the PR5I vaccine in response to a CBER IR dated June 14, 2018, pertaining to IND 14496/0.123. The information in the present BLA amendment was also submitted to IND 14496/0.136. Two IR (September 27, 2018, and October 15, 2018) were issued to the sponsor after discussing information provided in this amendment (0.38). Responses to the IR were submitted in Amendments STN 125563/0.43 and 0.44, and will be reviewed and summarized in separate review memos under those STN.

Review of the amendment

CBER Question 1:

Regarding the SOP and validation report for the D-antigen (b) (4) used to test (b) (4) final container stability, please submit a revised SOP that includes a description of the methods of calculation of results including assessment of (b) (4)

Sponsor's Response:

The company submitted three SOPs describing the D-antigen testing and analysis procedures:

- Testing procedure: SOP Q_0235328, "Polio D-antigen (b) (4) by (b) (4) Analysis".
- Procedure for the calculation: SOP Q_0235371, "Calculation Program for the Polio (b) (4) D antigen (b) (4)".
- Specification for the D-antigen (b) (4) calculation program: SOP Q_0268418, "Design Specification for D-antigen (b) (4) Calculation Program for Polio".

Reviewer's comment:

Regarding the assessment of (b) (4) validity criteria for the (b) (4) SOP Q_0235328) include control limits for the reference standard (b) (4), which are also reported on the worksheets/product reports (as on Page 55/203).

The SOP Q_0268418 includes analysis of the data for (b) (4) of the reference standard and test sample by the software (2.4.2. Page 11/203). To establish validity of the calculation part of the (b) (4) test, both of the Correlation Coefficients for the Standard and the Product should be no less than (b) (4), and a (b) (4) is performed as described on Page 62/203.

In general, the sponsor's responses were acceptable, but required clarifications. Responses to the IR were submitted in Amendment 0.44 and were reviewed and summarized in a separate memo under that STN.

The SOPs were reviewed by the statistical reviewer; comments pertaining to statistical analysis of the results were included in the IR of October 15, 2018 (Questions 3-5). Please refer to the statistical review memo for responses to these questions.

CBER Question 2:

The poliovirus D-antigen content acceptance ranges for release of PR5I (b) (4) stability monitoring of final containers should be based on the potencies of lots tested in clinical studies. This does not appear to be the case for the currently proposed ranges (b) (4) DU/dose Type 1, (b) (4) DU/dose Type 2 and (b) (4) DU/dose Type 3). Please comment.

Response:

The company stated that the acceptance criteria were established for other IPV combination products containing vIPV, which are all formulated to contain the same amount of vIPV antigens; the acceptance criteria by (b) (4) method are linked to the results from clinical study lots for other vIPV combination products (DTaP-IPV-Hib and Tdap-IPV).

The company stated that it performed over 200 clinical trials with different IPV-containing vaccines and observed robust immune response in all trials.

Results of clinical studies U01-A5I-302 Part III (Tdap-IPV; lot number X1322-4), and A5I15 (lot C2314A), A5I16 and A5I19 (lot C2315A) for DTaP-IPV-Hib Vaccine were provided. The D-antigen content in the clinical lots is summarized below:

Table. D-antigen content in the combination vaccines' clinical lots.

Serotype	Specification	Tdap-IPV Lot X1322-4	DTaP-IPV-Hib Lot C2314A	DTaP-IPV-Hib Lot C2415A
Type 1	(b) (4) DU/dose	28.7	28.8	27.5
Type 2	(b) (4) DU/dose	5.9	6.3	6.5
Type 3	(b) (4) DU/dose	24.7	22.8	22.9

D-antigen content in the PR5I clinical lots C3145, C3146 and C3147 was measured using the (b) (4) method in effect at the time of the lots' formulation. However, the lots failed stability testing. The sponsor determined that the (b) (4) method lacked robustness and switched to the more robust (b) (4) method. For that reason, the PR5I clinical lots were released based on the results of the immunogenicity test in rats, which is the in-vivo potency release test for the vaccine. As such, there are no D-antigen content results for the clinical lots at release. The lots were tested for the D-antigen content in stability studies by the (b) (4) starting at the 12 to 18-month time points.

The results for the consistency and clinical lots in the stability study were within the acceptance criteria (Types 1-2-3):

- Lot C3145A: 25-7-24 at 18 months; 25-7-23 at 48 months;
- Lot C3146B: 25-6-22 at 12 months; 26-7-22 at 48 months;
- Lot C3145A: 23-6-19 at 12 months; 23-6-23 at 48 months;
- Lot (b) (4) 26-7-22 at 3 months; 26-7-21 at 48 months (the consistency lot (b) (4) was manufactured later and was not used in the clinical studies).

Reviewers' comment:

This response was discussed, and an IR (below) was issued to the company on September 27, 2018. The response to the IR was submitted in Amendment 43. An assessment of that response is presented in a separate review memo of Amendment 43.

CBER Question 3:

The (b) (4) calculation method is used for release of PR5I (Vaxelis proprietary name) in the EU; however, the IPV content of this product is reported as 40 D-antigen units (DU) Type 1, 8 DU Type 2, and 32 DU Type 3 per dose, which appear to be potencies that would be obtained from use of the (b) (4) calculation method (which is not performed on Vaxelis (b) (4)). Please clarify the method of calculation applied for the release and stability monitoring of PR5I in the EU and provide a detailed comparison between the methods used for PR5I in the EU and the proposed methods for PR5I in the US including a comparison of acceptance criteria.

Sponsor's Response:

The company stated that the D-antigen content is assessed for PR5I US and EU at release and stability monitoring using the same method, which is the D-Ag (b) (4) method. The D-Ag content indicated in the Product information for the US market is based on (b) (4) method (29-7-26 DU/dose, of Types 1-2-3, respectively). For EU, the values are 40-8-32 DU/dose, based on the (b) (4) method, which is used for (b) (4). However, the IPV (b) (4) used for PR5I US and PR5I EU are identical and strictly formulated and tested for D-Ag content the same way using the same acceptance criteria. The sponsor referred to the IND 14496/0.124 (SN #123), in which the company confirmed that the final drug product compositions are identical for PR5I US and EU formulations. The D-antigen (b) (4) method is used for PR5I at IPV (b) (4) stage while the (b) (4) method is used for PR5I at the (b) (4) Product stage and during the stability monitoring program. The company stated that the method of calculation is the same for both markets. The calculation method is provided in Response 1. The D-antigen content acceptance criteria are the same for both markets.

Comments to relay to the sponsor:

After internal discussions of the Amendment 125563/0.38, the questions below were relayed to the company (IR of September 27, 2018).

A response to the IR was submitted in Amendment STN125563/0.43 and will be reviewed and summarized in a separate memo under that STN.

Question 1 (IR of September 27, 2018):

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), and (b) (4), for poliovirus Types 1, 2, and 3, respectively), if applicable in this situation.

Question 2 (IR of September 27, 2018):

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.