Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: 27 November 2006

To: **STN 125145/0/17** Diphtheria & Tetanus Toxoids & Acellular Pertussis (5-component) Vaccine Adsorbed & Inactivated Poliovirus Vaccine combined with Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)

Sanofi Pasteur Limited (License No. 1726)

From: Nancy Waites, Facility Reviewer, MRB1/DMPQ/OCBQ/HFM-675 REVIEWED

Subject: Review of DMPQ issues in the Response to CR Letter submitted electronically by Sanofi Pasteur Limited, received 07 Sep 2006.

Through: Robert Stevenson, Acting Branch Chief /MRB1/DMPQ/OCBQ/HFM-675

Cc: Theresa Finn, Chairperson, OVRR/DVRPA/BVB/HFM-481 APPROVED By Robert Stevenson at 2:24 pm, Nov 28, 2006

Conclusion: I recommend approval of this submission if all other review disciplines do not have any concerns.

Review Narrative and Comments

This submission is a response to the CR letter, dated 26 May 2006, sent out for the original electronic Biologics License Application for the "*Haemophilus b* Conjugate Vaccine (Tetanus Toxoid Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Poliovirus Vaccine Inactivated (PENTACEL)".

PENTACEL™ is the product combination of *Haemophilus b* Conjugate Vaccine (Tetanus Protein-Conjugate) reconstituted with Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed and Poliovirus Vaccine Inactivated (HCPDT-IPV). HCPDT-IPV Vaccine is manufactured at Sanofi Pasteur Limited and *Haemophilus b* Conjugate Vaccine (Tetanus Protein-Conjugate) Vaccine referred to as PRP-T Vaccine is manufactured at Aventis Pasteur SA. PRP-T Vaccine (filled and freeze-dried) is received, at Sanofi Pasteur Limited, where it is labeled and co-packaged with labeled HCPDT-IPV Vaccine.

The following is a list of DMPQ questions included in the CR letter along with Sanofi's response.

Question 145

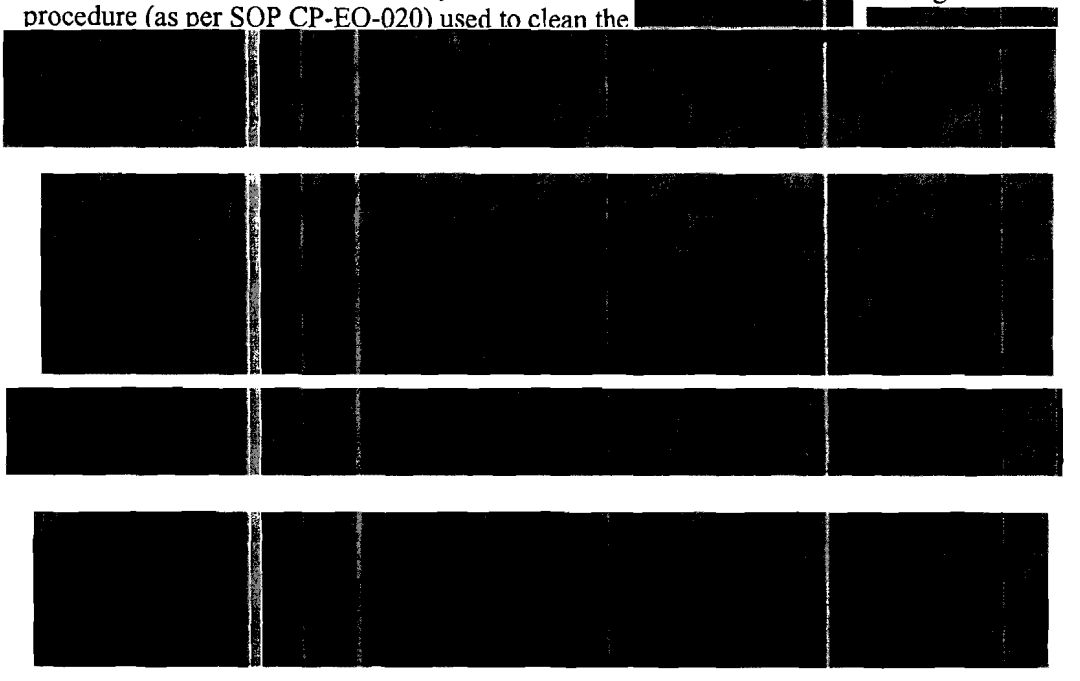
The Containment and Cross Contamination document, Section 2.1.1.3.10.1 states that cleaning validation for the [redacted] (for FHA) was not completed due to manufacturing constraints, and this validation will be completed during 2004; the results will remain on file at Aventis Pasteur Limited. Please submit a copy of the completed cleaning validation for the [redacted] to this BLA.

