Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Vaccines Research and Review
Division of Vaccines and Related Product Applications

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From: Theresa M. Finn, Ph. D.
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Food and Drug Administration

Subject: Immunogenicity Review of Pentacel

To: BLA STN# 125145

Through: Douglas Pratt, MD
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Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

cc: Karen Farizo, M.D.
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1 General Information

1.1 Review Identifiers and Dates

1.1.1 BLA #: 125145/0

1.1.2 Related INDs and BLAs:

- BLA STN # 103940 (POLIOVAX), approved November 20, 1987
- BLA STN #103935 (ActHIB, PLA 90-0689 and ELA 90-0690)), approved March 30, 1993
- IND #---- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DAPTACEL), Aventis Pasteur Limited
- BLA STN# 103666/0 DAPTACEL, approved May 2002
- IND #---- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine combined with Inactivated Poliovirus Vaccine used to reconstitute ActHIB (*Haemophilus influenzae* type b Conjugate Vaccine) (proposed tradename Pentacel)
- IND #---- Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (ADACEL), Aventis Pasteur Limited
- BLA STN #125111 Adacel; approved June 2005
- DAPTACEL BLA Supplement STN #103666/5071: A Labeling Supplement included data from Study P3T06, which is also a pivotal study to support licensure of Pentacel. The supplement was approved November 10, 2006.
- DAPTACEL BLA Supplement #103666/5069: In this Efficacy Supplement, the applicant requested approval of ---------- the acellular pertussis antigens contained in DAPTACEL. This Supplement includes data from Study M5A03 Stage I (doses 1-3), in which subjects received Pentacel containing an acellular pertussis component from the ---------- (N=2,260) or the ---------- (N=760). This supplement was approved August 23, 2006. This study was not submitted to the Pentacel BLA.

1.1.3 Reviewer Name, Division, and Mail Code

Theresa Finn, Ph. D
Division of Vaccines and Related Products Applications
HFM-481

1.1.4 Submission Received by FDA: July 26, 2005

1.1.5 Review Completed:

June 17, 2008

1.2 Product:

1.2.1 Proper Name: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine.

1.2.2 Tradename: Pentacel

1.2.3 Product Formulation:

DTaP-IPV is a suspension supplied in single dose vials which is used to reconstitute the lyophilized US-licensed ActHIB to form Pentacel.

DTaP- IPV (per 0.5 mL dose)**:**
Active Ingredients:
20 µg Pertussis Toxoid (PT)
20 µg Filamentous hemagglutinin (FHA)
5 µg Fimbriae 2 & 3 (FIM)
3 µg Pertactin (PRN)
15 LF Diphtheria toxoid
5 LF Tetanus toxoid
40 DAU poliovirus type 1 (Mahoney)
8 DAU poliovirus type 2 (M.E.F.I.)
32 DAU poliovirus type 3 (Saukett)
10 ug PRP conjugated to 24 ug tetanus toxoid
Adjuvant: 1.5 mg Aluminum phosphate (0.33 mg aluminum)
Excipient: 0.6% (3.3 mg) 2-phenoxyethanol
Tween 80 ~10 ppm
BSA: ≤ 50 ng
Neomycin < 4 pg
Polymyxin B sulphate < 4pg
Formaldehyde: ≤ 0.001% (≤ 5 ug)
Gluteraldehyde: < 100 ppb (< 50 ng)
(Source: June19, 2008 submission summary_amend069.pdf)

Act-HIB
10ug polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) conjugated to 24 ug tetanus toxoid
No preservative

1.3 Applicant: Aventis Pasteur Limited (APL) /sanofi pasteur Ltd, Canada.

1.4 Pharmacologic Class: Vaccine

1.5 SPL Proposed Indications: Active immunization against, diphtheria, tetanus, pertussis, poliomyelitis and invasive disease caused by *Haemophilus influenzae* type b in infants and children 6 weeks through 4 years of age (prior to fifth birthday).

1.6 Dosage Forms and Routes of Administration: Pentacel is to be administered intramuscularly. It will be supplied in 5-dose packages containing 5 vials of DTaP-IPV component to be used to reconstitute five single dose vials of lyophilized ActHIB. Each dose is 0.5mL.

1.7 Revisions to Package Insert: A draft package insert was included with the submission. Revisions were ongoing at the time this review was finalized.

2 Table of Contents

3.0 Immunogenicity Executive Summary

Pentacel Vaccine
Pentacel is a combination DTaP-IPV/Hib vaccine. The DTaP-IPV component is used to reconstitute lyophilized Haemophilus b conjugate vaccine (Tetanus Toxoid Conjugate), ActHIB.

The proposed vaccination regimen is four intramuscular doses administered at 2, 4, 6 and 15-18 months of age.

Table 1 shows the antigen composition of Pentacel and comparator vaccines that were used in pivotal controlled clinical studies. HCPDT is a non-US-licensed DTaP vaccine which contains the same quantities of pertussis antigens, diphtheria and tetanus toxoids as contained in Pentacel. DAPTACEL, also manufactured by sanofi pasteur Ltd contains the same diphtheria and tetanus toxiods and pertussis antigens as Pentacel and HCPDT but with reduced quantities of PT and FHA as compared to these vaccines. POLIOVAX (sanofi pasteur Ltd) and IPOL (sanofi pasteur SA) are US-licensed inactivated poliovirus vaccines. The poliovirus components of Pentacel are the same as those in POLIOVAX. For manufacture of POLIOVAX the polioviruses are grown in MRC-5 cells. For manufacture of IPOL, the polioviruses are grown in VERO cells.

Table 1: Antigen composition of Pentacel, HCPDT, ActHIB, POLIOVAX, DAPTACEL and IPOL (per dose):

Antigen	Pentacel	HCPDT[1]	DAPTACEL[2]	ActHIB[3]	POLIOVAX[4]	IPOL[5]
Diphtheria toxoid	15 Lf	15 Lf	15 Lf	-	-	-
Tetanus toxoid	5 Lf	5 Lf	5 Lf	-	-	-
Pertussis toxoid	20ug	20ug	10ug	-	-	-
Filamentous hemagglutinin	20ug	20 ug	5 ug	-	-	-
Fimbriae 2 & 3	5 ug	5 ug	5 ug	-	-	-
Pertactin	3 ug	3 ug	3 ug	-	-	-
Poliovirus 1	40 DAU	-	-	-	40 DAU	40 DAU
Poliovirus 2	8 DAU	-	-	-	8 DAU	8 DAU
Poliovirus 3	32 DAU	-	-	-	32 DAU	32 DAU
PRP-T	10 ug (+ 24 ug tetanus toxoid)	-	-	10 ug (+ 24 ug tetanus toxoid)	-	

1 HCPDT: DTaP manufactured by Sanofi Pasteur Limited; not licensed in the U.S.
2 DAPTACEL DTaP manufactured by Sanofi Pasteur Limited; licensed in the U.S.
3. ActHIB: Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur SA
4 POLIOVAX: Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited
5 IPOL: Poliovirus Vaccine Inactivated, Sanofi Pasteur S.A.
DAU = D-antigen Units
PRP-T = polyribosyl-ribitol-phosphate conjugated to tetanus toxoid
Source: Compiled by FDA reviewer.

The Pentacel BLA contains four pivotal immunogenicity studies: 494-01, 494-03, P3T06 and 5A9908. These studies evaluated lot consistency, non-inferiority relative to separately administered control vaccines and the effect of Pentacel on concurrently administered recommended vaccines. In addition, a serological bridge of pertussis immune responses following Pentacel administered in Study 494-01 to the response to DAPTACEL in the Sweden I efficacy trial was provided. Summary data from one supportive study, M5A07, designed to

assess the effect of Prevnar on the response to Pentacel antigens were provided. Additional anti-PRP immunogenicity data from Study M5A10 were provided during review of the application. Results and conclusions based on data submitted in the application are summarized in this section.

Efficacy of Pentacel

Evaluation of the effectiveness of the tetanus, diphtheria, polio and PRP-T components of Pentacel was based on a comparison of immune responses, using established correlates of protection and for some antigens, geometric mean antibody titers (GMTs), relative to separately administered vaccine components (HCPDT+ POLIOVAX + ActHIB) or all U.S. licensed vaccines (DAPTACEL + IPOL + ActHIB) in US children. The evaluation of the effectiveness of the pertussis component, which does not have a generally accepted correlate of protection, was based on: 1) a comparison of immune responses following four doses of Pentacel in U.S. children to responses following three doses of DAPTACEL in the Sweden I efficacy Trial, and 2) a comparison of immune responses following Pentacel relative to DAPTACEL in US children.

The Pentacel BLA contains two studies comparing the immune response of Pentacel to that of separately administered control vaccines: Study 494-01 evaluated non-inferiority of Pentacel antigens relative to separately administered HCPDT, ActHIB and POLIOVAX. In Study P3T06 control subjects were administered DAPTACEL, ActHIB and IPOL. In this study non-inferiority was evaluated for the response to diphtheria, tetanus, pertussis and PRP-T components.

Polio virus type 1, 2 and 3

Following three doses of Pentacel in Studies 494-01 and P3T06, >99% of subjects had protective neutralizing antibody against each poliovirus serotype.

Diphtheria and tetanus toxoids

Based on review of post-dose 3 anti-tetanus toxoid levels measured using the sanofi pasteur-US ELISA and assessment of the ability of these sera to ---------- ---------- ELISA anti-tetanus toxoid levels $\geq$ 0.1 IU/mL are considered the minimum protective level.

Literature data indicate that an anti-diphtheria toxin level $\geq$0.01 IU/mL is the lowest giving some degree of protection while a level $\geq$0.1 IU/mL may be needed for full protection.

Following three doses of Pentacel in Study 494-01 and P3T06, >99% of subjects had an anti-tetanus level $\geq$0.1 IU/mL and >99% had an anti-diphtheria level $\geq$0.01 IU/mL. Following three doses of Pentacel in Study 494-01 92 % of subjects had an anti-diphtheria level $\geq$0.1 IU/mL.

PRP-T

Anti-PRP has been shown to correlate with protection against invasive *H. influenzae* type b (Hib) disease. Based on efficacy studies with Hib polysaccharide (not Hib-conjugate) vaccines and data from passive antibody studies, a post-vaccination anti-PRP level of 0.15µg/ml has been accepted as correlating with at least short-term protection[1] and 1.0 µg/ml with long-term (one year) protection[2,3]. Although the relevance of these levels to Hib conjugate vaccines is not

[1] Robbins JB, Parke JC, Schneerson R. Quantitative measurement of "natural" and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. Pediatr Res 1973;7:103

[2] Kayhty H, et al. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis 1983;147:1100

entirely clear, they have been used to evaluate the effectiveness of Hib conjugate vaccines and combination vaccines containing Hib components.

The immune response following three doses of ActHIB or Pentacel in the pivotal studies and supportive study is summarized in Table 2. All assays were performed by sanofi pasteur-US in either Building --------- (Section 5.5).

In the two comparative pivotal studies, Pentacel was non-inferior to separately administered ActHIB with regard to post-dose 3 anti-PRP levels $\geq$0.15 µg/mL. However, these two studies showed contradictory results with regard to anti-PRP levels $\geq$1.0 µg/mL and GMTs:
In Study 494-01 the proportion of subjects with anti-PRP levels $\geq$ 1.0 µg /mL and the GMT were lower following three doses of Pentacel compared to three doses of separately administered ActHIB (Table 2, 20 and 21). In Study P3T06 the proportion of subjects with anti-PRP levels $\geq$1.0 µg /mL and the GMT were similar following three doses of Pentacel or separately administered ActHIB (Tables 2, 96, and 98). However, the anti-PRP responses following both Pentacel and ActHIB in Study P3T06 were lower than observed in Study 494-01, with the most notable differences in the ActHIB arms of the two studies (e.g., post-dose 3 GMT 2.29 µg/mL for Study P3T06 and 6.23µg/mL for Study 494-01) (Table 2).

In comparative Study M5A10 the anti-PRP response following three doses of Pentacel or separately administered ActHIB was similar (Table 2, 142, 143).

In studies which did not include an ActHIB comparator (Studies 494-03 and M5A07), following the third dose of Pentacel, the anti-PRP GMT ranged from 2.8-3.6 ug/mL and the proportion of subjects with PRP antibody levels $\geq$ 1.0 ug/mL ranged from 75.6-79.6%, consistent with the Pentacel arms of the comparative studies.

[3] Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis 1984;149:1034

Table 2: Response to PRP-T following three doses of Pentacel or ActHIB in Pivotal and supportive BLA studies –assays performed at Aventis –US Blg -- (shaded cells) or Blg -- (not shaded cells)

	Pentacel					
Study	**Study 494-01 (N=1127)**	**494-03 (n = 270)**	**P3T06 (N=365)**	**M5A07 (P+P) (N=433)**	**M5A07 (P-P) (N=427)**	**M5A10 (N=826)**
Post dose 3						
% ≥0.15 ug/mL	95.4 (94.0, 96.5)	94.4 (91.0, 96.9)	92.3 (89.1, 94.8)	95.8 (93.5, 97.5)	95.3 (92.9, 97.1)	93.8 (92.0, 95.4)
% ≥1.0 ug/mL	79.1 (76.7, 81.5)	75.6 (70.0, 80.6)	72.1 (67.1, 76.6)	77.1 (72.9, 81.0)	79.6 (75.5, 83.3)	75.1 (72.0, 78.0)
GMT	3.19 (2.91, 3.50)	2.80 (2.30, 3.41)	2.31 (1.94, 2.75)	3.32 (2.85, 3.87)	3.60 (3.09, 4.20)	2.52 (2.25, 2.81)
Pre-dose 4	**(N=829)**		**(N = 335)**			
% ≥0.15 ug/mL	68.6 (65.4, 71.8)	NA	65.4 (60.0, 70.5)	NA	NA	NA
	ActHIB Vaccine					
Study	**494-01 (N=401)**		**P3T06 (N=1128)**			**M5A10 (N = 421)**
Post dose 3						
% ≥0.15 ug/mL	98.3 (96.4, 99.3)		93.3 (91.6, 94.7)			90.3 (87.0, 92.9)
% ≥1.0 ug/mL	88.8 (85.3, 91.7)		70.8 (68.1, 73.5)			74.8 (70.4, 78.9)
GMT	6.23 (5.40, 7.18)		2.29 (2.08, 2.53)			2.38 (2.01, 2.81)
Pre-dose 4	**(N = 276)**		**(N = 323)**			
% ≥0.15 ug/mL	80.8 (75.6, 85.3)		60.7 (55.1, 66.0)			NA

494-01 pooled Pentacel data, P3T06 pooled DAPTACEL + ActHIB groups
M5A07 (P+P) Pentacel administered concurrently with Prevnar, M5A07 (P-P) Prevnar administered 1 month weeks after each dose of Pentacel.

