

**From:** [Dana.Harrison@sanofipasteur.com](mailto:Dana.Harrison@sanofipasteur.com)  
**To:** [Hoffman\\_Kelsy](mailto:Hoffman_Kelsy)  
**Cc:** [Krissy.Carrington@sanofipasteur.com](mailto:Krissy.Carrington@sanofipasteur.com); [Rivers\\_Katie](mailto:Rivers_Katie); [Dana.Harrison@sanofipasteur.com](mailto:Dana.Harrison@sanofipasteur.com)  
**Subject:** RE: BLA 125563/0 Information Request  
**Date:** Friday, April 17, 2015 4:27:56 PM

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Dear Kelsy,

I acknowledge receipt of this additional information request.

Kind Regards,  
Dana

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**From:** Hoffman, Kelsy [mailto:Kelsy.Hoffman@fda.hhs.gov]  
**Sent:** Friday, April 17, 2015 12:32 PM  
**To:** Harrison, Dana (sanofi pasteur)  
**Cc:** Carrington, Krissy (sanofi pasteur); Rivers, Katie  
**Subject:** BLA 125563/0 Information Request

Ms. Harrison,

We have the following requests for additional information regarding your BLA, STN125563/0:

**DTaP Bulk (b) (4)**

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1. (b) (4) [Redacted]

**PR5I Drug Product**

2. In Section 3.2.P.2.4, you provide extractable-leachable data on studies performed on the (b) (4) stopper that will be used in the final container. The information provided is not sufficient.
  - a. Please include your results for both extractable and leachable studies in both µg/dose and ppm.
  - b. You have included a list of potential extractable compounds that were provided by the stopper manufacturer. You have also included lists of potential extractable

compounds for each of the three extractable studies performed. Please provide your rationale for the selection of the specific compounds tested in the leachable study that was conducted during storage of vaccine in the final containers. Please provide your justification for why all the compounds listed as potential extractables by the stopper manufacturer and from your three extractable studies were not included in the leachable study. Please provide a detailed assessment as to why (b) (4) was not evaluated during your leachable study.

- c. Please provide details on the procedures used in your evaluation of leachables including test methods and validation.
- d. Please provide the complete data for the leachable study to include all time points (0, 15, and 36 months). Please provide an assessment if any trends are noted.
- e. Please provide an assessment about any potential leachables released from the in-process equipment and containers used for vaccine production.
- f. You have only provided a toxicological assessment on (b) (4). Please provide a risk assessment of the impact of leachables on product quality and safety including potential interaction of leachables with vaccine components as well as a safety assessment based on (b) (4) impurity limits or established thresholds of toxicological concern for parenteral drug products for all leachables.
- g. You state that (b) (4) was detected in the Tdap-IPV Vaccine at a concentration of (b) (4) at the 15-month time-point and at a concentration of (b) (4) at the 36 month time-point. Please provide the concentration of (b) (4) at the time zero time-point. Please provide your investigation into what specific compound the (b) (4) is from and your assessment of any potential reaction of the (b) (4) containing compound with your product. Please provide your assessment that the (b) (4) (b) (4) is not resulting in the (b) (4) reacting with product to have a detrimental effect on product quality.
- h. You have performed the leachable study on a different combination vaccine. We do not concur with this approach. Please commit to provide leachable data on PR5I for the proposed shelf-life post approval.

3. In Section 3.2.P.3.5, you provide process validation data for bulk intermediate (b) (4) of PRP-OMPC. The information provided is not sufficient.

- a. (b) (4)  
[Redacted]

4. In Section 3.2.P.5.6, you provide justification for a (b) (4) specification of (b) (4). The proposed acceptance criterion is based on the 2-sided 99/99 tolerance interval accounting for assay and lot-to-lot variability calculated using the release and stability monitoring data.

We do not concur with your proposal. We request that the specifications be set using the tolerance intervals with 99% coverage and 95% confidence, which is the level of confidence usually accepted when tolerance intervals is used to set product specifications. In addition, we request that only release data be used to calculate the specification.

