FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: January 29, 2007

FROM: Bruce D. Meade, Ph.D., LMDQC, DBPAP

TO: Theresa Finn, Ph.D., Chair, Review Committee

SUBJECT: BLA STN 125145 (Pentacel™, sanofi pasteur DTaP-IPV/Hib vaccine)
Clinical: Review of methods for pertussis clinical serology

THROUGH: Richard I. Walker, Ph.D., Director, DBPAP

REFERENCE: STN 125145

SCOPE OF REVIEW:

Product: Pentacel ™ vaccine produced by sanofi pasteur Ltd. (SPL) – Canada Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus Vaccine and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined (DTaP-IPV/Hib Combined)

Indication: Immunization of infants and toddlers with a four-dose series at 2, 4, 6, and 15-18 months of age

My review has focused primarily on the methodology and validation of the assays used to measure the antibody response to the pertussis component of DTaP-IPV/HIB and on the pertussis immunogenicity studies that relied on these assays. At the end of this review, I list the specific documents in the original submission that were reviewed. This memo will provide documentation of my review of the original submissions and any relevant information received from the sponsor in response to an Information Request (IR) Letter sent to the sponsor on May 26, 2006.

OVERALL CONCLUSIONS:

1. The immunoassays used to measure the antibody response to the pertussis antigens are adequate for the purposes for which they were used in this application. Demonstration of acceptable performance of the assays is essential in order to approve the BLA, because immunogenicity data provided the primary evidence supporting efficacy of the pertussis components.

2. I have reviewed the evidence in the BLA related to the effectiveness of the acellular pertussis component. In my opinion, while the data raise some concerns, the available evidence supports the effectiveness of the pertussis component of Pentacel.

PERTUSSIS CLINICAL SEROLOGY: REVIEW OF VALIDATION

All pertussis assays used for this file were conducted in the clinical serology laboratories at the Canadian facilities of SPL. The assay procedures used to support the Pentacel file are the same as those used in support of the Adacel file (STN125111), and have been reviewed in detail under IND [redacted] and BLA STN125111. During review of STN125145 (Pentacel), I have confirmed the continued acceptability of the procedures.

NOTE: While not relevant to the Pentacel BLA, reviewers should note that the clinical serology laboratories at the Canadian facilities of SPL [redacted] and all pertussis assays for SPL are now being performed in the US facility [redacted] The methods transfer and validation studies for the [redacted] clinical serology laboratories were submitted for review under IND [redacted]

In the clinical evaluation of the efficacy of the pertussis component, two types of immunogenicity endpoints were relevant:

1. Geometric mean concentration (GMC).
   Comment: All quantitative comparisons are made within a given study. Thus, when quantitative comparisons were made, all sera from comparator groups were measured in the same laboratory within a limited period of time. Although the sponsor has demonstrated reasonable stability of the assays, caution should be exercised when making quantitative comparisons between assays done at different times.

2. Vaccine responses
   For this application, some of the immunogenicity endpoints were based on the proportion of subjects with a four-fold increase in antibody above baseline.
   Comment: Use of these booster response definitions requires a demonstration that the assay variability is sufficiently low that, when a 4-fold rise is observed, there is a high probability that this represents a true increase rather than random variation. I have reviewed the assay precision data provided by the sponsor, and have concluded that the sponsor has provided evidence that the precision was adequate to support the booster response definitions used above.

Additional Reviewer Comments:

For this application, the major efficacy analysis requires the direct, quantitative comparison of antibody responses in infants immunized with Pentacel to responses in infants in Sweden trial I immunized with 3 doses of DTaP. The sponsor made this comparison by re-assaying the Sweden I post-immunization sera in parallel (i.e., in the same laboratory during the same period of time) with the sera from Pentacel trial 494-01. Essential to this analysis is the assumption that the Sweden trial I sera have not lost significant antibody activity during the 10-plus years since collection. This issue was addressed in my review of BLA STN125111, and the conclusions from that review are relevant here because the assays for the Pentacel bridging study were done

concurrently with the Adacel bridging study. In my review for Adacel, I concluded that the data provided by SPL suggested that assay results obtained for the Swedish sera in the Adacel/Pentacel bridging study appear to be representative of those obtained at collection, however, some minor changes cannot be ruled out. For additional detail, please refer to STN125111.

EFFECTIVENESS OF THE PERTUSSIS COMPONENT: REVIEW COMMENTS

The primary evidence supporting efficacy of the pertussis components came from immunogenicity data from a series of pivotal trials, primarily study 494-01, P3T06, and the Serology Bridging Study. In these immunogenicity studies, the majority of pre-specified endpoints were met, however, some pertussis primary endpoints were not met. These missed endpoints (summarized in item 6 below) raise important concerns; however, my opinion, based on review of the available body of evidence in the BLA, is that the sponsor has provided adequate evidence to support the effectiveness of the pertussis component.

Rather than provide a complete summary of all relevant data, I will summarize the most important evidence that led me to this conclusion.