In Studies 494-01 and P3T06, the post-dose 3 anti-PRP responses appeared to influence the proportion of subjects with seroprotective levels at 15 months of age prior to receipt of a fourth dose of PRP-T: In Study 494-01 67% of subjects administered Pentacel had anti-PRP levels ⩾ 0.15 ug/mL compared with 81% of subjects administered ActHIB separately. At 15-16 months of age prior to administration of the fourth dose of PRP-T 61-65% of P3T06 subjects had anti-PRP levels ⩾0.15 ug/mL (Table 2).

Sanofi pasteur and CBER have considered whether the anti-PRP immune response seen in Pentacel studies is consistent with previous ActHIB experience. CBER has also considered whether the observed variability in anti-PRP responses may be due to differences in assays, lot to lot variability, co-administered vaccines and/or the race/ethnicity of subjects. Discussion of these items may be found in the Conclusions section of this review.

Effectiveness of the pertussis components of Pentacel

The efficacy of three doses of DAPTACEL (2, 4, and 6 months) against pertussis was demonstrated in a clinical study in Swedish infants (Sweden I). Following three doses of DAPTACEL in US infants, antibody responses to PT, FHA and FIM were similar to those observed in the Swedish infants. The immune response to pertactin (seroconversion rates

[proportion of subjects with a four-fold rise in antibody level following vaccination relative to pre-vaccination level] and GMTs) following three doses in US infants was significantly lower than in Swedish infants. The antibody responses to all pertussis antigens in North American infants after four doses of DAPTACEL (2, 4, 6, and 17-20 months) was comparable to that achieved after three doses in Swedish infants. Based on these data, four doses of DAPTACEL constitute a primary immunization course for pertussis in U.S. children (see Section 4.4.2 for a detailed discussion).

Because the pertussis antigens of Pentacel are the same as those contained in DAPTACEL, effectiveness of the pertussis component of Pentacel was evaluated by comparison of the immune response of US-children administered Pentacel to that of infants administered DAPTACEL. The response to the FHA, FIM and pertactin antigens following four doses of Pentacel in Study 494-01 were compared to the response of infants administered three doses of DAPTACEL in the Sweden I efficacy study. The PT -------- performed at the sanofi pasteur, Canada, laboratory was determined to be non-specific thus, a comparison of anti-PT levels are not available for this serology bridge analysis. Immunogenicity of the pertussis component of Pentacel compared to DAPTACEL was also evaluated in Study P3T06 following three and four doses of each vaccine. A comparison of anti-PT levels was only available for a subset of sera from this study which were reassayed in the laboratory of sanofi pasteur, U.S.

Serology bridge to Sweden I Although not pre-specified as non-inferiority analyses, the immune response to FIM and pertactin was diminished following three doses of Pentacel in Study 494-01 compared to three doses of DAPTACEL in Sweden I (Table 47). Following four doses of Pentacel compared to three doses of DAPTACEL in Sweden I non-inferiority was demonstrated for, FHA and FIM seroconversion rates and GMTs for FHA, FIM and pertactin (Table 44 and 45). Non-inferiority was not demonstrated for pertactin seroconversion rates (89.2% vs. 98.8%; UL of 95% CI for difference DAPTACEL minus Pentacel = 13.2%) (Table 44).

Study P3T06 Following three doses of each vaccine, non-inferiority of Pentacel relative to DAPTACEL was demonstrated for seroconversion rates and GMT for all pertussis antigens (FHA, FIM and pertactin: Table 94 and 95; PT: Table 118 and 119). Following four doses of each vaccine, non-inferiority of Pentacel relative to DAPTACEL was demonstrated for seroconversion rates for all antigens (FHA, FIM, pertactin: Table 105; PT: Table 120) and GMT for PT, FHA and FIM (FHA and FIM: Table 106 and 113, PT Table 121). Although the quantity of pertactin in both vaccines is the same, the post-dose 4 GMT to pertactin was significantly diminished in Pentacel recipients as compared to DAPTACEL recipients (93.6 EU/mL vs. 186.1 EU/mL; UL of 90% CI for GMT ratio DAPTACEL/Pentacel = 2.25) (Table 106).

Reduced response to Pertactin
In the absence of a correlate for pertussis protection the clinical significance of a diminished response to pertactin is unclear. The BLA contains a number of analyses to investigate potential explanations and implications for the reduced response to pertactin following Pentacel, a discussion of these items may be found in Section 7.0 of this review.

Lot consistency
Study 494-01 evaluated consistency of manufacture of three lots of Pentacel through analysis of seroprotection/seroresponse rates and GMT response to each of the antigens contained in Pentacel. Equivalence was demonstrated for seroconversion/seroprotection rates for PRP, FHA, FIM, pertactin, diphtheria and tetanus toxoids and polio virus serotypes (Table 19). Equivalence was demonstrated for the GMT to FHA, FIM, pertactin, diphtheria and tetanus toxoids (Table 18). Equivalence criteria were not met with regard to GMT for PRP and polio virus serotypes

however; CBER considered this in the context of demonstration of lot-consistency for rates of seroprotective antibody levels for these antigens and concluded there are no major concerns with respect to lot consistency.

Because the PT ------- values used for evaluation of lot consistency were generated in the assay performed at sanofi pasteur, Canada, data are not available to support lot consistency of the PT antigen of Pentacel.

Response to co-administered vaccines

Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), (Prevnar, Wyeth Pharmaceuticals Inc.)

In Study P3T06 Prevnar was administered with control, standard of care vaccines or Pentacel at 2, 4 and 6 months of age. Protective levels of antibody to pnuemococcal polysaccharides have not been determined, based on advice provided to the applicant by CBER at the time the study was conducted the proportion of subjects with antibody levels $\geq$0.15 ug/mL and $\geq$0.5 ug/mL to each of the pneumococcal serotypes was evaluated. In P3T06 following three doses of Prevnar administered with Pentacel or control vaccines the proportion of subjects with antibody levels $\geq$0.15 ug/mL and $\geq$0.5 ug/mL to each of the pneumococcal serotypes appeared similar in both groups. Similarly, the GMT to each of the serotypes appeared similar between groups. (Table 97 and 98)

In Study 494-03 a comparison of antibody levels $\geq$ 0.15 ug/mL and $\geq$ 0.5 ug/mL, and GMT to each of the pneumococcal serotypes following a fourth dose of Prevnar administered with Pentacel or administered with MMR and varicella at 15 months of age demonstrated non-inferiority for each comparison (Table 78 and 79). All subjects in this study had received three previous doses of Prevnar concomitantly administered with Pentacel.

No data are available on responses to the first three doses of Prevnar administered concomitantly with or at different times from Pentacel.

Hepatitis B Vaccine Recombinant (RECOMBIVAX HB, Merck & Co., Inc.)

In Studies 494-01 and P3T06 RECOMBIVAX HB was administered concomitantly with Pentacel at 2 and 6 months of age. Children enrolled in these studies received their first dose of hepatitis B vaccine prior to enrollment in the study. In Study 494-03 receipt of a birth dose of hepatitis B was not an inclusion criterion; subjects who had received a birth dose of hepatitis B vaccine were administered RECOMBIVAX HB concomitantly with Pentacel at 2 and 6 months of age while subjects who had not received a birth dose were administered RECOMBIVAX HB concomitantly with Pentacel at 2, 4 and 6 months of age. The hepatitis B vaccines administered at birth were not recorded. Across these three pivotal studies, 89.8%-100% of subjects achieved a protective level of anti-HBsAg following the third dose of hepatitis B vaccine. Within each comparative study the response to hepatitis B when coadministered with Pentacel appeared similar to that observed when administered with control vaccines (Table 22, 97 and 98).

Measles, Mumps, and Rubella Virus Vaccine Live (MMR_{II}, Merck & Co., Inc.) and Varicella Virus Vaccine Live (Oka/Merck) (VARIVAX, Merck & Co., Inc.)

A secondary endpoint of Study 494-03 was an evaluation of the response to MMR_{II} and varicella vaccine when administered with Pentacel compared to the response when these vaccines were administered with Prevnar at 15 months of age. Co-administration of MMR_{II} and VARIVAX with Pentacel did not adversely affect the seroresponse rates for measles, mumps, rubella or varicella (Table 76)

Rotavirus Vaccine, Live, Oral, Pentavalent (Rotateq Merck & Co., Inc.) and Rotavirus Vaccine, live, Oral (ROTARIX, GlaxoSmithKline Biologicals)
Rotateq and ROTARIX were approved February 3, 2006, and April 3, 2008, respectively. No data submitted to the BLA address co-administration of Pentacel with rotavirus vaccine.

Canadian Epidemiologic Data
The BLA contains Canadian epidemiologic data from post-marketing experience in Canada, submitted in support of effectiveness of the Hib and pertussis components of Pentacel. These data and US-epidemiologic data are presented in Section 7.0.

Vaccines and Related Biological Products Advisory Committee
The adequacy of the immunogenicity data provided in the BLA to support effectiveness of Pentacel was considered by the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) on January 25, 2007. The committee voted that the immunogenicity data were adequate to support the efficacy of Pentacel although several members expressed concern regarding effectiveness of the Hib and pertussis components and advocated post-licensure surveillance for invasive Hib disease and pertussis.

Post-marketing Studies
In coordination with CDC and the Active Bacterial Core Surveillance program sanofi pasteur will submit surveillance data on cases of invasive *Haemophilus influenzae* type b (Hib) disease among children 0-4 years of age identified by the for at least 6 years. Sample surveys will provide brand-specific vaccine exposure data and calculate product-specific rates of invasive Hib disease within the monitored population.

In coordination with the ---------- and the Wisconsin Department of Health and Family Services sanofi pasteur will report surveillance data on cases of pertussis among children less than 5 years of age in the State of Wisconsin, over at least 5 years. Data from the Wisconsin vaccine registry will provide brand-specific vaccine exposure data and calculate product-specific rates of pertussis within the monitored population.

A safety study to further characterize the safety profile of Pentacel in at least 10,000 infants is also planned.

Conclusions and Recommendations
Following three doses of Pentacel over 99% of subjects had seroprotective antibody levels to diphtheria and tetanus toxoids and poliovirus types 1, 2, and 3. Based on these data and non-inferiority analyses the effectiveness of the diphtheria, tetanus and polio components of Pentacel can be expected to be similar to that of separately administered control vaccines.

The data to support the effectiveness of the PRP-T component are inconsistent: In one study the immune response to the PRP-T component of Pentacel was diminished as compared to separately administered ActHIB. In two comparative studies non-inferiority was demonstrated however, the response to separately administered ActHIB was lower than expected based on historical data. The results of these two studies provide evidence that the effectiveness of the PRP-T component of Pentacel against invasive *H. influenzae* type b disease is expected to be similar to the effectiveness of currently administered ActHIB in the US.

Four doses of Pentacel were expected to constitute the primary immunization series for pertussis. However, the response to the pertussis antigen, pertactin, was diminished following Pentacel as compared to control vaccines. The clinical relevance of this diminished response is unknown.

4 Clinical and Regulatory Background

4.1 Diseases to be Prevented and Available Interventions

See Pentacel Clinical Safety Review.

4.2 Previous Human Experience with Pentacel Including Foreign Experience

See Pentacel Clinical Safety Review.

4.3 Regulatory Background Information Regarding Pentacel BLA

See Pentacel Clinical Safety Review.

4.4 Historical Background on the Evaluation of the Efficacy of DAPTACEL against Pertussis

4.4.1 Sweden I Efficacy Trial

The Sweden I efficacy trial conducted from 1992-1995 evaluated the absolute efficacy of three doses of DAPTACEL and two other non-US licensed DTaP vaccines administered at 2, 4 and 6 months of age to prevent pertussis relative to a DT vaccine manufactured by SBL-vaccin AB (Stockholm, Sweden). The efficacy of DAPTACEL against WHO defined pertussis (≥ 21 days of paroxysmal cough with culture or serologic confirmation or epidemiologic link to a confirmed case) was 84.9% (95% CI 80.1-88.6) after three doses. The efficacy of three doses of DAPTACEL against mild pertussis (≥ 1 day of cough with laboratory confirmation) was 77.9% (95% CI 72.6-82.2).

4.4.2 Pertussis Responses in US and Canadian Children Administered DAPTACEL

To support licensure of DAPTACEL in the US, the pertussis antibody responses of US children following 3 doses of DAPTACEL were compared to those of a subset of the infants enrolled in the Sweden I efficacy study. In a US study (US Bridging Study), the same lot of DAPTACEL used in the Sweden I Efficacy Trial (lot 6) and a subsequently manufactured lot (lot 9) were administered to US infants at 2, 4, and 6 months of age. As noted in DAPTACEL Package Insert (May 14, 2002 version), "Antibody responses to all the antigens were similar except for those to the PRN component. For both lots of DAPTACEL, the geometric mean concentration (GMT) and percent response to PRN in US infants (Lot 006, n = 107; Lot 009, n = 108) were significantly lower after three doses of vaccine than in Swedish infants (n = 83)." Tables 3 and 4 present the data comparing the response of Swedish infants and US infants administered Lot 006 at 2, 4 and 6 months of age.

Table 3. U.S. Bridging Study and Sweden I efficacy trial-- comparison of post-dose 3 DAPTACEL anti-pertussis GMTs

	Sweden I Lot 6 N=83 GMT (EU/ml)	US Bridging Lot 6 N=106-107 GMT (EU/ml)	Ratio of GMTs US Lot 6/Sweden Lot 6 (90% CI)
PT	72.61	89.05	1.23 (1.01,1.49)
FHA	43.17	42.51	0.98 (.84, 1.16)
FIM	323.9	376.0	1.16 (.91, 1.49)
PRN	**121.21**	**65.65**	**0.54 (.43, .69)***

* CI is out of the equivalency boundary of (0.5, 2.0) applied retroactively by the sponsor.

