

From: Hoffman, Kelsy
To: dana.harrison@sanofipasteur.com
Cc: [Rivers, Katie](mailto:Rivers_Katie); krissy.carrington@sanofipasteur.com
Subject: BLA 125563/0 Information Requests
Date: Friday, April 10, 2015 12:50:00 PM

Dear Ms. Harrison,

We have the following requests for information regarding STN 125563/0:

We have the following comments regarding the Final Drug Product:

1. In sections 3.2.P.2.4 Container Closure System (page 3 of 14), you state that “equivalent container closure systems (b) (4), glass, bromobutyl stopper), as described for PR5I, are used for other licensed Sanofi Pasteur Limited combination vaccines and were proven to be suitable for the purpose of formulation of Final Bulk Product and storage of Final Bulk Product and Filled Product.” Please provide the names of the licensed vaccines that are stored in the same types of (b) (4) and filled in the same 2-mL glass containers with bromobutyl stoppers. For these licensed products, please include the duration and conditions of the hold times for each Final Bulk Product and approved shelf life for each Filled Product and specify if there are any differences in the preparation (e.g., wash and sterilization) of the primary packaging components (glass vials and stoppers) compared to Pentacel (DTaP-IPV component) or other licensed vaccines.
2. Regarding the filling step, please confirm that the filling into the 2-mL glass vials is conducted by transferring (b) (4)

3. In your amendment of September 12, 2014 you proposed a 42-month shelf life for (b) (4) and you included stability data for up to the 42-month time point for all stability indicating parameters. Please provide pending results for all stability tests performed at the 48-month time point.

We also have the following comments regarding the IPV assays:

4. With regard to D-antigen (b) (4) tests:
 - a. Please provide a description of the procedures for monitoring the stability and performance of reference standards and controls used in the (b) (4) _____ used to quantify D-antigen content in IPV (b) (4) _____ Drug Product.
 - b. Please provide a description of the D-antigen testing format at each manufacturing stage (i.e., number of samples tested, number of replicates, (b) (4) type).
 - c. Please submit the Standard Operating Procedure (SOP) for the (b) (4) _____ used to determine D-antigen content in (b) (4) vaccine (b) (4) .
 - d. With regard to the D-Antigen (b) (4) validation, your specificity assessment (Section

- 3.2.P.5.3_D-Antigen (b) (4) Product, Table 8, Page 8/19) involves comparing observed results to expected results. Please define the basis for assigning values used as the “expected result” and clarify whether the same (b) (4) format (b) (4)) was used for all measurements.
- e. With regard to the D-Antigen (b) (4) validation, it is not clear if a spike-recovery assessment was performed (i.e., spiking a known amount of antigen in the (b) (4) (b) (4) If this was performed, please indicate where this information is presented. If it was not performed, please provide a rationale.
 - f. We note that the D-antigen content measured by the (b) (4) method is shown for the three (b) (4) in Table 18 (3.2.P.5.6_Justification of specification, Page 32/49), and the results are higher for all three serotypes as compared to typical measurements shown for these lots in stability results. Please explain.
 - g. Please define criteria for sample validity in the (b) (4) and for re-testing.
 - h. Please provide the name and site of the laboratory where the D-Antigen (b) (4) was validated and the name and site where the assays will be performed to determine D-antigen Units (DU) content in (b) (4) vaccine.
5. With regard to lot release specifications, a monovalent concentrate (particularly Type 2) that marginally fails the specification for (b) (4) measured by the (b) (4) method (e.g., intended for IPOL) might pass the same specification if the (b) (4) method is used (as for (b) (4)). Please comment.
6. With regard to the Rat Immunogenicity assay performed on (b) (4) product:
- a. Please provide qualification report Q_0294513 for Pediacel Lot (b) (4)
 - b. The DTaP-IPV-Hib reference vaccine lot (b) (4) was used in performing the IPV Rat Immunogenicity Assay for lots C3145, C3146, C3147 and (b) (4) for release and stability monitoring. Please provide qualification data for this lot and identify the method used to measure D-antigen content.
 - c. The certificate of analysis for reference Lot (b) (4) stated a (b) (4) year re-test date from the date of manufacture. The planned re-test date was September 10, 2014. Please provide these results and identify the method used to measure D-antigen content.

Please let me know if you have any questions.

Thanks,

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