1. Efficacy for the SPL acellular pertussis (aP) component was evaluated in two controlled efficacy studies:

   Sweden Trial I: the SPL aP component was evaluated and shown to be effective using the Daptacel formulation (10 μg pertussis toxin (PT), 5 μg filamentous hemagglutinin (FHA), 5 μg fimbriae types 2 and 3 (FIM2/3), and 3 μg pertactin (PRN).
   Sweden II: the SPL aP component was evaluated and shown to be effective using the HCPDT formulation (20 μg PT, 20 μg FHA, 5 μg FIM2/3, and 3 μg PRN.

   In both of the studies, the pertussis component was shown to be highly effective in the prevention of pertussis in immunized subjects.

2. Effectiveness is supported by the experience in Canada. Pentacel has been the only pertussis vaccine used in Canada since April 1998, when the transition from whole-cell to acellular pertussis vaccines was completed. The epidemiological data suggest that pertussis has been adequately controlled during this period. The Canadian experience is supportive, but cannot stand alone as evidence for effectiveness in the US. Specific limitations include: a) detailed information on the surveillance procedures have not been submitted for review; b) the vaccines used concurrently with Pentacel in Canada may not be the same as in the US, e.g., universal use of the pneumococcal conjugate vaccine has been implemented only within the last 2-3 years; c) the demographics of the US and Canadian populations are not identical; d) there has been, to my knowledge, no direct comparison demonstrating comparable immunogenicity of Pentacel in the US and Canadian populations.

3. The immunogenicity of Pentacel was evaluated in two US controlled pivotal trials, 494-01 and P3T06. In study P3T06, Pentacel was compared to the US licensed vaccine, Daptacel, while in study, 494-01, Pentacel was compared to the formulation equivalent product,

HCPDT (not licensed in US). In these trials, the Pentacel group met all GMC and percent responder endpoints following the 3rd dose of the four dose series (table 1). Thus, for the period of time between dose three and dose four, responses to Pentacel are non-inferior to the currently licensed product. While not designed to demonstrate superiority, it should be noted that the post-dose three responses to Pentacel appear higher than the responses to Daptacel for PT and FHA, presumably a reflection of the higher PT and FHA antigen content of Pentacel.

Table 1: Evaluation of responses following immunization with three doses of Pentacel compared to responses following three doses of control vaccine in two pivotal studies 494-01 and P3T06.

Post dose three (7 months)				
	Comparison with study controls			
	P3T06		494-01	
	vs. Daptacel		vs. HCPDT	
Antigen	≥4-fold ↑	GMC	≥4-fold ↑	GMC
PT	pass	pass	pass	pass
FHA	pass	pass	pass	pass
FIM2/3	pass	pass	pass	pass
PRN	pass	pass	pass	pass

Pass = met pre-defined non-inferiority criteria for GMC and percentage of population with 4-fold or greater increase in antibody

4. In the trials, 494-01 and P3T06, the Pentacel group met all GMC and percent responder endpoints following the 4th dose of the four dose series (table 2), with the important exception of the PRN GMC. Thus, following dose four, the concentrations of circulating PRN antibody appear to be lower for subjects immunized with Pentacel than for those immunized with Daptacel. This reduced response to PRN following a the 4th dose raise concerns, however the data from the Bridging Study (see item 5 below) suggest significant effectiveness even in the presence of these attenuated responses.

Table 2: Evaluation of responses following immunization with four doses of Pentacel compared to responses following four doses of control vaccine in two pivotal studies 494-01 and P3T06.

Post dose four (16 months)				
	Comparison with study controls			
	P3T06		494-01	
	vs. Daptacel		vs. HCPDT	
Antigen	≥4-fold ↑	GMC	≥4-fold ↑	GMC
PT	pass	pass	pass	pass
FHA	pass	pass	pass	pass
FIM2/3	pass	pass	pass	pass
PRN	pass	**fail**	pass	**fail**

Pass = met pre-defined non-inferiority criteria for GMC and percentage of population with 4-fold or greater increase in antibody.
Fail = did not meet pre-defined non-inferiority criteria for GMC and percentage of population with 4-fold or greater increase in antibody.

5. Bridging Study.
Additional pre-specified pivotal endpoints relate to the comparison of the Pentacel post-dose four responses to those of the efficacy population in Sweden I trial. All GMC endpoints were met for all four components, including PRN (table 3). Thus, while the randomized US trials have demonstrated the concentration of PRN antibody produced following the 4th dose of Pentacel is lower than that following the 4th dose of the control vaccines, the quantity of antibody in the Pentacel group is similar to that observed in the Swedish infants in whom efficacy was demonstrated. Thus, in my opinion, the effectiveness following four doses of Pentacel is likely to be similar to that observed following three doses in Sweden Trial I.