Source: DAPTACEL BLA Clinical Review, page 19, FDA briefing document VRBPAC November 3, 2000, page 9

Table 4. U.S. Bridging Study and Sweden I efficacy trial: comparison of rates of four-fold rise in pertussis antibodies from pre-dose 1 to post-dose 3 DAPTACEL

	Sweden I Lot 6		US Bridging Lot 6		Difference in % with 4-fold rise U.S. Lot 6 – Sweden Lot 6 (90% CI)
	N	%	N	%	
PT	76	82.9	82	89	6.1 (-3, 15.2)
FHA	76	63.2	83	63.9	0.7 (-11.9, 13.3)
FIM	50	84	79	84.8	0.8 (-10, 11.6)
PRN	61	96.7	80	72.6	-24.2 (-33.2, -15.2)*

Source: DAPTACEL BLA Clinical Review, page 19
*statistical criteria for evaluation were not defined.

In a separate Canadian study, in which children received four doses of DAPTACEL at 2, 4, 6, and 17-18 months of age "antibody responses following the fourth dose (n= 275) were equivalent or higher than those seen in the Swedish infants after 3 doses…" These data are shown in Table 5.

Table 5: Pertussis GMTs post dose 4, post dose 4 DAPTACEL and post –dose 3 DAPTACEL Sweden I efficacy study.

	Sweden I (post dose 3)		Canada (post dose 4)	
	N	GMT (95% CI)	N	GMT (95% CI)
PT	83	72.6 (61,1, 86.4)	273	171 (153, 191.1)
FHA	83	43.2 (37.7, 49.4)	273	117.6 (107.5, 128.6)
FIM	83	323.9 (258.1, 1406.5)	275	518.6 (451.2, 596.1)
PRN	83	121.1 (102.6, 143.2)	275	241.7 (214.2, 272.8)

Source: DAPTACEL BLA Clinical Review, page 40. Statistical analysis criteria were not presented.

Based on the data from the US Bridging Study and the Canadian Study, the DAPTACEL Package Insert notes "...the antibody response to all antigens in North American infants after 4 doses of DAPTACEL at 2, 4, 6 and 17-20 months of age was comparable to that achieved in Swedish infants in whom efficacy was demonstrated after 3 doses of DAPTACEL at 2, 4 and 6 months of age". The DAPTACEL package insert (November 8, 2006) states: "Four doses of DAPTACEL vaccine constitute a primary immunization course for pertussis."

4.4.3 Sweden II Efficacy Trial

Efficacy data on HCPDT from the Sweden II Efficacy Trial were considered supportive for licensure of DAPTACEL and have been submitted with the Pentacel BLA as supportive data. The HCPDT efficacy data from Sweden II previously were reviewed under the DAPTACEL BLA and will only be summarized here.

Sweden II evaluated the efficacy of the non-US licensed HCPDT and two additional non-US licensed DTaP vaccines relative to a non-US licensed whole cell DTP vaccine manufactured by Evans Medical (previously Wellcome). Approximately 20,000 infants were included in each of the four study groups. The majority of infants who received HCPDT (approximately 18,000) were vaccinated at 3, 5, and 12 months of age. The primary analyses estimated the efficacy of three doses of the acellular pertussis vaccines relative to three doses of the whole-cell pertussis vaccine. In these analyses, following HCPDT, the relative risk for culture-confirmed pertussis with at least 21 days of paroxysmal cough was 0.85 (95% CI 0.41, 1.79), and the relative risk for

culture-confirmed pertussis with cough of any duration or without cough was 1.35 (95% CI 0.75, 2.43). Based on these data the null hypothesis of a relative risk for pertussis of ≥ 1.5 following HCPDT compared to DTwP was not rejected for either case definition.

5 Immunogenicity Data Sources, Review Strategy and Data Integrity

5.1 Material reviewed

The data sources used were the final study reports for the four pivotal studies of Pentacel, the serology methodology section and a summary of immunogenicity data for an on-going study provided in the integrated summary of immunogenicity. Additional information submitted in amendments to the file was also reviewed. Component lot numbers were accessed from the CMC section as necessary. `

5.1.1 BLA files which served as the basis for Immunogenicity review

Immunogenicity data from the following submissions served as the basis for the immunogenicity review:

File name

July 26, 2005 submission

49401si.pdf
49401sii.pdf
49403si.pdf
49403sii.pdf
5a9908.pdf
p3t06si.pdf
p3t06sii.pdf
bridge.pdf
isi.pdf
serology.pdf
compilation_hib_responses.pdf
hib_epidemiology.pdf

September 13, 2005 submission

red_00005321.pdf

September 7, 2006 submission

questions1_133.pdf
questions134_140.pdf
questions141_156.pdf
questions157_164

December 8, 2006 submission

response_fax09nov06.pdf

January 29, 2007 submission

proposed.pdf

March 5, 2007

response_ir20feb2007.pdf

October 26, 2007

m5a10prp_si_hib_report.pdf

December 4, 2007

m5a10_prot_v4.pdf

December 20, 2007

p3t06_retest_rep.pdf

June 19, 2008

Summary_amend069.pdf

The following data presented to the VRBPAC by sanofi have not been submitted to the BLA thus, have not been reviewed and are not presented in this review:

- Comparison of pertussis immune responses following four doses of Pentacel in US study P3T06 to responses following three doses of DAPTACEL in the Sweden I efficacy trial.
- Epidemiologic data from the International Circumpolar Surveillance for invasive bacterial diseases.
- Post dose 4 data from Study M5A07.

The following data presented to the VRBPAC and subsequently to the BLA (March 2, 2007) in response to CBER's February 22, 2007 IR letter) have been reviewed by other committee members:

- Use of antibody levels in the Swedish Household contact study to predict efficacy of the pertussis component of Pentacel (extrapolation of data from the Stoersaeter publication).

5.1.2 Post marketing experience

Pentacel was first registered in Canada in May 1997, and is currently licensed in Argentina, Australia, Brazil, Canada, Colombia, Israel, Mexico and Turkey. Since 1997-1998, Pentacel (at 2, 4, 6 and 18 months of age) and DTaP-IPV manufactured by sanofi pasteur Limited (at 4-6 years of age) have been used exclusively in all Canadian provinces to prevent pertussis, poliomyelitis and Hib disease through early childhood. Between 5/1/97 and 4/30/06, a total of approximately 13.5 million doses of Pentacel were distributed outside the U.S., 92% of them in Canada.

5.2 Table of Clinical Studies

Four pivotal clinical studies to support the safety and effectiveness of Pentacel were conducted under U.S. IND and included in the BLA. Information on the design and size of each of these studies is summarized in Table 6.

Table 6. Summary of Pivotal Pentacel Studies

Protocol Number/ Country/ Dates	Objectives	Pentacel Schedule	Study Groups and Study Vaccines	Study Design	Number of Subjects in PP immunogenicity populations[1]
494-01/ US/ 12.29.99-4.23.02	Pentacel lot consistency Safety and immunogenicity of Pentacel relative to HCPDT + POLIOVAX + ActHIB Pentacel immunogenicity bridge to DAPTACEL efficacy (Sweden I)	2, 4, 6, 15 months	Doses 1-3: Group 1: Pentacel Lot 1 Group 2: Pentacel Lot 2 Group 3: Pentacel Lot 3 Group 4: HCPDT + POLIOVAX + ActHIB Groups 1-4: Prevnar at 2, 4, and 6 mo. (introduced after study initiation); RECOMBIVAX HB at 2 and 6 mo. (1st dose of Hepatitis B vaccine outside of study) Dose 4: Group 1: Pentacel Group 2: HCPDT + POLIOVAX + ActHIB	Randomized, controlled, multi-center	Post dose 3: Pentacel :1136 HCPDT+POLIOVAX +ActHIB: 403 Post dose 4: Pentacel: 883, HCPDT+POLIOVAX+ActHIB: 291
494-03/ US/ 7.10.00-12.26.02	Safety and immunogenicity; Assessment of co-administration of Dose 4 with other recommended vaccines	2, 4, 6, 15 or 16 months	Doses 1-3: All subjects: Pentacel + Prevnar + RECOMBIVAX HB (not given at 4 months if prior dose of Hepatitis B vaccine) Dose 4: Group 1: Pentacel at 15 mo. Group 2: Pentacel + MMR_{II} + VARIVAX at 15 mo. Group 3: Pentacel + Prevnar at 15 mo. Group 4: Pentacel at 16 mo.; MMR_{II} + VARIVAX + Prevnar at 15 mo.	Randomized (for Dose 4 Groups), controlled (for Dose 4 co-administration) multi-center	Post dose 3: Pentacel: 274 Post dose 4: Pentacel: 218 Pentacel+MMR+VARIVAX: 222 Pentacel + Prevnar: 214 Prevnar+MMR+VARIVAX: 165
5A9908 Canada/ 8.15.00 - 10.21.01	Safety and immunogenicity of fourth dose in subjects who previously received three doses of Pentacel	15 to 18 months	Group 1: Pentacel at 15 mo. Group 2: Pentacel at 16 mo. Group 3: Pentacel at 17 mo. Group 4: Pentacel at 18 mo.	Randomized, multi-center	Post-dose 4 Pentacel: 735
P3T06/ US/ 5.4.01-1.21.04	Safety and immunogenicity; Comparison to separate administration of licensed-components;	2, 4, 6, 15-16 months	Doses 1-3: Group 1: DAPTACEL Lot 1 + IPOL + ActHIB Group 2: DAPTACEL Lot 2 + IPOL + ActHIB Group 3: DAPTACEL Lot 3 + IPOL + ActHIB	Randomized, controlled, multi-center	Post dose 3: Pentacel: 374 DAPTACEL + IPOL+ActHIB: 371

	DAPTACEL lot consistency; Assessment of co-administration of Dose 4 DAPTACEL with other recommended vaccines		Group 4: Pentacel Groups 1-4: Prevnar at 2, 4, 6 mo.; RECOMBIVAX HB at 2 and 6 mo. (1st dose of Hepatitis B vaccine outside of study) Dose 4: Group 1: DAPTACEL + ActHIB Group 2: DAPTACEL + ActHIB + MMR_{II} + VARIVAX + Prevnar Group 3: ActHIB + MMR_{II} + VARIVAX + Prevnar at 15-16 mo; DAPTACEL at 16-17 mos. Group 4: Pentacel		Post-dose 4: Pentacel: 371 DAPTACEL + ActHIB: 349

[1]The Per Protocol Immunogenicity Population is defined in the individual study reports
Source: Pentacel Clinical Safety Review by Dr. Farizo and Jan. 25, 2007 CBER VRBPAC Briefing Document

The effectiveness of the pertussis component of Pentacel was evaluated by comparison of the immune response of US-children administered Pentacel in Study 494-01 to the immune response of infants administered DAPTACEL in the Sweden I efficacy study. Effectiveness of the pertussis component of Pentacel was also evaluated in study P3T06 by comparing the immune response to the pertussis antigens of Pentacel with that of US-licensed DAPTACEL.

At CBER's request, a summary of post-dose 3 immunogenicity data from Study M5A07, also conducted under IND, was included in the BLA. This study was designed to evaluate the immunogenicity and safety of four doses of Pentacel administered at different times from or concurrently with Prevnar. In this study, a total of 586 subjects were randomized to receive Pentacel with Prevnar and 580 subjects were randomized to receive Pentacel, with Prevnar one month later.

On October, 26, 2007, in response to CBER's request for additional pre-licensure clinical data to support effectiveness of the Hib component of Pentacel sanofi pasteur submitted a summary of post-dose 3 immunogenicity data from Study M5A10.

5.3 Review Strategy

The four pivotal studies of Pentacel were reviewed. To support effectiveness of the pertussis component of Pentacel the serology bridge to Sweden I was also reviewed. Summary data from Study M5A07 and Study M5A10 were also reviewed.

5.4 Good Clinical Practices and Data Integrity

See Clinical Safety Review.

5.5 Immunogenicity Assays

Table 7 summarizes the assay methodology and the laboratory used to evaluate samples from the pivotal clinical studies. All assay validation reports have been reviewed by other committee members.

Table 7: Serology assays and laboratory performing assays for each of the Pentacel pivotal immunogenicity studies

Antigen	Antibody Assay	Study			
		49401	**49403**	**P3T06***	**5A9908**
PT*, FHA, FIM, PRN	----------	----------			
PRP	----------	----------	----------	----------	----------
tetanus toxin	ELISA------	----------			
diphtheria toxin	----------	----------			
poliovirus 1, 2, 3	----------	----------			
HBsAg	----------	----------	----------	----------	ND
Pneumococcal type 4, 6B, 9V, 14, 18C, 19F, 23F capsular polysaccharide	----------	----------			ND
Measles	ELISA Plaque reduction neutralization test (PRNT) if measles ELISA <300 mIU/ml	ND	----------	----------	ND
Mumps	ELISA PRNT if mumps ELISA <500 U/ml	ND	----------	----------	ND
Rubella	ELISA	ND	----------	----------	ND
Varicella	ELISA Fluorescent antibody to membrane antigen (FAMA) if ELISA <300 mIU/ml	ND	----------	----------	ND

ND: Not Done
AvP = AventisPasteur/sanofi pasteur
*a reassay of anti-PT levels for a subset of sera from Study P3T06 was determined in an ----------
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--. Assay transfer protocols and validation reports have been reviewed by other committee members.

Assay methodology
Each of the serology assays has been reviewed by a member of the BLA review committee and found to be acceptable. The following is a summary of the assay methodology and pertinent information relevant to interpretation of the immunogenicity data. Sanofi pasteur refer to the geometric mean antibody levels as titers (GMT) irrespective of the assay used to measure levels, this review will be consistent with the terminology used by sanofi.

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Data Handling:
For values of antigen antibodies recorded as <LOQ, the following approach was used in the calculation of GMT ratios and seroconversion/seroprotection rates:
For vaccine response/seroconversion/seroprotection rates and GMTs, <LOQ will be converted to 0.5 LOQ. For calculating a fold-rise, <LOQ will be converted to 0.5 LOQ for a numerator and <LOQ will be converted to LOQ for a denominator when only one of either the numerator or denominator is <LOQ. If both the numerator and denominator are <LOQ, then both will be converted in the same way. (isi.pdf page 42)

6 Clinical Studies

6.1 Trial #1

6.1.1 Applicants Protocol # and Protocol Title

Study 494-01: Safety, Immunogenicity and Lot-consistency Study of Hybrid Pertussis Vaccine in Combination with Diphtheria and Tetanus Toxoids Adsorbed and inactivated Poliomyelitis Vaccine Used to Reconstitute Lyophilized *Haemophilus influenzae* type b Tetanus Toxoid Conjugate vaccine (Hybrid $CP_{20/20/5/3}$DT-mIPV//RPR-T, Pentacel) in Infants and Toddlers.