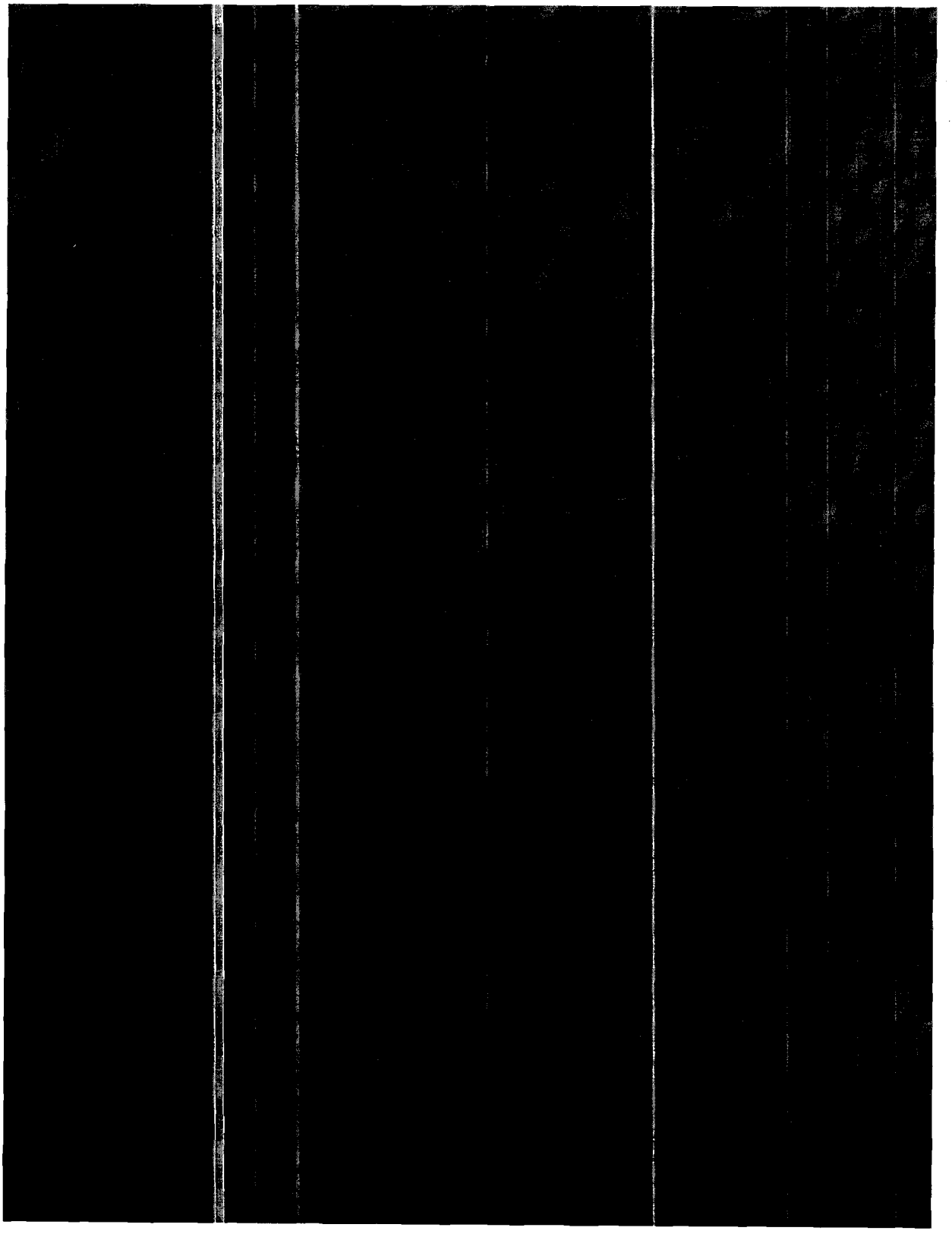
Note: This [redacted] is dedicated for FHA purification. At the time the original BLA (STN 125145/0) was submitted the [redacted] was validated for the number of times the packed [redacted] could be cleaned and reused, but the cleaning of the empty [redacted] had not been validated. This addendum to the original cleaning validation report is for the [redacted] cleaning of the empty [redacted]

