FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: 9 February 2007

TO: File, STN 125145
Aventis Pasteur, Inc.
Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) Reconstituted with Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Poliovirus Vaccine Inactivated: PENTACEL™
Theresa Finn, Committee Chair

FROM: Milan S. Blake, Ph.D., Deputy Director,
Division of Bacterial, Parasitic, and Allergenic Products, OVRR

SUBJECT: Product review of Haemophilus component and serology

Summary

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). The current "US standard of care" to which PENTACEL™ is intended to replace is DAPTACEL™, IPOL™, and ActHIB™ given separately. HCPDT-IPV Vaccine is manufactured at Aventis Pasteur Limited (Canada) and Haemophilus b Conjugate Vaccine (Tetanus Protein-Conjugate) Vaccine referred to as PRP-T Vaccine is manufactured at Aventis Pasteur SA (France). PRP-T Vaccine (filled and freeze-dried) is received, at Aventis Pasteur Limited, where it is labeled and co-packaged with labeled HCPDT-IPV Vaccine.

PRP-T Vaccine (Act-HIB®) is a *Haemophilus influenzae* type b conjugate Vaccine (polysaccharide Tetanus protein conjugate) formulated to contain 10 µg purified Polyribose Ribitol Phosphate Capsular Polysaccharide (PRP) of *Haemophilus influenza* Type b covalently bound to 24 µg of Tetanus protein per dose. Act-HIB® is licensed and actively marketed in the USA for immunization of infants (2, 4, 6, and 18 months of age). The PRP-T Vaccine information was presented as a summary document in the CMC section and reflected the information currently on file with the FDA (Act-HIB® license

STN: BLA 103935). Prior agreement to submit only summarized information from the US Act-HIB® license was granted by FDA in a response letter dated 19 September 2001. There has been no major change in the manufacturing process description for PRP-T since the initial license application.

PENTACEL™ Vaccine is indicated for active immunization for prevention of disease due to *H. influenzae* Type b, pertussis, diphtheria, tetanus and poliovirus types 1, 2 and 3 to be administered intramuscularly as a four dose primary series at 2, 4, 6 and 15 to 18 months of age.

Serology

The serological correlate of protection from *H. influenzae* Type b disease was established in studies to protect agammaglobulinemic children with passive immune therapy as well as studies of naturally acquired antibody levels in healthy individuals. These studies documented that 0.15 μg/ml of antibodies reactive with polyribitol phosphate (PRP), the *H. influenzae* Type b capsule, was a conservative estimate of antibody concentration that was protective. Moreover, that if an antibody concentration of 1 μg/ml was achieved, a protective antibody concentration of ≥ 0.15 μg/ml would be maintained for over 1 year. These values were confirmed and substantiated in numerous double-blind, placebo controlled efficacy trials of both PRP polysaccharide vaccines and PRP-protein conjugate vaccines. These values have also been the basis of licensure of PRP vaccines. Because PENTACEL™ was meant to replace the US licensed stand-alone Act-HIB® vaccine, the evaluation criteria used was the % of individuals achieving a concentration of ≥ 0.15 μg/ml of PRP reactive antibodies after the primary series, the % of individuals achieving a concentration of ≥ 1.0 μg/ml of PRP reactive antibodies after the primary series, the % of individuals achieving a concentration of ≥ 1.0 μg/ml of PRP reactive antibodies after the primary series plus the booster dose 4, and that these values would be non-inferior to Act-HIB® given separately but concurrently with the polio and the pertussis-tetanus-diptheria combined components as the control vaccines. In addition, these criteria would be non-inferior when PENTACEL™ was administered with other US "standard of care" vaccines for the intended age group.