6.1.1.1 Rationale/Objectives

Study 494-01 was conducted to demonstrate that the safety and immunogenicity of each antigenic component of Pentacel is not compromised by their combination; to demonstrate lot-to-lot consistency of Pentacel in terms of safety and immunogenicity; and to demonstrate the compatibility of Pentacel with other already approved vaccines.

Specific objectives relevant to the immunological evaluation of PENTACEL and co-administered vaccines are listed below for Stages I and II of Study 494-01.

Primary Immunogenicity Objectives

Stage I

1. To assess the lot-consistency (immunogenicity) of PENTACEL when given as an infant series.

2. To assess the immunogenicity of PENTACEL as compared to the control vaccines when given as an infant series.

Stage II

1. To assess the immunogenicity of the antigens in PENTACEL as compared to the control vaccines when given as a 4^{th} dose.

Secondary Immunogenicity Objectives

Stage I – none
Stage II – none

Observational Immunogenicity Objectives

Stage I

1. To describe the immunologic compatibility of PENTACEL with a hepatitis B vaccine.

2. To describe the relative frequencies of seroconversion and antibody geometric mean titers with 95% CI for the Pertussis antigens (PT, FHA, FIM 2&3 and PRN) in PENTACEL according to the number of pneumococcal conjugate vaccine doses coadministered with PENTACEL or separately administered control vaccines during the infant series.

3. To compare the immune responses elicited by a pneumococcal conjugate vaccine when co-administered with PENTACEL or separately administered control vaccines based on GMT ratios and seroresponse rate differences (≥ 0.15 and ≥ 0.5 ug/mL). Only subjects who receive three doses of the pneumococcal conjugate vaccine co-administered with PENTACEL or control vaccines will be included in this analysis.

4. To compare the anti-tetanus and anti-diphtheria seroprotective levels ≥ 0.1 IU/mL following PENTACEL or HCPDT

Stage II

1. To describe the relative frequencies of seroconversion and antibody geometric mean titers (GMTs) with 95% CI for the Pertussis antigens (PT, FHA, FIM 2&3 and PRN) in PENTACEL after Dose 4 according to the number of pneumococcal conjugate vaccine doses co-administered with PENTACEL or separately administered control vaccines during the infant series.

2. To compare the anti-tetanus and anti-diphtheria immune responses elicited by the 4th dose of PENTACEL or HCPDT stratified by pre-dose 4 seroprotection thresholds.

6.1.1.2 Design Overview

Study 494-01 was a two-staged, randomized, multicenter study with Stage I vaccines administered at 2, 4 and 6 months of age and Stage II vaccines administered at 15 months of age. Assessments of immunogenicity of Pentacel compared to control vaccines were based on an open label design.

Subjects who met eligibility requirements were randomized to receive one of three lots of Pentacel or control separately administered vaccines. Subjects who received one of three lots of Pentacel in Stage I received Pentacel in Stage II. Subjects who received separately administered control vaccines in Stage I received these in Stage II.

The planned duration of the study, per subjects, was to 60 days following the fourth dose of Pentacel or control vaccines.

6.1.1.3 Population

The study period from the beginning of Stage I to the end of Stage II was December 29, 1999 through April 23, 2002. Subjects were enrolled in 16 centers in the US.

Inclusion and Exclusion criteria are detailed in the clinical safety review.

6.1.1.4 Products mandated by the protocol

Study vaccines – schedule of administration

The schedule of vaccine administration is shown in Table 8 and Table 9.

Table 8: Study 494-01 Schedule of vaccine administration during Stage I

Group	2, 4 and 6 months	0, 2 and 6 months
1	Pentacel Lot 1	Hepatitis B vaccine
2	Pentacel Lot 2	Hepatitis B vaccine
3	Pentacel Lot 3	Hepatitis B vaccine
4	HCPDT, POLIOVAX, ActHIB	Hepatitis B vaccine

All subjects received hepatitis B vaccine at 0, 2 and 6 months of age; the first dose (manufacturer not specified) was administered outside the study, the second and third dose were with RECOMBIVAX HB, administered as part of the study.
Prevnar was licensed and recommended after the study initiated, some subjects received Prevnar co-administered with study vaccines at 2, 4 and 6 months of age.

Table 9: Study 494-01 Schedule of vaccine administration during Stage II

Group	15 months
1 (Stage I group 1, 2 and 3)	Pentacel
2 (Stage I group 4)	HCPDT, POLIOVAX, ActHIB

MMR, varicella and Prevnar were offered at 12 months of age

Study vaccines – formulation and lot numbers

All study vaccines except Pentacel and HCPDT are licensed in the US. The composition of each of the three lots of Pentacel and the control lots of HCPDT, ActHIB and POLIOVAX are shown in Table 10. Pentacel lot 3, composed of DTaP-IPV lot C0155A used to reconstitute ActHIB lot UA480A (R0181 bulk) was administered to subjects in Group 3. Subjects in Group 4, administered control vaccines, received the same DTaP, IPV and ActHIB lots administered as separate vaccines (HCPDT, POLIOVAX and ActHIB) as those subjects administered Pentacel lot 3.

- Pentacel (DTaP-IPV used to reconstitute ActHIB).

  DTaP- IPV, composition per 0.5 mL dose**:**

  Active Ingredients:

  20 µg Pertussis Toxoid (PT)
  20 µg Filamentous hemagglutinin (FHA)
  5 µg Fimbriae 2 & 3 (FIM)
  3 µg Pertactin (PRN)
  15 LF Diphtheria toxoid
  5 LF Tetanus toxoid
  40 DAU poliovirus type 1 (Mahoney)
  8 DAU poliovirus type 2 (M.E.F.I.)
  32 DAU poliovirus type 3 (Saukett)
  10 ug PRP conjugated to 24 ug tetanus toxoid

  Adjuvant: 1.5 mg Aluminum phosphate (0.33 mg aluminum)
  2-phenoxyethanol: 0.6% (3.3 mg)
  Tween 80: 10ppm
  Neomycin: trace
  Polymyxin B sulphate: trace
  Bovine serum: -----
  (source: July 25, 2005 49401si.pdf page 4527)

Lot numbers for Stage I: C0094A (Group 1), C0154B (Group 2), and C0155A (Group 3). Lots contained ----------.

Lot number for Stage II: C0790BA ----------

ActHIB, composition per 0.5mL dose:
10ug polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) conjugated to 24 ug tetanus toxoid
No preservative

Lot number for Stage I: P1394 (Group 1) P1332 (Group 2) and UA480A (R0181 bulk, Group 3))
Lot number for Stage II: UA480A (R0181 bulk)

- HCPDT

HCPDT, composition per 0.5mL dose:
Active Ingredients:
20 µg Pertussis Toxoid (PT)
20 µg Filamentous Haemagglutinin (FHA)
5 µg Fimbriae Types 2 and 3 (FIM)
3 µg Pertactin (PRN)
15 Lf Diphtheria Toxoid
5 Lf Tetanus Toxoid
Adjuvant: 1.5 mg aluminum phosphate (0.33 mg aluminum)
Excipient: 0.6% 2-phenoxyethanol

Lot number for Stage I: C0123A
Lot number for Stage II: C0756AA

- POLIOVAX

POLIOVAX, composition per 0.5mL dose
Active ingredients:
40 D antigen units Poliovirus Type 1 Mahoney
8 D antigen units Poliovirus Type 2 MEF-1
32 D antigen units Poliovirus Type 3 Saukett
Preservative: 0.6% 2-phenoxyethanol
Other Ingredients:
---------- (by calculation)
--------- bovine serum (by calculation)
Traces polymyxin B and neomycin

Lot number for Stage I: 8445-12 ----------
Lot number for Stage II: C0880AB ----------

- ActHIB, Haemophilus b Conjugate Vaccine produced by Aventis Pasteur SA, is a lyophilized powder reconstituted with saline diluent. Each 0.5 ml dose is formulated to contain 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid.

Lot number for Stage I: UA480A (R0181 bulk lot)
Lot number for Stage II: UA480A

- RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant), Merck & Co., Inc]: Each 0.5 ml dose contains 5 µg of purified HBsAg without preservative.

Lot number used in Stage I: 1948H, 0134J, 1032K, 1423K, or 1381J

- Prevnar, [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), Wyeth]: Each 0.5 ml dose of Prevnar contains 2 µg of each polysaccharide for *Streptococcus pneumoniae* serotypes 4, 9V, 14, 18C, 19F, and 23F and 4 µg of serotype 6B (16 µg total polysaccharide); approximately 20 µg of CRM_{197} protein; and 0.125 mg of aluminum as aluminum phosphate adjuvant.

Lot number for Stage I and II: 471-212 (Wyeth-Lederle Bulk # 1970-0103) and 474-723 (Wyeth-Lederle Bulk # 1970-0118)

- MMR_{II} (Measles, Mumps, and Rubella Virus Vaccine Live, Merck & Co., Inc.): Each 0.5 ml dose contains not less than 1,000 TCID50 (tissue culture infectious doses) of measles virus; ---------- TCID50 of mumps virus; and 1,000 TCID50 of rubella virus. Each dose of the vaccine contains approximately 25 µg of neomycin; sorbitol and hydrolyzed gelatin as stabilizers. The product contains no preservative.

MMRII Final lot 1179K (Measles lot 2057076, Mumps lot 2027108 and rubella lot 2028688). Sterile diluent for live viruses Final Lot 1012K and 1013K

- VARIVAX [Varicella Virus Vaccine Live (Oka/Merck); Merck & Co., Inc.]: Each 0.5 ml dose contains a minimum of 1350 plaque forming units of Oka/Merck varicella virus. The product contains no preservative. Lot numbers were recorded at time of use.

Table 10: Final container lot numbers, antigen concentrate lot numbers for Pentacel, DTaP, IPV and ActHIB used in Study 494-01 Stage I and II

Source summary.pdf page 19, bridge.pdf page 30, 49401si.pdf appendix 13 (September 30, 2005 submission) , 49401sii.pdf appendix 13, 49401sii.pdf page 49

Stage II	Pentacel	Control Vaccines: HCPDT, POLIOVAX, ActHIB
HCPDT-IPV Lot	----------	NA
HCPDT	------	C0756AA
HCPDT Bulk lot	----------	C0756
IPV trivalent bulk	----------	C000000374
IPV lot #	---	C00880AB
PRP-T bulk lot	----------	R0181
PRP – final lot	----------	UA480A

Source summary.pdf page 19, bridge.pdf page 30, 49401si.pdf appendix 13 (September 30, 2005 submission) , 49401sii.pdf appendix 13, 49401sii.pdf page 49

Study vaccines: route of administration

Pentacel, HCPDT, ActHIB, Prevnar, POLIOVAX and RECOMBIVAX HB were injected intramuscularly. MMR_{II}, and VARIVAX were injected subcutaneously.

6.1.1.5 Immunogenicity Endpoints and Evaluation Criteria

Antibody Assays

See Section 5.5 for an overview of serological assays.

Primary Endpoints and Evaluation Criteria

Stage I – Pentacel Lot consistency

Table 11 presents the criteria for evaluation of lot consistency of three lots of Pentacel following administration at 2, 4 and 6 months of age.

Table 11. Study 494-01 Primary endpoints and criteria for equivalence for evaluation of lot consistency of three lots of Pentacel, post-dose 3

Antigens	Endpoint	Equivalence Criteria
PT FHA FIM 2 & 3 PRN Diphtheria toxoid Tetanus toxoid PRP poliovirus type 1 poliovirus type 2 poliovirus type 3	GMT*	90% CI for each GMT ratio within (>2/3, <1.5)
	seroresponse/seroprotection**	
PT FHA FIM 2 & 3 PRN	% ≥4-fold rise	90% CI difference >-10%, <10%
Diphtheria toxoid Tetanus toxoid	% ≥0.01 IU/mL % ≥0.01 IU/mL	
PRP	% ≥1.0 ug/mL	90% CI difference >-10%, <10%
poliovirus type 1 poliovirus type 2 poliovirus type 3	% ≥1:8 % ≥1:8 % ≥1:8	90% CI difference >-5%, <5%, (and LL 90% CI ≥90%).

* GMT ratios: Lot 1/Lot 2, Lot 1/Lot 3 and Lot 2/Lot 3

** Seroresponse/seroprotection: Lot 1 – Lot 2, Lot 1 – Lot 3 and Lot 2 - Lot 3 subjects may or may not have been administered concomitant Prevnar

Source: eBLA Item 8, Study 494-01. Appendix 1, Version 13.0, 7 Evaluation Criteria. 7.1 page 4542 of 28200, 7.1.2 (page 4544 of 4593) and 8.1.2.1 (page 4553 of 4593) (49401si.pdf)

Stage I: Non-inferiority of Pentacel relative to control vaccines (HCPDT + POLIOVAX + ActHIB)

Table 12 presents the endpoints and non-inferiority criteria for comparison of seroconversion/seroprotection and GMTs following three doses of Pentacel relative to control vaccines.

Table 12: Study 494-01 Stage I: Primary endpoints, comparisons and non-inferiority criteria for evaluation of seroconversion/seroprotection rates and GMTs following 3 doses of Pentacel (pooled lots) compared to separately administered HCPDT, POLIOVAX, and ActHIB:

Antigens	Comparisons	Non-inferiority Criteria
PT, FHA, FIM 2 & 3, PRN	GMT ratio (Pentacel/Control) % ≥4-fold rise* (Control – Pentacel)	LL of 90% CI for GMT ratios >2/3
Diphtheria toxoid Tetanus toxoid	% ≥0.01 IU/ml (Control – Pentacel)	UL of 90% CI for difference in rates <10%
PRP	GMT ratio (Pentacel/Control) % ≥1.0 ug/mL (Control – Pentacel)	LL of 90% CI for GMT ratios >2/3 UL of 90% CI for difference in rates <10%
poliovirus type 1 poliovirus type 2 poliovirus type 3	% ≥1:8 (Control – Pentacel) % ≥1:8 % ≥1:8	UL 90% CI for difference in rates <5%, (and LL 90% CI ≥90%).