5. In Section 3.2.P.5.6, you provide justification for a (b) (4) PRP-OMPC specification of (b) (4) at release. This value was set based on the 99/99 lower tolerance interval accounting for assay and lot-to-lot variability. We do not concur with your proposal. We request that the specifications be set using the tolerance intervals with 99% coverage and 95% confidence, which is the level of confidence usually accepted when tolerance intervals is used to set product specifications. In addition, please verify that only release data were used in the calculation of the release specification.
6. In Section 3.2.P.5.6, you provide justification for a (b) (4) PRP-OMPC release and stability specification of (b) (4). This value was set based on the 99/99 lower tolerance interval accounting for assay and lot-to-lot variability calculated using the release and stability monitoring data. We do not concur with your proposal. We request that the specifications be set using the tolerance intervals with 99% coverage and 95% confidence, which is the level of confidence usually accepted when tolerance intervals is used to set product specifications. We also request that only release data be used to calculate the release specification. In addition, the data provided show a (b) (4) on stability. Therefore, we do not concur that the release and stability specification should be the same. Please set your release specification to ensure that a stability specification of (b) (4) can be met at expiry.
7. In Section 3.2.P.5.6, you provide justification for PRP Content release specification of (b) (4). You state that this value was set on assay variability (b) (4) variance about the 3 µg/dose target). You also state that a 95/99 tolerance interval accounting for assay and lot-to-lot variability was used to confirm that the proposed release specification limit is acceptable. We request that the specifications be set using the tolerance intervals with 99% coverage and 95% confidence, which is the level of confidence usually accepted when tolerance intervals is used to set product specifications. We also request that only release data be used to calculate the release specification. Please provide the details on your calculation of the 95/99 tolerance interval including the data used in the calculation, the (b) (4), and the tolerance interval result.
8. In Section 3.2.P.5.6, you provide justification for the (b) (4) release specification of (b) (4). This specification is based on a 99/99 tolerance interval. A tolerance interval with 95% confidence and 99% coverage is normally accepted provided the number of lots is not too small. Since you have only (b) (4) data points ((b) (4) final lots), using a tolerance interval approach would result in an unacceptably (b) (4). Therefore, we request that you set the (b) (4).
9. In Section 3.2.P.5.3, you provide a summary of the validation for the assay that is used for both, (b) (4) of PRP-OMPC for (b) (4) Product and Identity of PRP-OMPC for

(b) (4) Labelled Filled Product. The information provided is not sufficient.

- a. For specificity, please provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results. In addition, for the Identification specificity testing, a negative result was confirmed for the (b) (4) containing samples. Please specify what (b) (4) containing samples were tested. Please provide the results if (b) (4) was tested.
- b. For accuracy, please provide data using a minimum of 9 determinations over a minimum of 3 concentrations covering the specified range of the assay using manufacturing samples.
- c. For linearity, please provide data to include graphs, slope, y-intercept, and correlation coefficient to compare the linearity of the reference standard and manufacturing sample to cover a minimum of 5 concentrations.
- d. For precision, please provide data using a minimum of 9 determinations covering the specified range (3 concentrations, 3 replicates) using manufacturing samples. In addition, please provide data to show that there is no difference between analysts, plate readers, and coat times.
- e. The range of the assay was determined to be (b) (4). Please provide the data to support this determination.
- f. A robustness study was performed after the validation. Please provide the robustness data. Please note that any changes in SOP based on data from the robustness studies may require additional validation data to support performance of the assay when performed according to the SOP.
- g. The method transfer from Merck to Sanofi was verified by testing (b) (4) lots (b) (4) times in each lab. This does not provide sufficient data to verify a procedure's suitability under actual conditions of use for a specified drug substance or drug product. Please provide additional data for a minimum of 6 lots to show suitability under actual conditions. Please provide data on manufacturing samples with varying concentrations. Comparative studies should include evaluation of accuracy and precision with regard to assessment of inter-laboratory variability. For stability indicating assays, forced degradation samples or samples containing pertinent product-related impurities should also be analyzed at both sites.
- h. The method was changed substantively after the transfer to Sanofi. These changes include a change in reference standard, data analysis, analyte measured, (b) (4)  
(b) (4)  
(b) (4) Method verification was performed on samples covering the expected range of the manufacturing process and the range of the assay. We do not concur that method verification is sufficient. The changes in the method are substantial and the original validation is not adequate as can be seen above. Please revalidate the assay or provide data for the method validation.

10. In Section 3.2.P.5.3, you provide a summary of the validation for PRP Content for (b) (4) Product. The information provided is not sufficient.