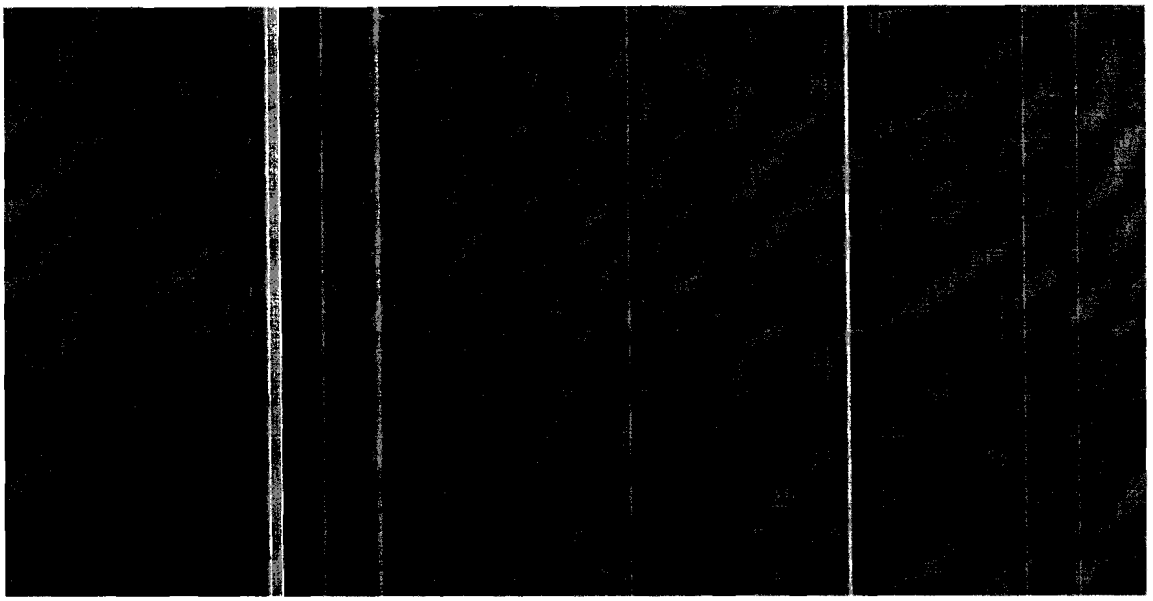
Critique

Serological assay for PRP reactive antibodies

The serological determinations of anti-PRP antibody were performed using a [redacted] as has been previously described by [redacted] and is a well known, widely used, standard assay for such measurements. The well recognized CBER reference standard human anti-*H. influenzae* type b capsular polysaccharide antibody Lot 1983 was incorporated into each of the assays. The protocol and validation documents for this assay was submitted by the sponsor on the 15 February 2000 and approved by CBER in a letter dated 20 October 2000. The concentration of anti-PRP antibody in the serum sample is determined from the concentration response curve generated from the titration results of [redacted] serial dilutions of the reference standard analyzed in the assay. These

documents demonstrate that the PRP [redacted] was a reliable and accurate method for measuring anti-PRP antibodies in human clinical samples. The validation report established that this assay was precise, had linearity if the corresponding % bound PRP antigen for each dilution was within the range of [redacted] was rugged, and had a LOD as well as LLOQ of [redacted]

Serological assay for pneumococcal polysaccharide reactive antibodies



Serological clinical data supporting PENTACEL™'s effectiveness in protection from *H. influenzae* Type b disease

Act-HIB® was first licensed in the US in March 1993 and became implemented into the infant series of vaccines. There have been numerous efficacy trials that have demonstrated that Act-HIB® alone or in combinations is safe and effective protection from *H. influenzae* Type b disease. It is one of two PRP-conjugate vaccines that is widely available and makes up the US "standard of health care". Surveillance of *H. influenzae* Type b disease in the US further substantiates the effectiveness of this "standard of health care" with *H. influenzae* Type b disease being almost non-existent in the US for sometime. In comparison, there has been a recent increase of *H. influenzae* Type b disease in the UK and The Netherlands. In study P3T06, PENTACEL™ is compared to this standard with one arm of the study receiving PENTACEL™ within the infant series and boost with the control being Daptacel, IPOL, and Act-HIB® administered separately but concurrently. Primary objective 3 in this study was to demonstrate that the seroprotection rates elicited by the PRP-T antigen in Pentacel™ is not inferior to that of ActHIB® administered concurrently at a different injection site with DAPTACEL® when these vaccines are co-administered with other recommended vaccines after the infant series. Non-inferiority was demonstrated if the upper limit of the 90% CI for the difference in seroprotection rates between the Pentacel™ group and Groups 1 to 3 combined (ActHIB®) was <10%. As demonstrated

in Table 5.6, the Pentacel group had 92.3% of the individuals achieving a seropertective concentration of ≥ 0.15 μg/ml while the control group had 93.3% one month following the infant series. Similarly, in the measure of long term seroprotection, a concentration of ≥ 1.0 μg/ml, the Pentacel group had 72.1 % of the individuals while the control group had 70.8 %. The non-inferiority end point was achieved in both measurements. The GMT of the PRP reactive antibodies post-dose 3 are seen in Table 5.8 and show the Pentacel group had a GMT of 2.31 μg/ml and the control group 2.29 μg/ml, again achieving non-inferiority. It should be noted that all of these values are within the range of PRP-conjugate vaccines that historically have been found to be efficacious. After the booster dose, the Pentacel group had 97.8 % of the individuals with a concentration of ≥ 1.0 μg/ml while the control group had 95.9 %. The GMT of the PRP reactive antibodies post-dose 4 show the Pentacel group had a GMT of 17.71 μg/ml and the control group 20.49 μg/ml. It is clear from these studies that Pentacel compares well with the control group.