Source: eBLA Item 8, Study 494-01. Appendix 1, protocol Version 13.0, Section. 7.1 page 4542 and 7.1.2 (page 4544 of 4593) and 8.1.2.2 (page 4554 of 4593) (49401si.pdf)

Stage II - Non-inferiority of Pentacel relative to control vaccines (HCPDT + POLIOVAX + ActHIB)

The comparisons and criteria for evaluation of non-inferiority of a fourth dose of Pentacel relative to control vaccines are shown in Table 13.

Table 13: Study 494-01 Stage II: Primary immunogenicity endpoints, comparisons and non-inferiority criteria for evaluation of seroconversion/seroprotection rates and GMTs following a fourth dose of Pentacel compared to separately administered HCPDT, POLIOVAX, and ActHIB (Control)

Antigens	Comparisons	Non-inferiority Criteria
PT FHA FIM 2 & 3 PRN	GMT ratio (Pentacel/Control) % ≥4-fold rise* (Control – Pentacel)	LL of 90% CI for GMT ratios >2/3 UL of 90% CI for difference in seroconversion/seroprotection rates <10%
Diphtheria toxoid Tetanus toxoid	% ≥0.1 IU/ml (Control – Pentacel)	UL of 90% CI for difference in seroconversion/seroprotection rates <10%
PRP	GMT ratio (Pentacel/Control) % ≥1.0 ug/mL (Control – Pentacel)	LL of 90% CI >2/3 UL of 90% CI for difference in rates <10%
Poliovirus type 1 Poliovirus type 2 Poliovirus type 3	% ≥1:8 (Control – Pentacel) % ≥1:8 (Control – Pentacel) % ≥1:8 (Control – Pentacel)	UL 90% CI for difference in rates <5%, (and LL 90% CI rate ≥90%).

* 4-fold rise relative to pre-dose 1.
Souce: 49401sii.pdf page 1644

Observational Endpoints:
Stage I – observational endpoints

Table 14 presents the observational endpoints as specified in the protocol.

Table 14: Study 494-01 Immunogenicity endpoints to be presented following three doses of Pentacel or control vaccines

Antigen	Endpoint	Descriptive Analyses
HepB	% ≥10 mIU/mL GMT	Pentacel recipients vs. specifications in RECOMBIVAX HB PI
PT FHA FIM 2&3 Pertactin	% ≥4x rise GMT	Pentacel (pooled) + 1, 2 or 3 concurrent Prevnar vs. Control + 1, 2 or 3 concurrent Prevnar.
Pneumococcal 4, 6B, 9V, 14, 18C, 19F and 23F	% ≥0.15 µg/mL (Control - Pentacel) % ≥0.5 µg/mL (Control - Pentacel) GMT (Pentacel/Control)	Pentacel + Prevnar vs. Control + Prevnar (only those subjects with 3 doses of coadministered Prevnar) 2-sided 90% CI
D T	% ≥0.1 IU/mL (Control - Pentacel)	2-sided 90% CI

Source: Study 494-01 Protocol version 13.0 Section 7.3.1.1 (49401si.pdf page 4547-4548)

Stage II – observational endpoints

Table 15 presents the observational endpoints as specified in the protocol

Table 15: Study 494-01 Immunogenicity endpoints to be presented following four doses of Pentacel or HCPDT

Antigen	Endpoint	Descriptive analyses
PT, FHA, Fim, Pertactin	% ≥4x rise GMT	According to the number of co-administered Prevnar in the infant series
D T	% ≥1.0 IU/mL % ≥0.4 IU/mL (if pre ≤0.1 IU/mL) % 4x rise (if pre ≥0.1-2 IU/mL) % 2x rise (if pre ≥ 2 IU/mL)	Rates and 2-sided 90% CI

6.1.1.6 Surveillance/Monitoring

Immunogenicity
In Stage I, serum samples were to be collected from the first 478 subjects enrolled and randomized to each group prior to vaccination at Visit 1 (42-89 days of age) and 28-48 days after the third dose of Pentacel or control vaccines at 7 months of age. In Stage II, immune responses were assessed 28-48 days following the fourth immunization with Pentacel or control vaccines at 15 months of age in those subjects who were bled in the infant series.
Immune responses were not assessed following vaccines administered at 12 months of age (MMR_{II}, VARIVAX, and Prevnar for all Study Groups).

6.1.1.7 Statistical Considerations

Samples size and statistical power
The planned total sample size was 3400 subjects randomized to receive one of three lots of Pentacel or control vaccines (800 subjects per Pentacel group and 1000 in the control group). The total sample size was based on safety. An attrition rate of 10% to the end of Stage I and an additional 10% to dose 4 was considered for statistical power calculations. Power calculations presented for Stage I lot consistency were based on 430 subjects per group and indicated 80% - 100% power for each endpoint. Power calculations for Stage I non-inferiority were based 1,290 Pentacel subjects and 430 control subjects. Power to conclude non-inferiority of anti-fimbriae GMT after administration of Pentacel as compared to Control is 66.44%, for all other endpoints power ~100%. Power calculations for Stage II non-inferiority were based on 1,161 Pentacel subjects and Control subjects. Power to conclude non-inferiority was 94-100% for each endpoint.

Analysis populations
The analyses for immunogenicity were performed on the per protocol (PP) and intent to treat (ITT) populations.

Intent to Treat immunogenicity population
Stage I: The ITT for immunogenicity included any subject who received at least one dose of Pentacel or Control vaccines, the post-dose 3 blood draw and had a valid serology test result for at least one antigen regardless of whether they adhered to the study eligibility criteria or their immunization and bleeding visits were within the protocol specified windows.
Stage II: The ITT Immunogenicity Population included subjects who received 4 doses of Pentacel or control vaccines, had the post-Dose 4 blood draw and had a valid serology test result for at least 1 antigen, regardless of whether they adhered to the study eligibility criteria or their immunization and bleeding visits were within the protocol-specified windows.

Per-protocol immunogenicity(PPI) population
Stage I: The PP analysis for immunogenicity included all eligible subjects who had received the correct dosage (according to the assigned treatment) for all doses, had all doses and blood draws within windows as specified in the protocol and had a valid serology test result for at least 1 antigen at post-Dose 3 (Stage I). This PP population was used only for the immunogenicity analysis.
Stage II: The PP analysis for immunogenicity included subjects who met all eligibility criteria, received Dose 4 according to the assigned treatment and within the specified age window, and had the pre- and post-Dose 4 blood samples collected within windows as specified in the protocol. The PP Population was used only for immunogenicity analyses. Of note as described in 49401sii.pdf page 83 these subjects had received three doses of vaccine in Stage I – regardless of treatment error- and the correct randomized vaccine for dose4. In response to an item in the May 26, 2007 CR letter the applicant states that there was one subject included in the Stage II PPI Pentacel population who did not receive the correct vaccine for at least one of the previous three doses.

As described in 49401si.pdf page 4557-4558 the "per-protocol" population included all subjects who do not have protocol violations but included subjects with "protocol deviations". Protocol violations were defined as:
1. Not meeting the Inclusion or Exclusion criteria.
2. Study vaccines scheduled at 2, 4 or 6 months of age for Stage I or at 15 months of age for Stage II applied out of the specified windows.
3. Refusal of bleeding by the parent or legal guardian (except at 12 months of age).
4. A bleeding scheduled at 7 months of age for Stage I or at 16 months of age for Stage II occurring outside of the specified windows.

A protocol deviation was a failure to follow any specification of the protocol that does not constitute a "protocol violation". As noted in the protocol the PP population included "subjects that had a protocol violation for which a "sponsor waiver" was obtained by the study site. The only sponsor representatives that are authorized to give sponsor waivers are the Medical Monitors. Examples of sponsor waivers may include but are not limited to:
• Subject born with a gestational age between 35 and 37 weeks, if at the opinion of the Investigator the subject is otherwise healthy.
• Subjects with an age between 84 and 89 days at the time of recruitment, if the subject could not have attended an earlier appointment.
• Subjects that miss the allowed time window for the third vaccine dose, if by attending an earlier appointment they would have been not yet 6 months of age at the time of receiving the third dose of hepatitis B vaccine."

In response to an item in the May 26, 2006 CR letter the applicant stated that the number of subjects with protocol deviations cannot be provided. In addition, although the protocol stated that the PP population included subjects with protocol violations if a waiver had been obtained that subjects with protocol violations, with or without a waiver, were not included in the PP analyses populations (September 7, 2006 questions1_133.pdf page 56).

<u>Statistical criteria for equivalence and non-inferiority analyses:</u>
The protocol-specified criteria for equivalence and non-inferiority comparisons were based on 2-sided 90% CIs. CBER currently recommends use of 2-sided 95% CIs such analyses.

6.1.2 RESULTS

6.1.2.1 Populations enrolled/analyzed

The number of subjects evaluated for immunogenicity represented a subset of those vaccinated in Study 494-01. Table 16 presents a summary of the immunogenicity populations for Stage I and II of Study 494-01 relative to the number of subjects planned and presented in the sample size calculations. Of note, there were fewer subjects in both the Stage I and Stage II PPI populations than presented in the power calculations.

Table 16: Study 494-01 Subject Disposition – number of subjects randomized, immunized, bled and included in the immunogenicity population relative to the number planned

	Lot 1	Lot 2	Lot 3	Pooled Pentacel	Control
Stage I					
Randomized And received one dose of vaccine* And received 3 doses of vaccine*	**836** **772**	**836** **768**	**834** **754**	**2506** **2294**	**1032** **900**
Number of sera planned	**478**	**478**	**478**	**1434 (100%)**	**478 (100%)**
Bled pre-dose 1[4]	**449**	**458**	**452**	**1359**	**516**
Received 3 doses of vaccine and bled post dose 3	**429**	**428**	**429**	**1286 (89%)**	**468 (97%)**
Invalid test result (QNS, NS, NR) for all antigens[1]	0	1	0	1	2
Missing test result for all antigens	4	4	9	17	8
ITT immunogenicity	**425**	**423**	**420**	**1268 (88%)**	**458 (96%)**
Protocol violations: did not satisfy eligibility criteria, tx error, visit out of window interval, other	 0 8 31 0	 5 4 34 0	 1 8 41 0	 6 20 106 0	 6 4 44 1
PP Immunogenicity Population[2]	**386**	**380**	**370**	**1136 (79%)**	**403 (84%)**
Stage II					
Received dose 4*				1862	739
Number of sera planned (based on expected 10% attrition during Stage I and additional 10% between end Stage I and beginning to Stage II)				*1161 (100%)*	*387 (100%)*
Serology subset subjects enrolled at dose 4				**NA**	**NA**
Bled pre-dose 4[4]				**1039**	**357**
Received 4 doses of vaccine and bled post dose 4				**988 (85%)**	**341 (88%)**
Invalid test result (QNS, NS, NR) for all antigens[1]				2	0
Missing test result for all antigens				14	2
ITT immunogenicity				**974 (83%)**	**339 (87%)**
Protocol violations: did not satisfy eligibility criteria, tx error, visit out of window interval				 4 5 82	 5 13 30

PP Immunogenicity Population[3]				**883 (76%)**	**291 (75%)**

Source. Derived from 49401si.pdf page 87 and 49401sii.pdf page 83
*Number of vaccinated subjects classified according to actual treatment received at dose 1
[1] QNS = Quantity of sera not sufficient, NS = bled but sample broken/spilled/lost, NR = not –reportable
[2] Stage I PPI Population: Defined as all eligible subjects who received the correct dosage for all doses, had all doses and blood draws within windows and had a valid serology test result for at least 1 study vaccine antigen at post-Dose 3
[3] Stage II PPI Population Defined as all eligible subjects who received all 3 doses (regardless of treatment error) in Stage I and the correct randomized vaccine for Dose 4, had Dose 4 and post-Dose 4 blood draw within windows and had a valid serology test result for at least 1 study vaccine antigen at post-Dose 4. September 7, 2006 submission (questions1_133.pdf page 60) states one subject randomized to Pentacel received control vaccines at visit 2. This subject was included in the ITT population for Stage I and the PPI population for Stage II.
[4] Number of subjects bled pre-dose 1 and pre-dose 4 September 7, 2006 submission questions1_133.pdf page 251

6.1.2.2 Immunogenicity Analyses and Data Presentation

In this review results of primary analyses and selected additional analyses are presented (no secondary immunogenicity analyses were specified in the protocol). Results are presented for the PPI population. Results for the ITT immunogenicity population were similar.

None of the analyses include the entire PPI population. Approximately 12-15% of subjects were excluded from Stage I and II PP immunogenicity population analyses of fold-rise to pertussis antigens, the majority were excluded due to missing pre-dose 1 values. Fewer subjects (~1-5%) were excluded from analyses of seroprotection rates and GMTs, the majority were excluded due to insufficient sera (September 7, 2006 amendment response to item #27).

After submission and review of the pertussis immunogenicity data submitted in the initial BLA CBER became aware that the PT ----- performed at the sanofi pasteur, Canada, laboratory was non-specific. Thus, neither an evaluation of lot consistency of the PT antigen of Pentacel nor a comparison of anti-PT levels following Pentacel or separately administered vaccines is available.

Pre-vaccination antibody levels

Pre-vaccination antibody levels were presented for the FHA, FIM and pertactin.

Table 17: Study 494-01: Pre-dose 1 GMTs for antibodies to the pertussis antigens*, Stage I PPI population

Parameters	Control Group			Pentacel (Combined Groups)		
	N	GMT	(95%CI)	N	GMT	(95%CI)
FHA (EU/mL)	350	5.66	(5.03, 6.36)	1012	5.51	(5.14, 5.89)
FIM (EU/mL)	348	12.75	(11.83, 13.73)	1009	13.08	(12.47, 13.73)
PRN (EU/mL)	350	3.00	(2.72, 3.32)	1012	3.23	(3.03, 3.43)
PRP, D, T, polio		NA			NA	

*anti-PT values generated in the ------ assay performed at sanofi pasteur, Canada – during review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
Source: 49401si.pdf page 3275 (Table 9.60)
NA: not available

Stage I Pentacel Lot consistency - GMT ratios: Using 2-sided 90% CIs for ratios of GMTs, the statistical criteria for equivalence between lots (2-sided CIs for the ratios of GMTs of the 3 Pentacel groups >2/3 and <1.5) were met for FHA, FIM and pertactin and the diphtheria and tetanus components. Anti-PT levels were generated in the sanofi pasteur laboratory in Canada in an assay which has been determined to be non-specific thus these data are not presented. Equivalence criteria were not met for the ratio of GMTs for poliovirus serotypes and PRP-T. Table 18 presents the lot consistency analyses based on the 90% CI for the GMT ratios. Similar results were obtained for the ITT immunogenicity population. In a post-hoc presentation of equivalence of GMTs using the 95% CI of the ratio of GMTs conclusions regarding equivalence remain the same as those using the 90% CI.