Table 3: Evaluation of responses following immunization with four doses of Pentacel compared to responses following three doses of Daptacel in Sweden I efficacy trial

Post dose four (16 months)				
	Comparison vs. efficacy population			
	P3T06		494-01	
	vs. Sweden I (Daptacel post 3rd)			
Antigen	≥4-fold ↑	GMC	≥4-fold ↑	GMC
PT	pass	pass	pass	pass
FHA	pass	pass	pass	pass
FIM2/3	pass	pass	pass	pass
PRN	**fail**	pass	**fail**	pass

Pass = met pre-defined non-inferiority criteria for GMC and percentage of population with 4-fold or greater increase in antibody.
Fail = did not meet pre-defined non-inferiority criteria for GMC and percentage of population with 4-fold or greater increase in antibody.

Table 3 also indicates that the percentage of subjects with a 4-fold or greater rise in PRN antibody did not meet the pre-specified criterion. However, the sponsor has demonstrated that the baseline values in PRN antibody (i.e., those used as the denominator when calculating the fold rise) were different in the two comparator populations, with the Sweden I population having lower concentrations. Differences in baseline values are problematic in analyses evaluating the proportion of subjects with a specified fold-rise. The lower baseline values in Sweden subjects have the potential to introduce some bias in the results. The retrospective analyses performed by the sponsor support the conclusion that the comparisons were influenced by the different baseline distributions; however, the data do not allow the magnitude of the influence to be quantified. Thus, although the failure to meet this pre-specified endpoint raises questions, my concerns are reduced by the observation that the post-dose three and post dose four 4-fold response criteria were met in the more direct within-study comparisons summarized in tables 1 and 2.

6. Although I believe that the body of evidence supports the conclusion that Pentacel will be effective when administered as a four-dose series in the US, the most important specific observations that raised questions are summarized for completeness. These limitations do not, in my opinion, preclude the approval of the BLA, but do suggest that ongoing monitoring of the field effectiveness of Pentacel should be encouraged.
   a. In the US studies, the PRN responses following three doses of Pentacel are significantly lower than that observed following three doses of Daptacel in the Sweden I trial. Although this was not a primary endpoint, the observation is consistent with that observed in the US Bridging Studies considered in the license application for Daptacel.

   b. In the US studies, the PRN responses following four doses of Pentacel are similar to, but do not exceed, those observed following three doses of Daptacel in the Sweden I trial. The PRN GMC criterion met the pre-specified criterion (upper end of the 90% confidence interval was less than 1.5-fold); however, the upper limit of the 90% confidence interval was 1.49. This observation differs from that observed with Daptacel, in that the PRN responses following four doses of Daptacel exceeded those observed following three doses of Daptacel in the Sweden I trial.

   c. In US study P3T06, the PRN responses following four doses of Pentacel were significantly lower than those observed following four doses of Daptacel in a randomized trial in which the two products were compared directly.

   d. In US study 494-01, the PRN responses following four doses of Pentacel were significantly lower than those observed following four doses of the formulation equivalent product (HCPDT) in a randomized trial in which the two products were compared directly.

   e. The data submitted by the sponsor to date do not rule out the possibility that co-administration of Pentacel with Prevnar (pneumococcal conjugate vaccine) could

attenuate the response to the pertussis component of Pentacel, particularly the PRN response following the 4th dose of Pentacel. This merits ongoing evaluation.

f. In the discussion above, all missed endpoints were related to the responses to the PRN component of Pentacel. Although not a primary endpoint, one observational FIM2/3 endpoint should be noted. Specifically, in the US studies, the FIM2/3 responses following three doses of Pentacel were lower than that observed following three doses of Daptacel in the Sweden I trial. My concerns regarding this are reduced by the observation that all FIM2/3-related post-dose three and post dose four endpoints were met in the more direct within-study comparisons summarized in tables 1 and 2.

APPENDIX 1: Documents reviewed from original submission (26 July 2005)

Item 3: Summary
- Application Overview

Item 8: Clinical
- Clinical Summary
- Serology Bridging Study Report
- Integrated Summary of Immunogenicity
- Serology Methodology
- Assay procedures and validation reports
  - SOP 2SE-114: AvP CIP-CA SOP [redacted] Method for the Detection of Human Antibodies to PT Antigen
  - VR 2SE-114, AvP Validation Report '[redacted] Method for the Detection of Human Antibodies to PT Antigen".
  - SOP 2SE-113: AvP CIP-CA SOP '[redacted] Method for the Detection of Human Antibodies to FHA Antigen".
  - VR 2SE-113, AvP Validation Report [redacted] Method for the Detection of Human Antibodies to FHA Antigen"
  - SOP 2SE-112, AvP CIP-CA SOP '[redacted] Method for the Detection of Human Antibodies to FIM (2+3) Antigen".
  - VR 2SE-112, AvP Validation Report '[redacted] Method for the Detection of Human Antibodies to Fimbrial Agglutinogens (2+3) Antigen
  - SOP 2SE-115, AvP CIP-CA SOP '[redacted] Method for the Detection of Human Antibodies to Pertactin (PRN) Antigen"
  - VR 2SE-115, AvP Validation Report '[redacted] Method for the Detection of Human Antibodies to PRN Antigen"