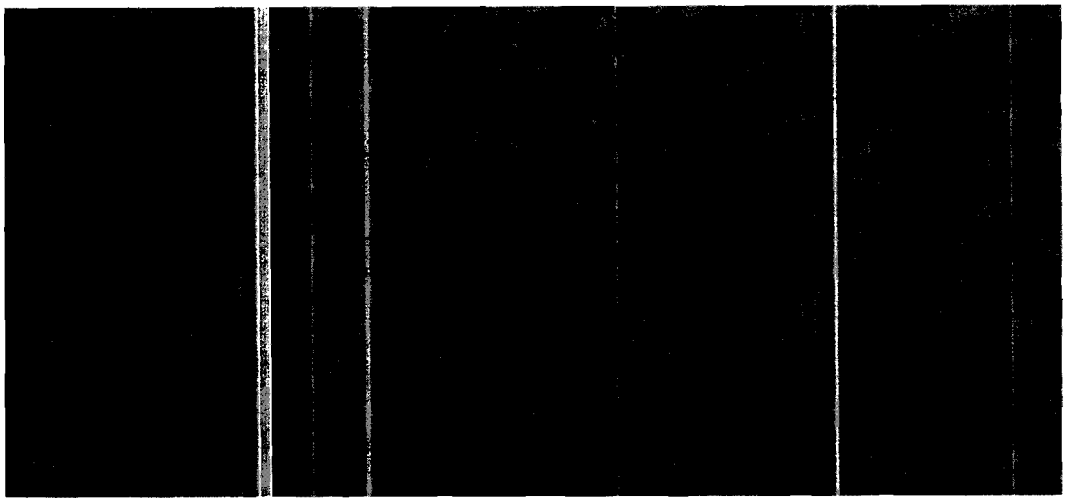
Response 145

A copy of the report summarizing the validation of the cleaning procedure for the empty [redacted] used for purification of Filamentous Haemagglutinin (FHA) is provided in Report C009302 Cleaning Validation Report for the Empty [redacted] and Used for FHA Purification in CP90; Addendum to Report CV99-008-REP. The cleaning of the [redacted] was performed a total of [redacted] times.

This study was carried out in the component pertussis manufacturing (cP) area in building [redacted] The purpose of the study was to validate the efficacy of the cleaning procedure (as per SOP CP-EO-020) used to clean the [redacted]







Conclusion
The results of this study, along with supportive monitoring data from the routine cleaning of the , show the current procedure outlined in SOP CP-EQ-020 to be effective at reducing residues. As a result, the cleaning process outlined in SOP CP-EQ-020 is validated for use on the (used for FHA purification) as originally reported in CV99-008-REP and as well for the empty cleaning as reported here in this Addendum. This completes the original validation objectives set in CV99-008-PRO.

This response is acceptable.

Question 146
The Executed Batch Production Record (BPR-300-FP-06-02 Bulk Lot C0154B) for the Filling Work Record states that vials are required for sterility testing. However, the record does not identify when during the filling process the vials were removed for testing. Please provide this information and amend the master production record accordingly (21 CFR 211.186).