Table 18: Study 494-01 Stage I: GMTs*, GMT ratios, and lot equivalence analyses, post-dose 3, PPI population

	Pentacel			Lot consistency GMT ratio			
Antigen	Lot 1 N = 374-382* GMT (95% CI)	Lot 2 N = 367-379 GMT (95% CI)	Lot 3 N = 358-367 GMT (95% CI)	Lot 1/Lot 2 (90% CI) (95% CI)	Lot 1/Lot 3 (90% CI) (95% CI)	Lot 2/Lot 3 (90% CI) (95% CI)	Equivalence criteria based on 90% CI met/not[1]
PRP (ug/mL)	3.14 (2.67, 3.69)	2.86 (2.43, 3.38)	3.64 (3.12, 4.25)	1.10 (0.91, 1.32) (0.87, 1.37)	0.86 (0.71, 1.04) (0.69, 1.08)	0.79 (**0.65**, 0.95) (0.63, 0.99)	**No**
FHA (EU/mL)	78.86 (73.11, 85.07)	72.85 (67.85, 78.22)	77.13 (71.57, 83.11)	1.08 (0.99, 1.18) (0.98, 1.20)	1.02 (0.94, 1.12) (0.92, 1.14)	0.94 (0.87, 1.03) (0.85, 1.05)	Yes
FIM (EU/mL)	304.21 (279.17, 331.50)	245.91 (225.22, 268.49)	263.35 (240.38, 288.51)	1.24 (1.11, 1.37) (1.09, 1.40)	1.16 (1.04, 1.28) (1.02, 1.31)	0.93 (0.84, 1.04) (0.82, 1.06)	Yes
Pertactin EU/mL	41.55 (37.37, 46.19)	41.11 (36.78, 45.95)	36.11 (32.43, 40.20)	1.01 (0.89, 1.15) (0.87, 1.18)	1.15 (1.01, 1.31) (0.99, 1.34)	1.14 (1.00, 1.30) (0.98, 1.33)	Yes
Diphtheria IU/mL	0.60 (0.53, 0.66)	0.53 (0.47, 0.59)	0.48 (0.43, 0.54)	1.12 (0.98, 1.28) (0.96, 1.31)	1.24 (1.08, 1.41) (1.05, 1.45)	1.10 (0.96, 1.26) (0.94, 1.29)	Yes
Tetanus IU/mL	1.42 (1.32, 1.54)	1.23 (1.13, 1.33)	1.16 (1.06, 1.26)	1.16 (1.06, 1.27) (1.04, 1.30)	1.23 (1.12, 1.35) (1.10, 1.38)	1.06 (0.96, 1.17) (0.95, 1.19)	Yes
Polio 1 (1/dil)	730.76 (640.08, 834.28)	393.98 (338.41, 458.68)	478.44 (417.18, 548.70)	1.85 (1.57, **2.19**) (1.52, 2.26)	1.53 (1.29, **1.80**) (1.25, 1.86)	0.82 (0.70, 0.97) (0.67, 1.01)	**No**
Polio 2 (1/dil)	1628 (1444.9, 1834.3)	1212.0 (1061.9, 1383.4)	1363.8 (1211.2, 1535.7)	1.34 (1.16, **1.55**) (1.13, 1.60)	1.19 (1.03, 1.38) (1.00, 1.42)	0.89 (0.77, 1.03) (0.75, 1.06)	**No**
Polio 3 (1/dil)	1313.9 (1152.6, 1497.8)	1126.5 (989.88, 1281.9)	976.69 (852.74, 1118.7)	1.17 (1.00, 1.36) (0.97, 1.40)	1.35 (1.15, **1.57**) (1.12, 1.62)	1.15 (0.99, 1.35) (0.96, 1.39)	**No**

N= Number of subjects with available data post-dose 3

*anti-PT values generated in the ------ assay performed at sanofi pasteur, Canada – during review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.

[1] equivalence is achieved when the lower limit of each 90% CI is >2/3 and the upper limit <1.5 for Lot1/Lot2, Lot1/Lot3 and Lot2/Lot3

Bold: Equivalence criteria not met using 90% CIs (shaded cells). Source: 49401.pdf page 96-97 and 3340 and 3342

Stage I Pentacel Lot consistency - Seroconversion/seroprotection rates: Using 2-sided 90% CI for the difference in seroconversion/seroprotection rates the statistical criteria for equivalence between lots (2-sided CIs for the difference between the Pentacel groups were >-10% and <+ 10% for all antigens except poliovirus which was >-5% and <+ 5%) were met for all antigens except PT (during review of the BLA the PT ------ performed in the laboratory of sanofi pasteur, Canada was non-specific thus, anti-PT levels generated in this assay are not acceptable to CBER) . Table 19 presents the lot consistency analyses. Sanofi provided post-hoc analyses of equivalence using the 2-sided 95% CI for the difference in seroconversion/seroprotection rates between lots (49401si.pdf page 3348). With the exception of the percent of subjects with anti-PRP levels ⩾ 1.0 ug/mL (Lot 2-Lot3) and seroresponse to pertactin (Lot 1–Lot 3) conclusions regarding equivalence were the same using the 95% or 90% CIs. Similar results were obtained with the ITT population.

Table 21: Study 494-01 Stage I Seroconversion/Seroprotection rates* and lot equivalence analyses, post-dose 3, per-protocol immunogenicity population

		Pentacel Lots			Lot Consistency			
Antigen	Criteria	**Lot 1** **n/N** **%** **(95% CI)**	**Lot 2** **n/N** **%** **(95% CI)**	**Lot 3** **n/N** **%** **(95% CI)**	**Lot 1 . Lot 2** **(90% CI)** **(95% CI)**	**Lot 1 . Lot 3** **(90% CI)** **(95% CI)**	**Lot 2 . Lot 3** **(90% CI)** **(95% CI)**	**Equivalence Based on 90% CI[1]**
PRP (µg/mL)	≥0.15[2]	361/382 94.5 (91.7, 96.6)	359/378 95.0 (92.3, 96.9)	355/367 96.7 (94.4, 98.3)	-0.47 (-3.14, 2.19) (-3.65, 2.70)	-2.23 (-4.69, 0.24) (-5.17, 0.71)	-1.76 (-4.16, 0.65) (-4.62, 1.11)	Yes
	≥1.0	300/382 78.5 (74.1, 82.5)	292/378 77.2 (72.7, 81.4)	300/367 81.7 (77.4, 85.6)	1.29 (-3.67, 6.24) (-4.62, 7.19)	-3.21 (-8.01, 1.59) -8.93, 2.51)	-4.50 (-9.36, 0.37) **(-10.30, 1.31)**	Yes
FHA (EU/mL)	≥4-fold rise	273/336 81.3 (76.7, 85.3)	265/334 79.3 (74.6, 83.6)	261/325 80.3 (75.6, 84.5)	1.91 (-3.15, 6.96) (-4.11, 7.93)	0.94 (-4.10, 5.98) (-5.07, 6.95)	-0.97 (-6.11, 4.18) (-7.10, 5.16)	Yes
FIM (EU/mL)	≥4-fold rise	291/335 86.9 (82.8, 90.3)	286/332 86.1 (82.0, 89.7)	278/325 85.5 (81.2, 89.2)	0.72 (-3.63, 5.07) (-4.46, 5.91)	1.33 (-3.09, 5.74) (-3.93, 6.59)	0.61 (-3.87, 5.08) (-4.72, 5.94)	Yes
PRN (EU/mL)	≥4-fold rise	250/336 74.4 (69.4, 79.0)	247/334 74.0 (68.9, 78.6)	231/325 71.1 (65.8, 75.9)	0.45 (-5.11, 6.02) (-6.17, 7.08)	3.33 (-2.37, 9.02) **(-3.46, 10.12)**	2.88 (-2.85, 8.60) (-3.94, 9.69)	Yes
Diphtheria (IU/mL)	≥0.01	380/381 99.7 (98.5, 100.0)	377/378 99.7 (98.5, 100.0)	366/366 100.0 (99.0, 100.0)	0.00 (-0.61, 0.62) (-0.73, 0.73)	-0.26 (-0.70, 0.18) (-0.79, 0.26)	-0.27 (-0.71, 0.18) (-0.79, 0.26)	Yes
	≥0.1	359/381 94.2 (91.4, 96.3)	346/378 91.5 (88.3, 94.1)	331/366 90.4 (87.0, 93.2)	2.69 (-0.38, 5.76) (-0.97, 6.35)	3.79 (0.59, 6.99) (-0.02, 7.60)	1.10 (-2.36, 4.55) (-3.02, 5.21)	Yes
Tetanus (IU/mL)	≥0.01	380/380 100.0 (99.0, 100.0)	379/379 100.0 (99.0, 100.0)	366/366 100.0 (99.0, 100.0)	0.00 N/A N/A	0.00 N/A N/A	0.00 N/A N/A	Yes
	≥0.1[3]	379/380 99.7 (98.5, 100.0)	379/379 100.0 (99.0, 100.0)	366/366 100.0 (99.0, 100.0)	-0.26 (-0.70, 0.17) (-0.78, 0.25)	-0.26 (-0.70, 0.18) (-0.79, 0.26)	0.00 N/A N/A	Yes

Polio 1 (titer)	≥1:8 dilution	377/377 100.0 (99.0, 100.0)	366/369 99.2 (97.6, 99.8)	358/358 100.0 (99.0, 100.0)	0.81 (0.05, 1.58) (-0.10, 1.72)	0.00 N/A N/A	-0.81 (-1.60, -0.03) (-1.75, 0.12)	Yes
Polio 2 (titer)	≥1:8 dilution	376/376 100.0 (99.0, 100.0)	368/368 100.0 (99.0, 100.0)	358/358 100.0 (99.0, 100.0)	0.00 N/A N/A	0.00 N/A N/A	0.00 N/A N/A	Yes
Polio 3 (titer)	≥1:8 dilution	374/374 100.0 (99.0, 100.0)	367/367 100.0 (99.0, 100.0)	359/359 100.0 (99.0, 100.0)	0.00 N/A N/A	0.00 N/A N/A	0.00 N/A N/A	Yes

Source: 49401si.pdf page 92-94, Table 5.4, 49401si.pdf page 3348 and 3350
n is the number of subjects satisfying the condition in the PPI population.
*anti-PT values generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
N= number of subjects with available data in the PPI population
[1] For non-polio antigens equivalence is achieved when the upper limit of each 90% CI is <10% and the lower limit is >-10%. For Polio, equivalence is achieved when the upper limit 90% CI is <5% and the lower limit is >-5%.
Bold: post-hoc exploratory analysis of equivalence for which UL of 95% CI is not <10% and lower limit is not >-10%.
[2] Anti-PRP levels ≥0.15 ug/mL were not predefined as a primary endpoint with specified equivalence criteria (49401si. pdf page 56) although the data were presented by the manufacturer.
[3]. Anti-tetanus levels ≥0.1 IU/mL were not predefined as a primary endpoint with specified equivalence criteria although the data were presented by the manufacturer

Stage I Non-inferiority seroconversion/seroprotection rates following Pentacel relative to HCPDT administered with POLIOVAX and ActHIB. Table 20 presents the results of the primary non-inferiority analyses (Pentacel pooled versus the response to the control vaccines) for PRP, diphtheria, tetanus and polio seroprotection and pertussis seroconversion rates, post dose 3, based on the 90% CIs for the difference in rates. A comparison of anti-tetanus and anti-diphtheria levels ⩾0.1 IU/mL were observational objectives without pre-defined acceptance criteria, these results are also shown in Table 20. Non-inferiority criteria were not met for anti-PRP seroprotective levels ⩾1.0 ug/mL. For all other comparisons, non-inferiority relative to Control vaccines was demonstrated (anti-PT levels were determined in the assay performed at sanofi pasteur, Canada. This assay has been determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER.). Similar results were obtained for the ITT immunogenicity population. Exploratory analyses using the 95% CI for the difference in rates were provided (49401si.pdf page 3359-3361) and are shown in the table. Using the 95% CI for the difference the anti-pertactin seroconversion rate exceeded 10%, for all other comparisons the UL on the CI was less than 10% (or 5% for polio antigens).

Table 20: Study 494-01 Stage I: Seroconversion/seroprotection rates* following three doses of Pentacel (pooled) compared to Control (HCPDT + ActHIB + IPV) PPI Population

Antigens	Criteria	Pooled Pentacel. n/N % (95% CI)	Control n/N % (95% CI)	Difference Control minus Pentacel		
					90% CI[1]	95% CI
PRP (µg/mL)	≥0.15[2]	1075/1127 95.4 (94.0, 96.5)	394/401 98.3 (96.4, 99.3)	2.87	(1.38, 4.36)	(1.09, 4.64)
	≥1.0	892/1127 79.1 (76.7, 81.5)	356/401 88.8 (85.3, 91.7)	9.63	(6.36, 12.90)	(5.74, 13.52)
FHA (EU/mL)	≥4-fold rise[3]	799/995 80.3 (77.7, 82.7)	266/341 78.0 (73.2, 82.3)	-2.30	(-6.53, 1.94)	(-7.34, 2.75)
FIM (EU/mL)	≥4-fold rise[3]	855/992 86.2 (83.9, 88.3)	295/339 87.0 (83.0, 90.4)	0.83	(-2.67, 4.33)	(-3.34, 5.00)
PRN (EU/mL)	≥4-fold rise[3]	728/995 73.2 (70.3, 75.9)	268/341 78.6 (73.9, 82.8)	5.43	(1.10, 9.75)	**(0.27, 10.58)**
Diphtheria (IU/mL)	≥0.01	1123/1125 99.8 (99.4, 100.0)	398/399 99.7 (98.6, 100.0)	-0.07	(-0.53, 0.39)	(-0.62, 0.48)
	≥0.1 [4]	1036/1125 92.1 (90.4, 93.6)	368/399 92.2 (89.2, 94.7)	0.14	(-2.43, 2.71)	(-2.92, 3.21)
Tetanus (IU/mL)	≥0.01	1125/1125 100.0 (99.7, 100.0)	397/397 100.0 (99.1, 100.0)	0.00	N/A	N/A

	≥0.1[4]	1124/1125 99.9 (99.5, 100.0)	397/397 100.0 (99.1, 100.0)	0.09	(-0.06, 0.24)	(-0.09, 0.26)
Polio 1 (1/dil)	**≥1:8**	1101/1104 99.7 (99.2, 99.9)	388/388 100.0 (99.1, 100.0)	0.27	(0.01, 0.53)	(-0.04, 0.58)
Polio 2 (1/dil)	**≥1:8**	1102/1102 100.0 (99.7, 100.0)	388/388 100.0 (99.1, 100.0)	0.00	N/A	N/A
Polio 3 (1/dil)	**≥1:8**	1100/1100 100.0 (99.7, 100.0)	387/387 100.0 (99.1, 100.0)	0.00	N/A	N/A

Source: 49401si.pdf, page 99

*anti-PT values generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.