Study 494-01 was designed to assess the immunogenicity of the individual components of Pentacel™ (i.e. the anti-Pertussis, anti-Diphtheria, anti-Tetanus, anti-Poliovirus Types 1, 2, and 3, and anti-PRP responses) when Pentacel™ is given as an infant series as compared to the control vaccine, the co-administration of HCPDT, POLIOVAX®, ActHIB® in different injection sites as the infant series. This study also included a lot-consistency evaluation of three lots of Pentacel™. The primary immunogenicity endpoints for the PRP component was the percentage of subjects who achieved seroprotection to PRP based on the number (≤1, 2, or 3) of Prevnar® vaccine doses co-administered with Pentacel™ or the Control regimen and the GMT for PRP based on the number (≤1, 2, or 3) of Prevnar® doses co-administered with Pentacel™ or the Control regimen. The lot consistency of immunogenicity was assessed for equivalence in the PRP response using the criteria of the upper limit of the 90% CI δ-seroconversion [redacted] <10% and comparison of immunogenicity versus Controls for non-inferiority using the criteria of the upper limit of the 90% CI δ-seroconversion Control – Pentacel™ <10%. The GMT of the PRP response post dose 3 and 4 were assessed for lot consistency and versus control for non-inferiority using the criteria the upper limit of each 90% CI is <1.5 and the lower limit is >2/3.

The lot consistency was achieved in the seroprotection for PRP in that 94.5% to 96.7% of subjects attained a serum concentration of ≥0.15 μg/mL and long-term protection rates ≥1.0 μg/mL were achieved by 77.2% to 81.7% (see Table 5.4). The GMTs for PRP post dose 3, however, did not meet the statistical criteria for equivalence among the lots. The GMT for PRP was statistically higher in Lot 3 than in Lot 2 (3.64 μg/mL versus 2.86 μg/mL; lower bound of the 90% CI=0.65) (see Table 5.5). It should be noted in the demographics shown in Table 5.3 that Lot 3 has a slight increased % of Hispanic participants as compared to Lot 2. Hispanic populations historically seem to respond to PRP more aggressively as compared to other populations. Additionally, the pooled Pentacel™ group was non-inferior as compared to the Control group in achieving seroprotection anti-PRP concentrations of ≥0.15 μg/mL with 95.4% of Pentacel™ subjects and 98.3% of Control subjects attaining this concentration. This is the more important piece of data because this value has consistently with both PRP as well as PRP

conjugate vaccines been linked to efficacy and would suggest that both populations are protected from invasive *H. influenzae* Type b disease. However, the evaluation of the long-term PRP seroprotection rates, those having concentrations ≥ 1 μg/mL were lower in the Pentacel™ group than in the Control group (79.1% versus 88.8%; upper bound of the 90% CI=12.90). The significance of this value is it's relation to the % of individuals that remain protected until the 4th booster dose or in other words the % of individuals having a serum concentration of ≥0.15 μg/mL prior to the 4th dose. In this case, Pentacel™ group had 68.6 % having a serum concentration of ≥0.15 μg/mL prior to the 4th dose while the Control group had 80.8 %. Both are well within the ranges that historically have been found to be efficacious of licensed PRP vaccines. One should also note that similar data from study P3T06 established that both the Pentacel™ group and the Control group had similar values to the Pentacel™ group in study 494-01, 65.4 % and 60.7 % respectively. The Anti-PRP GMTs were also statistically lower in the subjects who received Pentacel™ (3.19 μg/mL) compared with subjects who received Control vaccines (6.23 μg/mL). It should be noted that the lower bound of the 95 % CI of the Pentacel™ remains well above ≥ 1 μg/mL. Furthermore, the GMC of Pentacel™ group in study 494-01 is similar to both the Pentacel™ group as well as the Control group in study P3T06. The post dose 3 anti-PRP for known efficacious licensed Hib vaccines have ranged from 1.1 to as high as 13.7 μg/mL. Moreover, the historical data on ActHIB® demonstrate that the range of anti-PRP post-dose three range from 2 to 10.8. There is some evidence as stated previously that some of this is due to particular strong PRP responses from certain populations. However, in other cases and even in the initial lot consistency trials for ActHIB®, the cause for the variability in immune response is unclear. Thus Pentacel™ fulfills all of the criteria which many of the licensed *H. influenzae* Type b vaccines have been licensed and are known to be efficacious but fails in the non-inferiority endpoint comparisons, specifically in study 494-01.

Recommendation:

My recommendation focuses specifically on whether in my opinion I believe Pentacel™ is efficacious and comparable to the current "US standard of healthcare" in protecting against *H. influenzae* Type b disease. The data clearly support this fact. Thus, I recommend the license application be approved for this indication.