

From: [Rivers, Katie](#)
To: krissy.carrington@sanofi-pasteur.com
Cc: [Hoffman, Kelsy](#) [Chattopadhyay, Rana](#)
Subject: RE: Request for Additional Information - STN125563/0
Date: Tuesday, March 17, 2015 11:24:57 AM

Hello Ms. Carrington,

Please see the response to your requests for clarification regarding CBER's February 23, 2015 Information Request below:

Regarding comment #1:

- Please provide the age information (*N*, *mean*, *SD*, *range (min, max)*) at the receipt of each infant series of vaccination regardless of the availability of serology results. The table in the previous request does not need to be by antigen. For example, the cell (3rd dose, PP-RW) under the PR5I column in the table in previous information request should show the age information for a number (*N*) of 924 PR5I recipients at receipt of the 3rd dose in the PP-RW population (shown in Table 11-1, Page 117 of 400 of the CSR for Study 005). The corresponding *N* for the control group was 460. Just for clarity, the table requested is provided below.

—We request that this table be provided for pivotal study 005.

—Please include the numbers of subjects and corresponding percentages with missing baseline titers by vaccination group, for each of the PP-RW, PP-OW and FAS populations. It is understood this has to be by antigen.

Infant series dose	PR5I												Control											
	PP-RW ¹				PP-OW ²				FAS ³				PP-RW ¹				PP-OW ²				FAS ³			
	N	M	SD	R	N	M	SD	R	N	M	SD	R	N	M	SD	R	N	M	SD	R	N	M	SD	R
1 st																								
2 nd																								
3 rd	924												460											
Toddler dose of Daptacel																								

N= Number of subjects; **M**= Mean age of the 'N' number of subjects at the receipt of the dose; **SD**= Standard Deviation of 'M'; **R**= Age Range (minimum, maximum) of 'N' number of subjects at the receipt of the dose.

¹PP-OW = Per-protocol-Original Windows (defined as vaccination window of Days 46 to 74 after the previous vaccination and a blood draw sample window of Days 28 to 44 following Dose 3 or the Toddler dose).

²PP-RW = Per-protocol-Revised Window (defined as vaccination window of Days 42 to 84 after the previous vaccination and a blood draw sample window of Days 28 to 51 following Dose 3 or the Toddler dose).

³FAS=full analysis set

Regarding question #8, please see the proposed table that was inadvertently excluded from the original information request below:

Solicited Systemic Adverse Events (Incidence > 0% in One or More Vaccination Groups):

Day 1 to Day 5 Following Any PR5I Infant Dose Vaccination (All Subjects as Treated Population), protocols 005 and 006, per Vaccine Age

	(N=3380)		Vaccine Age in Months											
			≥0 <6		≥6 <9		≥9 <18		≥18 <36		≥36 <42		≥42 ≤ 48	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	3370	(100)												
With one or more solicited systemic adverse events	3090	(100)												
With no solicited systemic adverse event	280	(100)												
Crying	2520	(100)												
Decreased appetite	1638	(100)												
Irritability	2743	(100)												
Pyrexia	1590	(100)												
Somnolence	2475	(100)												
Vomiting	889	(100)												

Please let me know if you have any additional questions.

Thank you,
Katie

From: Krissy.Carrington@sanofi-pasteur.com [<mailto:Krissy.Carrington@sanofi-pasteur.com>]

Sent: Tuesday, March 10, 2015 6:55 PM

To: Rivers, Katie

Cc: Hoffman, Kelsy

Subject: RE: Request for Additional Information - STN125563/0

Dear Katie

Upon review of Question no.1, we are requesting clarification from the reviewer as follows:

The table provided suggests the information request is based on Protocol 005 only. Is the information requested [i.e., summary information on infant ages in days (*N*, *mean*, *SD*, *range*) at the receipt of the doses] for Protocol 005 only or for both Protocols 005 and 006? Comment: Please note that the per-protocol statistical analyses were conducted on a per-antigen basis in V419 Protocols 005 and 006. Therefore, the Sponsor will provide the requested information by antigen, resulting in a total of 11 tables per study.