[1] Non-inferiority is achieved when the upper limit of the 90% CI for the difference in seroconversion/seroprotection rates was <10% (<5% for polio antigens).

[2] Anti-PRP levels ≥0.15 ug/mL were not predefined as a primary endpoint with specified non-inferiority criteria (49401si. pdf page 56) although the data were presented by the manufacturer.

[3] the anti-pertussis fold rise is calculated by post-dose 3/pre-dose 1 antibody level.

[4] Stage I Observational Objective #5 was to compare anti- tetanus and diphtheria toxoid levels ≥0.1 IU/mL one month following Pentacel or HCPDT "in an exploratory manner", non-inferiority criteria were not prespecifed in the protocol.

n is the number of subjects satisfying the condition in the PPI population.

N= number of subjects with available data in the PPI population

Shaded Cell: Pre-defined non-inferiority criterion not met using 90% CI for the difference.

Bolded: Post-hoc 95% CI for the difference in seroprotection/seroconversion rates not <10%.

Stage I Non-inferiority of GMTs following three doses of Pentacel relative to control vaccines

Table 21 presents the results of the primary non-inferiority analyses (pooled Pentacel versus Control vaccines) for response to the PRP and the pertussis antigens, post dose 3, based on the 90% CIs for the ratio of GMTs. The comparison of anti-PRP GMT ratios did not fulfill the criteria for non-inferiority, the response to PRP was diminished after administration of Pentacel as compared to ActHIB. For comparison of the response to FHA, FIM and pertactin non-inferiority of Pentacel relative to Control vaccines was demonstrated (anti-PT values were generated in the ----- performed in the laboratory at sanofi pasteur, Canada which CBER has determined to be non-specific). The GMTs to the diphtheria, tetanus and polio antigens is also presented in this table non-inferiority criteria were not pre-specified for these antigens and the GMT ratios and CIs were not provided.

Table 21: 494-01 Stage I: Post dose 3 GMTs to Pentacel (pooled) and Control Vaccines (HCPDT + ActHIB + POLIOVAX), and non-inferiority analyses for the PRP and pertussis antigens*. PPI population.

	Pooled Pentacel N GMT (95% CI)	Control N GMT (95% CI)	Ratio Control/Pentacel[1]		
				90% CI[1]	95% CI
PRP (µg/mL)	1127 3.19 (2.91, 3.50)	401 6.23 (5.40, 7.18)	1.95	(1.68, 2.26)	(1.63, 2.33)
FHA (EU/mL)	1117 76.24 (73.06, 79.56)	392 69.24 (64.18, 74.69)	0.91	(0.85, 0.97)	(0.83, 0.99)
FIM (EU/mL)	1119 270.29 (256.83, 284.46)	392 245.98 (227.67, 265.76)	0.91	(0.84, 0.99)	(0.83, 1.00)
PRN (EU/mL)	1118 39.55 (37.16, 42.10)	391 38.63 (34.93, 42.73)	0.98	(0.88, 1.08)	(0.87, 1.10)
Diphtheria (IU/mL)	1125 0.53 (0.50, 0.57)	399 0.48 (0.43, 0.53)	N/A	N/A	N/A
Tetanus (IU/mL)	1125 1.27 (1.21, 1.33)	397 1.81 (1.68, 1.95)	N/A	N/A	N/A
Polio 1 (titer)	1104 518.14 (477.13, 562.67)	388 766.00 (689.69, 850.74)	N/A	N/A	N/A
Polio 2 (titer)	1102 1392.77 (1296.65, 1496.02)	388 1520.60 (1377.37, 1678.71)	N/A	N/A	N/A
Polio 3 (titer)	1100 1132.98 (1049.76, 1222.80)	387 1105.98 (986.23, 1240.27)	N/A	N/A	N/A

[1] Non-inferiority is achieved when the UL 90% CI of the GMT ratio (Control/Pentacel) is <1.5
*anti-PT values generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
N = number of subjects with valid post-dose 3 bleed value.
N/A non-inferiority criteria were not pre-specified
The shaded cell indicates that the non-inferiority criterion was not met.
Source: 49401si.pdf page 100-101 and 3355.

Stage I Observational Analyses

Response to Hepatitis B vaccine: Children enrolled in 494-01 received their first dose of hepatitis B vaccine prior to enrollment (from birth to 21 days of age and ≥ 28 days before the first dose of Pentacel or Control vaccines). Which hepatitis B vaccine these children received as a first dose is not noted in the study report. Two dose of RECOMBIVAX HB were administered to children at 2 months and 6 months of age during the study. Table 22 presents the results of the observational objective to assess the compatibility of administering Pentacel with hepatitis B vaccine. The 494-

01 Stage I protocol stated that serologic results obtained would be compared in a descriptive manner to those contained in the RECOMBIVAX HB package insert. In the September 7, 2006, amendment to the BLA sanofi pasteur states that the apparently lower GMTs observed following RECOMBIVAX HB in study 494-01 cannot be reliably compared to those presented in the Comvax package insert due to differences in population, schedules, sample size, laboratories and coadministered vaccines. These data are discussed in more detail in Section 6.1.3.

Table 22: Study 494-01 Stage I: Post dose 3 hepatitis B GMTs and seroprotection rates by Pentacel lot, pooled Pentacel and Control vaccines. PPI Population.

	Pentacel				Control
Hepatitis B Parameter	Lot 1	Lot 2	Lot 3	Pooled lots	Control Group
N GMT (mIU/mL) (95% CI)	364 396.33 (335.95, 467.56)	364 341.28 (286.28, 406.84)	348 359.51 (303.36, 426.05)	1076 365.08 (330.96, 402.72)	386 303.25 (260.29, 353.31)
n/N % ⩾10 mIU/mL (95% CI)	- - -	- - -	- - -	1054/1076 98.0 (96.9, 98.7)	378/386 97.9 (96.0, 99.1)

Source: 49401si.pdf page 102
'n' is the number of subjects satisfying the condition.
'N' is the number of subjects with available data from the PP Immunogenicity Population.

Effect of concurrently administered Prevnar: The objective, as described in the protocol, was to evaluate the response to the pertussis antigens when Prevnar was administered concomitantly. APL also provided an assessment of anti-PRP response according to the number of doses of Prevnar administered concomitantly.

Table 23 provides the GMTs for PRP and the pertussis antigens according to the number of Prevnar doses coadministered with Pentacel or control vaccines (HCPDT, ActHIB and POLIOVAX) during the infant series. These data suggest that the post dose 3 FHA, FIM, pertactin and PRP GMT achieved following Pentacel or control vaccines may be affected by the number of doses of Prevnar co-administered. However, many of the CIs overlap and there are few subjects who received Pentacel or HCPDT with ≤1 dose of co-administered Prevnar (N=73-74 and N=27-28 respectively). Study M5A07 was designed to assess the immunogenicity of Pentacel after 3 and 4 doses when administered with and without Prevnar at 2, 4 and 6 months of age. A summary of the post-dose 3 immune response to PRP-T and the pertussis components was included in the BLA submission. These data (Section 6.5 of this review) suggest that the response to Pentacel antigens is similar when Pentacel is administered with Prevnar or separately (one month later).

Table 23: Study 494-01 Stage I: GMTs to PRP and pertussis antigens* one month following the third dose of Pentacel or Control vaccines (HCPDT + ActHIB + POLIOVAX) according to the number of doses of Prevnar co-administered at 2, 4 and 6 months of age, PPI population

Antigen **Number of concurrent Prevnar doses**	**Pentacel**		**Control**	
	N	**GMT (95% CI)**	**N**	**GMT 95% CI**
PRP (ug/mL)				
3	733	2.89 (2.58, 3.24)	252	5.99 (4.95, 7.25)
2	320	3.70 (3.10, 4.41)	121	7.06 (5.58, 8.94)
0-1	74	4.59 (3.30, 6.38)	28	5.13 (3.25, 8.10)
FHA (EU/mL)				
3	730	71.46 (67.83, 75.29)	248	66.24 (60.09, 73.01)
2	314	87.51 (80.76, 94.84)	117	71.52 (61.99, 82.51)
0-1	73	80.49 (67.83, 95.51)	27	90.38 (76.04, 107.41)
FIM (EU/mL)				
3	731	265.02 (249.30, 281.72)	248	239.76 (217.18, 264.69)
2	315	280.99 (254.10, 310.71)	117	251.54 (218.80, 289.17)
0-1	73	278.47 (220.61, 351.49)	27	282.51 (209.58, 380.80)
Pertactin (EU/mL)				
3	730	38.11 (35.35, 41.08)	248	35.48 (31.28, 40.24)
2	315	41.11 (36.27, 46.59)	116	43.50 (36.22, 52.24)
0-1	73	48.58 (37.87, 62.31)	27	50.73 (32.98, 78.03)

*anti-PT values generated in the ------ assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
Source: 49401si.pdf page 104 and 106

Table 240 provides the post-dose 3 seroprotection/seroconversion rates with 95% CIs for the FHA, FIM, pertactin and PRP according to the number of Prevnar doses coadministered with Pentacel or separately administered Control vaccines during the infant series. The seroresponse/seroprotection rates appear similar regardless of the number of doses of Prevnar co-administered.

Table 240: Study 494-01 Stage I: Anti-PRP seroprotection (≥ 1.0 ug/mL) and anti-pertussis seroresponse rates* one month following the third dose of Pentacel or Control vaccines (HCPDT + ActHIB + POLIOVAX) according to the number of doses of Prevnar co-administered at 2, 4 and 6 months of age, PPI population.

Antigen Number of concurrent Prevnar doses	Pentacel		Control	
	N	% (95% CI)	N	% 95% CI
PRP % ⩾ 1ug/mL				
3	733	76.5 (73.3, 79.6)	252	88.1 (83.4, 91.8)
2	320	82.8 (78.2, 86.8)	121	90.1 (83.3, 94.8)
0-1	74	89.2 (79.8, 95.2)	28	89.3 (71.8, 97.7)
FHA % ⩾ 4 fold rise				
3	652	79.8 (76.5, 82.8)	213	76.5 (70.3, 82.0))
2	273	82.4 (77.4, 86.7)	103	80.6 (71.6, 87.7)
0-1	70	77.1 (65.6, 86.3)	25	80.0 (59.3, 93.2)
FIM % ⩾ 4 fold rise				
3	651	86.5 (83.6, 89.0)	213	87.8 (82.6, 91.9)
2	273	84.6 (79.8, 88.7)	101	86.1 (77.8, 92.2)
0-1	68	89.7 (79.9, 95.8)	25	84.0 (63.9, 95.5)
Pertactin % ⩾ 4 fold rise				
3	652	74.4 (70.9, 77.7)	213	77.9 (71.8, 83.3)
2	273	70.3 (64.5, 75.7)	103	79.6 (70.5, 86.9)
0-1	70	72.9 (60.9, 82.8)	25	80.0 (59.3, 93.2)

*anti-PT values generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
Source 49401.pdf page 105 and 107

Response to Pneumococcal Conjugate Vaccine: This objective, as described in the protocol, was to compare the immune response to pneumococcal serotypes when Prevnar was co-administered with Pentacel or control vaccines. This analysis included only those PPI subjects who had received all three doses of Pentacel or control vaccines concomitantly with Prevnar.

Table 25 presents the results of an exploratory analysis of anti-pneumococcal serotype GMTs. Although the UL on the 2sided 90% and 95% CIs for ratio of GMTs to Serotype 6B exceeded 1.5 there were no pre-specified acceptance criteria and the 95% CIs overlap across groups. The GMTs for the other serotypes were approximately the same in both groups.

Table 25: Study 494-01 Stage I: Pneumococcal GMTs and ratios one month post –dose 3. PPI population who had received all three doses of Prevnar concurrently with control vaccines or Pentacel.

Antigen	Control N = 165 GMT (95% CI)	Pooled Pentacel. Lots N = 462 GMT (95% CI)	Ratio of GMTs: Control/Pentacel.		
				90% CI	95% CI
Serotype 4 (µg/mL)	2.23 (1.93, 2.58)	2.46 (2.26, 2.68)	0.91	(0.79, 1.04)	(0.77, 1.07)
Serotype 6B (µg/mL)	0.72 (0.55, 0.95)	0.61 (0.52, 0.73)	1.18	(0.90, 1.55)	(0.85, 1.64)
Serotype 9V (µg/mL)	1.79 (1.55, 2.06)	1.79 (1.63, 1.97)	1.00	(0.86, 1.16)	(0.83, 1.19)
Serotype 14 (µg/mL)	3.70 (3.02, 4.54)	3.95 (3.50, 4.45)	0.94	(0.77, 1.14)	(0.74, 1.19)
Serotype 18C (µg/mL)	2.67 (2.23, 3.20)	2.56 (2.32, 2.84)	1.04	(0.88, 1.23)	(0.85, 1.27)
Serotype 19F (µg/mL)	2.56 (2.14, 3.07)	2.65 (2.37, 2.95)	0.97	(0.81, 1.16)	(0.78, 1.20)
Serotype 23F (ug/mL)	1.32 (1.04, 1.67)	1.31 (1.15, 1.49)	1.01	(0.81, 1.25)	0.78, 1.31)

N = number of subjects in the PPI population who received Prevnar concomitantly with Pentacel or control vaccines at 2, 4 and 6 months of age and with available data.
Source: 49401si.pdf page 108-109.