Response 146
Samples for sterility testing are taken at the beginning, middle and end of a filling day. The master batch production record has been revised to indicate when samples are removed for sterility testing. The revised page from BPR 2021253 was provided and is acceptable.

Question 147
A short summary of the validation of the test of closure integrity was provided in Item 4: CMC HCPDT-IPV Container Closure System Section 6.3.1.2.

Question 147a
After the test, the vials are inspected in a In the validation report provided (PV01-033-PRO Table 2, page 9 of 12), the source is listed as a piece of equipment and the Calibration/Certification due date is

listed as N/A. Please explain how the [redacted] indicate the range of [redacted] output optimal for visual inspection.

Response 147a
The [redacted] source, referred to in Validation Report PV01-033-PRO, Table 2, page 9 of 12, is a [redacted] lamp. This lamp has two bulbs that [redacted] For this validation study, the lamp [redacted]. Therefore, a certification/calibration confirmation was not deemed a requirement. In addition, the minimum [redacted] output necessary for valid test performance was monitored for every analysis using the positive control, in which the [redacted] is near the limit of detection of the test. The positive controls would have failed if the light output was suboptimal, and the study would have been invalidated. Consequently, the [redacted] output optimal for visual inspection is controlled at [redacted]

This response is acceptable.

Question 147b
Please provide a copy of SS01-023-REP and the corresponding protocol.

Response 147b
Copies of Study Protocol SS01-023-PRO (Protocol for Closure Integrity Testing – Correlation between [redacted]) and Study Report SS01-023-REP (Report for Closure Integrity Testing – Correlation between [redacted]) were provided.

I reviewed the approved protocol and report and they both were acceptable.

[redacted]

[redacted]

Question 147c
Please provide a copy of PV-01-012-REP and the corresponding protocol.

Response 147c
Copies of Study Protocol PV-01-012-PRO (Validation Protocol for the Closure Integrity Testing of the [redacted] Method) and Study Report PV-01-012-REP (Validation Report for the Closure Integrity Testing of the [redacted] Method were provided.

I reviewed the approved validation protocol and validation report and they both were acceptable.

[redacted]

[redacted]

Question 147d
Please provide a copy of SOP 15QC-040.

Response 147d
A copy of SOP 15QC-040, Procedure for Closure Integrity Test, was provided.

Sanofi stated that this SOP has been archived and replaced with SOP A003898, Container Closure Integrity Test for Adsorbed Vaccines and Clear Products Using [redacted]. The testing procedure described in SOP A003898 is based on (1) PDA Technical Report Number 27, Pharmaceutical Package Integrity, Volume 52, issued 1998 and (2) FDA Guidance For Industry, Container Closure System for Packaging Human Drugs and Biologics, published on May 1999. The method using the [redacted] was used to test lots C0094A, C0154B and C0155A (from 494-01 Stage I clinical study) at the end of the stability study. In current stability programs, the current method using [redacted] is being used.

I reviewed both SOPs and found them to be acceptable.

Question 147e
Please describe how personnel are trained and qualified to perform this test.

Response 147e
New tests when transferred or developed for routine and stability testing require a test method validation. The operators participating in that validation are the qualified trainers for subsequent analysts.

To qualify additional analysts, Sanofi follows a standard On-the-Job training format, which is led by an instructor already qualified to perform the testing. This training

[redacted]

This response is acceptable.

Compliance

An inspection waiver memo was written and approved 04 May 2006. I have looked in FACTS and the last inspection for Sanofi Pasteur Limited (License Number 1280, Registration Number 3002888623) was conducted by TeamBio on 28 Mar 2006 and the result was VAI. There was no change in the Aventis Pasteur SA (License Number 1279, Registration Number 3002972083) inspection report from what was included in the waiver memo. The last TeamBio inspection occurred 28 Jun 2005 and resulted in VAI. Therefore, a new inspection waiver memo is not necessary.