- a. For specificity, please provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results.
- b. For accuracy, please provide data using a minimum of 9 determinations over a minimum of 3 concentrations covering the specified range of the assay using manufacturing samples.
- c. Precision was re-assessed in 2013. Please provide information on what samples were used in this study and how many determinations were made. Please provide data using a minimum of 9 determinations covering the specified range (3 concentrations, 3 replicates) using manufacturing samples.
- d. For linearity, please provide data to include graphs, slope, y-intercept, and correlation coefficient to compare the linearity of the reference standard and manufacturing sample to cover a minimum of 5 concentrations.
- e. The range was demonstrated to be (b) (4) . Please provide data to support this range.
- f. The method transfer from Merck to Sanofi was verified by testing (b) (4) lots (b) (4) times in each lab. This does not provide sufficient data to verify a procedure's suitability under actual conditions of use for a specified drug substance or drug product. Please provide additional data for a minimum of 6 lots to show suitability under actual conditions. Please provide data on manufacturing samples with varying concentrations. Comparative studies should include evaluation of accuracy and precision with regard to assessment of inter-laboratory variability. For stability indicating assays, forced degradation samples or samples containing pertinent product-related impurities should also be analyzed at both sites.

11. In Section 3.2.P.5.3, you provide a summary of the validation for (b) (4) PRP-OMPC for (b) (4) Product. The information provided is not sufficient.

- a. For specificity, please provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results.
- b. For accuracy, please provide data using a minimum of 9 determinations over a minimum of 3 concentrations covering the specified range of the assay using manufacturing samples.
- c. Precision was re-assessed in 2013. Please provide information on what samples were used in this study and how many determinations were made. Please provide data using a minimum of 9 determinations covering the specified range (3 concentrations, 3 replicates) using manufacturing samples.
- d. For linearity, please provide data to include graphs, slope, y-intercept, and correlation coefficient to compare the linearity of the reference standard and manufacturing sample to cover a minimum of 5 concentrations.
- e. The range was demonstrated to be (b) (4) . Please provide data to support this range. Please confirm that this range supports the specification range of (b) (4)
- f. The method transfer from Merck to Sanofi was verified by testing (b) (4) lots (b) (4) times in each lab. This does not provide sufficient data to verify a procedure's suitability under actual conditions of use for a specified drug substance or drug product.

Please provide additional data for a minimum of 6 lots to show suitability under actual conditions. Please provide data on manufacturing samples with varying concentrations. Comparative studies should include evaluation of accuracy and precision with regard to assessment of inter-laboratory variability. For stability indicating assays, forced degradation samples or samples containing pertinent product-related impurities should also be analyzed at both sites.

12. In Section 3.2.P.5.3, you provide a summary of the validation for (b) (4) Identity Test for Labeled Filled Product. The information provided is not sufficient to support test specificity. Please provide data on manufacturing samples to show that potential process impurities and excipients do not affect the test results.
13. In Section 3.2.P.6, you provide information on the qualification and re-evaluation of the reference standard used for (b) (4) PRP-OMPC and Identity of PRP-OMPC. The reference standard is an in-house PRP-OMPC Conjugate lot. The information provided is not sufficient.
  - a. Please provide detailed procedures on how the reference standard is chosen or made.
  - b. Please clarify who will be responsible for making and qualifying future reference standards. If Sanofi, please provide the procedures for making and qualifying future reference standards. If Merck, please provide procedures that Sanofi will perform to verify the qualification prior to use. Please note that since a Comparability Protocol was not submitted, we do not concur with your proposal to submit future reference standards in your Annual Report. Please withdraw this request.
  - c. Please provide detailed procedures on how the reference standard will be re-evaluated for extension of dating. Please provide limits on the number of times a reference standard can be re-evaluated and expiry extended. If the procedure allows for extension beyond the approved hold time of the PRP-OMPC Conjugate lot, please describe how the expiry is assigned and how the reference standard is monitored to ensure that the reference standard does not deteriorate in quality beyond the expected shelf life of the Conjugate Lot.
14. In Section 3.2.P.6, you provide information on the qualification and of the reference standard used for PRP Content and (b) (4) PRP-OMPC. The reference standard is prepared from at least <sup>(b) (4)</sup> lots of PRP (b) (4). The information provided is not sufficient.
  - a. Please clarify who will be responsible for making and qualifying future reference standards. If Sanofi, please provide the procedures for making and qualifying future reference standards. If Merck, please provide procedures that Sanofi will perform to verify the qualification prior to use. Please note that since a Comparability Protocol was not submitted, we do not concur with your proposal to submit future reference standards in your Annual Report. Please withdraw this request.