Also, it is noted regarding Question no. 8 that we did not receive the referred to attachment: "Please see the attached format (based on Appendix 2.5: 10) as an example" We acknowledge that the references in Question no. 8 are detailed but in case the reviewer provided a suggested format, it would be helpful for us to review to assure we are not missing any information and have interpreted the request correctly.

Thank you for your feedback on these points of clarification. Kind regards,
Krissy

From: Rivers, Katie [<mailto:Katie.Rivers@fda.hhs.gov>]

Sent: Monday, February 23, 2015 2:29 PM

To: Carrington, Krissy (sanofi pasteur)

Cc: Hoffman, Kelsy

Subject: Request for Additional Information - STN125563/0

Dear Ms. Carrington,

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

The following comments are related to clinical data:

1. In view of the two vaccination-windows (Revised Window and Original Window) used for Per Protocol (PP) population, please provide the following summary information (see table below) on infant ages in days (*N*, *mean*, *SD*, *range*) at the receipt of the doses.

Infant series dose	PR5I			Control		
	PP-RW ¹	PP-OW ²	FAS ³	PP-RW ¹	PP-OW ²	FAS ³
	N, mean, SD, range(min, max)	N, mean, SD, range(min, max)	N, mean, SD, range(min, max)	N, mean, SD, range(min, max)	N, mean, SD, range(min, max)	N, mean, SD, range(min, max)
st						

1						
2 nd						
3 rd						
Toddler dose of Daptacel						
¹ PP-OW = Per-protocol-Original Windows (defined as vaccination window of Days 46 to 74 after the previous vaccination and a blood draw sample window of Days 28 to 44 following Dose 3 or the Toddler dose). ² PP-RW = Per-protocol-Revised Window (defined as vaccination window of Days 42 to 84 after the previous vaccination and a blood draw sample window of Days 28 to 51 following Dose 3 or the Toddler dose). ³ FAS=full analysis set						

2. We acknowledge that the primary analyses in your submission were model based, adjusting for the brand of birth dose of hepatitis B vaccine, and also for pre-vaccination titers for Geometric Mean Titer (GMT) comparisons where applicable. To better evaluate the impact of these covariates on the analysis results, we have the following requests:

- Please provide non-inferiority analyses regarding PR5I antigen responses for all the primary immunogenicity endpoints in Protocol 005 using raw data, i.e., without adjustment for the actual brand of birth dose of hepatitis B vaccine or if applicable, pre-vaccination titers, for the PP-RW, PP-WO and FAS populations. Please follow the format as in Table 11-1 (Page 117) and Table 11-3 (Page 122) of the Study 005 Clinical Study Report (CSR) for presenting the raw analysis results.
- Please provide lot consistency results based on GMTs for Protocol 006 without using adjustment for brand of birth dose of hepatitis B vaccine and pre-vaccination titer, for the PP-RW and FAS populations.
- Please provide non-inferiority analysis of the primary endpoints for the primary population for Protocols 005 and 006 by suitable subgroups of brand of birth dose of hepatitis B vaccine.

The following comments are regarding chemistry, manufacturing, and controls:

- In Section 3.2.P.2 pages 51-53 you established a hold time of (b) (4) for the (b) (4) bulk intermediate hold time for your Phase 3 consistency lots. However, we note that the minimum hold time proposed in the BLA for commercial lots is (b) (4). Please specify the exact hold time in number of days for the (b) (4) bulk intermediate (i.e., (b) (4)).
- Taking into account your proposed PR5I shelf-life of 36 months, the data you provide in Section 3.2.P.5.6 [Justification of Specification(s)] does not support a specification for the (b) (4) for PR5I at release of (b) (4) deaths for the following reasons:
 - We disagree with including results from lots older than 36 months, the proposed expiry period for PR5I, in the analyses that you present to support your proposed acceptance criterion of (b) (4). Only results from tests performed on lots with age within the proposed expiry period (36 months or less) should be used to determine whether a new specification for the (b) (4) is warranted. Please provide revised analyses using only data obtained with lots within the proposed expiry period.
 - We also disagree with your assertion that (b) (4) in PR5I cannot occur because of the treatment with (b) (4). Recognizing the limited size of the dataset under consideration, the results of stability testing shown in Table 20 of Section 3.2.P.5.6 do not discount some (b) (4) occurring over time. Please acknowledge.
 - Your assay validation, described in Section 3.2.P.5.3 - Validation of Analytical Procedures, did not address the possibility that the PR5I matrix (b) (4) containing some residual toxic activity may by itself (b) (4) mice to the lethal effects of (b) (4) or enhance the (b) (4) effects of the pertussis toxin. Please provide any data that you might have that addresses this issue.
 - If you have supplementary information in support of your proposal to set the (b) (4) specification at release a (b) (4) deaths, such as additional detailed results of (b) (4) assays by other methods or (b) (4) assays, please provide it for review.
- With regards to testing data provided in Section 3.2.P.8.1, please indicate why the (b) (4) was not performed on the Finished Product at time 0 and on Final Bulk at (b) (4).
- Please confirm that the initiation date of the stability testing of each lot is its date of manufacture, which you propose to be the date of PR5I formulation.
- Please provide more detail regarding your statement in Section 3.2.P.5.6 that "the PR5I phase 3 lots were up to 30 months of age at the time of use in the US clinical studies." For instance, please specify the age of the lots used in the pivotal phase 3 studies and the number of subjects immunized with each lot.

8. To help our review and final decision on (b) (4) specification for PR5I, please provide information addressing the safety of the vaccine as it ages, in the context of potential (b) (4). For example, you may stratify the adverse events reported in Appendices 2.5: 8-11 of Section 2.5 (Clinical Overview), per vaccine age groups between (b) (4) stability testing points, as reported in Table 20 of Section 3.2.P.5.6. Please see the attached format (based on Appendix 2.5: 10) as an example. The format is provided as a suggestion and you are free to choose a suitable alternative that addresses our concerns.
9. The following comment pertains to document number RED_00073616, Version 1.0, Control Performance for the Diphtheria (b) (4) to Demonstrate Long-Term performance of the Assay (effective 19 Nov 2012).
 - a. The report includes control monitoring of the (b) (4) for the time period January 1999 to October 2012. According to the clinical study reports, pivotal studies 005 and 006 were completed in 2013, which is after the reporting period indicated in the trend report. Please provide the dates samples for study 005 and 006 were tested. If testing occurred after October 2012, please provide updated control performance monitoring for the (b) (4) to include the time period when samples were tested using this assay.
10. The following comment pertains to Document number RED_00073544, Version 1.0, Demonstration of the Long-Term Performance of the Anti-Tetanus IgG (b) (4) using Plots of Control Results (effective date 19 Nov 2012).
 - a. The report includes control monitoring of the anti-tetanus (b) (4) for the time period November 2001 to July 2012. According to the clinical study reports, pivotal studies 005 and 006 were completed in 2013, which is after the reporting period indicated in the trend report. Please provide the dates samples for study 005 and 006 were tested. If testing occurred after July 2012, please provide updated control performance monitoring for the tetanus assay to include the time period when samples were tested using this assay.
11. Sterility method validation (Section 3.2.P.5.3) for suitability of the method for the (b) (4) final container was performed by the (b) (4) method as described in the current (b) (4). Please provide the validation report (Validation Report – Q_0262868) to include your bacteriostatic and fungistatic test qualification reports with complete results for (b) (4) final container products.
12. Please provide your bacterial endotoxin test method validation report performed on the (b) (4) to show it is suitable for your test method. Please include your determination test sample dilution, (b) (4) batch numbers, and other suitability data.
13. Bioburden testing is performed for the In Process Controls (Step: (b) (4)) (Section 3.2.P.3.3). Please provide the Bacteriostasis and Fungistasis Validation Report to include the type of media, conformance lot numbers, and incubation conditions and duration to show suitability of the bioburden assay for the intended purpose.
14. In Section 3.2.P.3.3, endotoxin specification for (b) (4). In addition, you stated that this endotoxin specification is based upon (b) (4) in the finished product. It is not clear where the (b) (4) value comes from; the specification for pyrogenicity is only 'Non-Pyrogenic' (Section 3.2.P.5.1). Thus, please explain/clarify the proposed specification of (b) (4).

Please let me know if you have any questions.

Thank you,

Katie

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