- b. Please provide limits on the number of times a reference standard can be re-evaluated and extended. If the procedure allows for extension beyond the approved hold time of the PRP lot, please describe how the expiry is assigned and how the reference standard is monitored to ensure that the reference standard does not deteriorate in quality beyond the expected shelf life of the PRP Lot.

15. In Section 3.2.P.8, you provide stability data for PR5I Final Bulk Product to support your proposed expiry of (b) (4). These studies were performed in (b) (4) containers that are representative of the (b) (4) containers used in routine manufacturing.

(b) (4)

16. The stability information for the Filled Product in Section 3.2.P.8 was updated (amendment of September 12, 2014) with stability data for up-to the 48-month time point and a request to extend the shelf life of PR5I from 36 to 42 months. However, the amendment did not include an updated post-approval stability protocol and commitment for the 42-month shelf life. Please provide this information.

17. In Section 3.2.P.8.2, you provide your post approval stability commitment to place (b) (4) of PR5I on stability each year it is filled. Please revise section 3 of the Post-Approval Stability Protocol and Stability Commitment to provide detailed procedures on the post approval stability program, specifically, the procedures for handling (b) (4) testing on the Final Bulk Product and testing at the 12, 24, 36 and 42-month time points on the Filled Product. We note that Table 4 shows part of this information for the time (b) (4) testing and in the related footnote. Please describe these procedures in the text.

18. In Section 3.2.P.8.3 of the 12 September 2014 amendment, you provide stability data for PR5I filled Product to support your proposed expiry of 42 months at 2-8 °C. The 30 month time-point for Lot (b) (4) is listed as pending for (b) (4) (b) (4) PRP-OMPC, PRP Content, and (b) (4) PRP-OMPC. Please submit these data.

19. Section 3.2.P.5.1, Table 5 - Release Specification for PR5I Labelled Filled Product lists two alternative tests for identity of the HBsAg and OMPC components ((b) (4)). Please clarify when each method will be used. In addition, we note that no identity testing is proposed for the other vaccine components (DTaP and IPV), but that such testing was performed on consistency lots ((b) (4)). Please specify which

tests are performed to confirm the identity of the DTaP and IPV components in the Final Drug Product or Labeled Filled Product and modify the specifications for the Final Drug Product or Filled Product and the Lot Release Protocol as applicable.

20. In section 3.2.P.5.2 Analytical Procedures - Formaldehyde Content – (b) (4) Product, you state that “The result is reported as (b) (4) to the value defined as the specification limit.” In section 3.2.P.5.6 – Justification of Specifications, you state that “The acceptance criterion for the Formaldehyde Content Test (b) (4) ) is based on the (b) (4) . We request that you establish a specification reflective of the capacity of the manufacturing process to remove formaldehyde and that you report the actual results of the test in the certificates of analysis and lot release protocols for (b) (4) Product lots. As necessary, please modify this test method and validation to serve the purpose of a quantitative procedure.
21. In Section 3.2.P.5.3 Validation of Analytical Procedures, the verification reports are described for the compendial procedures used for the following: (b) (4) - Q\_0259174, (b) (4) - Q\_0521595, and (b) (4) - Q\_0521590. Please provide these documents for review.
22. In Section 3.2.P.5.4, you have provided a Certificate of Analysis for Final Bulk Product Lots (b) (4) . We note that you have provided (b) (4) data for each of these lots on a sample dispensed following the (b) (4) (b) (4) (b) (4) (b) (4) . We also note that this test was not listed in the Specification Table (Table 1 of Section 3.2.P.5.1). Please confirm that you are still performing this test for release. We request that this test be performed on all commercial lots and that the results are reported on the Lot Release Protocol.
23. In Section 3.2.P.5.1, you provide a list of release specifications for PR5I Final Bulk Product, Filled Product, and Labeled Filled Product. We note that you plan on performing the Pyrogen test on Filled Product. We request that you add an endotoxin test for release of PR5I (b) (4) Product. Please set your endotoxin specification to reflect manufacturing data. The presence of both a Pyrogen test and an Endotoxin test will provide assurance for both safety and consistency of manufacture.

Please let me know if you have any questions. Also, to expedite our review of this information, please submit responses as soon as they are available, rather than waiting until responses to all comments are complete. Preliminary submission of responses via email is acceptable.

Thanks,

Kelsy F. Hoffman, Ph.D.  
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