Table 26 presents the results of an exploratory analysis of post-dose 3 anti-pneumococcal seroresponse rates for those subjects who had received three doses of Prevnar concomitantly with either Pentacel or control vaccines (HCPDT + ActHIB + POLIOVAX). With the exception of serotype 6B the proportion of subjects with anti-pneumococcal levels $\geqslant$0.15 ug/mL and $\geq$0.5 ug/mL to each serotype were approximately the same in each group. Although the 95% CI on the difference in rates of anti-serotype 6B levels $\geqslant$0.15 ug/mL exceeded 10% there were no pre-specified acceptance criteria and the 95% CIs overlap across the groups

Table 26: 494-01 Stage I: Anti-pneumococcal seroresponse rates and difference one month post-dose 3. PPI population who had received all three doses of Prevnar concurrently with control vaccines or Pentacel.

Antigen	Criteria	Control N = 165 % (95% CI)	Pooled Pentacel. Lots N = 462 % (95% CI)	Difference in Seroresponse Rates Control minus Pentacel.		
				Difference	(90% CI)	(95% CI)
Serotype 4	≥0.15 µg/mL	97.6 (93.9, 99.3)	98.9 (97.5, 99.6)	-1.34	(-3.46, 0.78)	(-3.87, 1.19)
	≥0.50 µg/mL	94.5 (89.9, 97.5)	94.8 (92.4, 96.6)	-0.26	(-3.63, 3.11)	(-4.27, 3.75)
Serotype 6B	≥0.15 µg/mL	77.6 (70.4, 83.7)	74.9 (70.7, 78.8)	2.68	(-3.60, 8.97)	(-4.81, 10.18)
	≥0.50 µg/mL	58.8 (50.9, 66.4)	58.0 (53.4, 62.6)	0.78	(-6.57, 8.13)	(-7.98, 9.53)
Serotype 9V	≥0.15 µg/mL	98.8 (95.7, 99.9)	97.6 (95.8, 98.8)	1.17	(-0.65, 2.99)	(-1.00, 3.34)
	≥0.50 µg/mL	91.5 (86.2, 95.3)	90.5 (87.4, 93.0)	1.04	(-3.18, 5.26)	(-3.99, 6.06)
Serotype 14	≥0.15 µg/mL	97.6 (93.9, 99.3)	97.8 (96.1, 99.0)	-0.26	(-2.52, 2.00)	(-2.96, 2.44)
	≥0.50 µg/mL	92.7 (87.6, 96.2)	90.7 (87.7, 93.2)	2.03	(-1.97, 6.03)	(-2.73, 6.80)
Serotype 18C	≥0.15 µg/mL	94.5 (89.9, 97.5)	97.0 (95.0, 98.3)	-2.42	(-5.62, 0.77)	(-6.23, 1.38)
	≥0.50 µg/mL	92.7 (87.6, 96.2)	91.3 (88.4, 93.7)	1.39	(-2.58, 5.35)	(-3.33, 6.11)
Serotype 19F	≥0.15 µg/mL	97.0 (93.1, 99.0)	97.6 (95.8, 98.8)	-0.65	(-3.13, 1.84)	(-3.61, 2.31)
	≥0.50 µg/mL	87.9 (81.9, 92.4)	89.2 (86.0, 91.9)	-1.30	(-6.11, 3.51)	(-7.03, 4.43)
Serotype 23F	≥0.15 µg/mL	89.1 (83.3, 93.4)	90.3 (87.2, 92.8)	-1.17	(-5.76, 3.42)	(-6.64, 4.30)
	≥0.50 µg/mL	78.2 (71.1, 84.2)	79.0 (75.0, 82.6)	-0.82	(-6.96, 5.32)	(-8.14, 6.49)

N = number of subjects in the PPI population who received Prevnar concomitantly with Pentacel or control vaccines at 2, 4 and 6 months of age and with available data.
Source: 49401si.pdf page 109-110.

Comparison of the immune response following administration of three doses of Pentacel lot 3 or Control vaccines.
The bulk concentrate lots used to formulate Pentacel lot #3 (C0155A) were the same as those used to formulate the lots of HCPDT, ActHIB and POLIOVAX administered as control vaccines. The following is a presentation of the post-dose 3 serology data following administration of Pentacel or Control vaccines when the same antigen concentrates were administered as Pentacel or separately administered vaccines.

Table 27 presents the GMTs achieved one month post dose 3 in infants administered Pentacel lot 3 or control vaccines formulated with the same antigen concentrate lots. Table 28 presents seroconversion/seroprotection rates for these same groups of infants. These comparisons were not an objective of the study, no analyses or endpoints were pre-specified.

When ActHIB bulk lot #R0181 was administered as ActHIB the anti-PRP GMT was 6.23 (95% CI 5.4-7.2); when this same lot was reconstituted with DTaP-IPV and administered as Pentacel the anti-PRP GMT was 3.64 (95% CI 3.1-4.3). The GMT to tetanus toxoid and poliovirus serotype 1 was also lower (non-overlapping 95% CI) when the antigen was administered as Pentacel as compared to HCPDT or POLIOVAX respectively (Table 27).

Of subjects administered Pentacel 82% (95% CI 77.4-85.6) had anti-PRP ⩾1.0 ug/mL as compared to 88.8% (95% CI 85.3-91.7) of those infants who received ActHIB. In both groups 100% of infants evaluated had anti-tetanus ⩾0.1 IU/mL and poliovirus type 1 titer ⩾1:8, thus the clinical significance of the difference in tetanus and poliovirus type 1 GMT antibody levels is unclear (Table 28).

Table 27: Study 494-01 Stage I: Post dose 3 GMT/GMT for PRP, pertussis*, diphtheria, tetanus and polio antigens, following administration of Pentacel lot 3 or control vaccines. Pentacel and control vaccines were formulated from the same lots of antigen concentrates. PPI population

	Lot 3 Pentacel	**Control HCPDT, POLIOVAX and ActHIB**
Antigen	**N = 358-367 GMT (95% CI)**	**N = 387-401 GMT (95% CI)**
PRP (µg/mL)	**3.64 (3.12,4.25)**	**6.23 (5.40, 7.18)**
FHA (EU/mL)	77.13 (71.57,83.11)	69.24 (64.18, 74.69)
FIM (EU/mL)	263.35 (240.38,288.51)	245.98 (227.67, 265.76)
PRN (EU/mL)	36.11 (32.43, 40.20)	38.63 (34.93, 42.73)
Diphtheria (IU/mL)	0.48 (0.43, 0.54)	0.48 (0.43, 0.53)
Tetanus (IU/mL)	**1.16 (1.06, 1.26)**	**1.81 (1.68, 1.95)**
Polio 1 (titer)	**478.44 (417.18, 548.70)**	**766.00 (689.69, 850.74)**
Polio 2 (titer)	1363.8 (1211.2, 1535.7)	1520.60 (1377.37, 1678.71)
Polio 3 (titer)	976.69 (852.74, 1118.7)	1105.98 (986.23, 1240.27)

N = number of subjects with available data

Bold: GMT results with non overlapping 95% CIs
*anti-PT values generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
Source 49401si.pdf page 97 and 100

Table 28: Study 494-01 Stage I: Post –dose 3 pertussis*, diphtheria, tetanus and polio antigens seroconversion/seroprotection rates following administration of Pentacel lot 3 or control vaccines. Pentacel and control vaccines were formulated from the same lots of antigen concentrates. PPI population

Antigens	Criteria	Pentacel Lot 3. N= 325-367 % (95% CI)	Control N= 339-401 % (95% CI)
PRP ug/mL	**⩾0.15**	96.7 (94.4, 98.3)	98.3 (96.4, 99.3)
	≥1.0	81.7 (77.4, 85.6)	88.8 (85.3, 91.7)
FHA (EU/mL)	**≥4-fold rise**	80.3 (75.6, 84.5)	78.0 (73.2, 82.3)
FIM (EU/mL)	**≥4-fold rise**	85.5 (81.2, 89.2)	87.0 (83.0, 90.4)
PRN (EU/mL)	**≥4-fold rise**	71.1 (65.8, 75.9)	78.6 (73.9, 82.8)
Diphtheria (IU/mL)	**≥0.01**	100 (99.0, 100.0)	99.7 (98.6, 100.0)
	≥0.1	90.4 (87.0, 93.2)	92.2 (89.2, 94.7)
Tetanus (IU/mL)	**≥0.01**	100 (99.0, 100.0)	100 (99.1, 100.0)
	≥0.1	100 (99.0, 100.0)	100 (99.1, 100.0)
Polio 1 (1/dil)	**≥1:8**	100 (99.0 100.0)	100 (99.1, 100.0)
Polio 2 (1/dil)	**≥1:8**	100 (99.0 100.0)	100 (99.1, 100.0)
Polio 3 (1/dil)	**≥1:8**	100 (99.0 100.0)	100 (99.1, 100.0)

*anti-PT values generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
Source: 49401si.pdf, page 92 and 99

Stage II

Pre-dose 4 immunogenicity data:
Table 29 presents the pre-dose 4 immunogenicity data for those children in the Stage II PPI population. Prior to receipt of the fourth dose of PRP-T 68.6% of children who had received Pentacel had anti-PRP levels seroprotective levels ≥0.15 ug/mL as compared to 80.8 % of children administered ActHIB. The anti-PRP GMT was also lower (non-overlapping 95% CI) in those children who had been administered Pentacel as compared to ActHIB. The anti-tetanus GMTs and anti-polio type 1 levels were also lower (non-overlapping 95%CI) pre-dose 4 in those infants who had received Pentacel as compared to the levels in those infants administered HCPDT or POLIOVAX.

Table 29: Study 494-01 Stage II. Pre-dose 4 seroprotection rates and GMTs* for subjects who had been administered 3 doses of Pentacel or control vaccines at 2, 4 and 6 months of age. (PPI)

Antigen/Criteria	Control			Pentacel.		
	N		95% CI	N		95% CI
PRP (ug/mL)						
% ≥0.15	**276**	**80.8**	**(75.6, 85.3)**	**829**	**68.6**	**(65.4, 71.8)**
GMT EU/mL	**276**	**0.56**	**(0.46, 0.67)**	**829**	**0.31**	**(0.28, 0.34)**
FHA (EU/mL)						
GMT	266	9.95	(8.89, 11.15)	812	11.04	(10.38, 11.73)
FIM (EU/mL)						
GMT	**265**	**26.12**	**(23.32, 29.24)**	**811**	**36.20**	**(33.98, 38.57)**
PRN (EU/mL)						
GMT	266	7.19	(6.34, 8.15)	812	6.84	(6.36, 7.35)
Diphtheria (IU/mL)						
≥0.01	271/271	100.0	(98.6, 100.0)	808/808	100.0	(99.5, 100.0)
≥0.1	251/271	92.6	(88.8, 95.4)	757/808	93.7	(91.8, 95.3)
≥1.0		NA			NA	
GMT	271	0.47	(0.42, 0.54)	808	0.57	(0.53, 0.61)
Tetanus (IU/mL)						
≥0.01	268/269	99.6	(97.9, 100.0)	804/807	99.6	(98.9, 99.9)
≥0.1	246/269	91.4	(87.4, 94.5)	668/807	82.8	(80.0, 85.3)
≥1.0		NA			NA	
GMT	**269**	**0.40**	**(0.35, 0.45)**	**807**	**0.29**	**(0.27, 0.31)**
Polio 1 (1/dil)						
≥1:8	258/266	97.0	(94.2, 98.7)	750/802	93.5	(91.6, 95.1)
GMT	**266**	**90.40**	**(78.54, 104.04)**	**802**	**69.52**	**(62.70, 77.07)**
Polio 2(1/dil)						
≥1:8	266/267	99.6	(97.9, 100.0)	790/799	98.9	(97.9, 99.5)
GMT	267	217.66	(118.77, 250.98)	799	189.79	(172.62, 208.67)
Polio 3(1/dil)						
≥1:8	261/271	96.3	(93.3, 98.2)	778/803	96.9	(95.4, 98.0)
GMT	271	135.60	(112.75, 163.09)	803	139.13	(124.40, 155.61)

*anti-PT values generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
Source: 49401sii.pdf page 102, (Table 9.93) page 476, % anti-D and –T levels ⩾0.1 IU/mL September 7, 2006 amendment questions1_133.pdf page 264.
Bold – non overlapping 95% CIs

Stage II Non-inferiority of seroconversion/seroprotection rates elicited by four doses of Pentacel or control vaccines administered at 15 months of age

The results of the Stage II primary non-inferiority analyses are presented in Table 30 and 31.

Table 30 presents the results of non-inferiority analyses for the PRP, diphtheria, tetanus and polio seroprotection and pertussis seroconversion rates, post dose 4, based on the 90% CI for the difference in rates. Non-inferiority criteria were not pre-specified for the comparison of anti-tetanus and anti-diphtheria levels ⩾1.0 IU/mL. Non-inferiority relative to control vaccines was demonstrated for all pre-specified comparisons (except the comparison of anti-PT levels. These values were generated in the ------ performed in the laboratory at sanofi pasteur, Canada which

CBER has determined to be non-specific). Similar results were obtained for the ITT immunogenicity population.

Table 30: Study 494-01 Stage II: Post-dose 4 anti-PRP, -pertussis*, -diphtheria and -tetanus seroconversion/seroprotection rates and non-inferiority analyses (Pentacel versus Control vaccines: HCPDT + POLIOVAX + ActHIB), PPI population

Antigens	Criteria	Control n/N % (95% CI)	Pentacel. n/N % (95% CI)	Non-Inferiority Comparison Control - Pentacel. (90% CI) (95% CI	Non-Inferiority [1] (Based on 90% CI) Yes/No
PRP (µg/mL)	≥1.0	288/291 99.0 (97.0, 99.8)	858/874 98.2 (97.0, 99.0)	0.80 (-0.43, 2.03) (-0.66, 2.26)	Yes
FHA (EU/mL)	≥4-fold rise[2]	215/249 86.3 (81.4, 90.4)	703/779 90.2 (87.9, 92.2)	-3.90 (-7.88, 0.09) (-8.65, 0.85)	Yes
FIM (EU/mL)	≥4-fold rise[2]	217/247 87.9 (83.1, 91.7)	710/778 91.3 (89.1, 93.1)	-3.41 (-7.21, 0.40) (-7.94, 1.13)	Yes
PRN (EU/mL)	≥4-fold rise[2]	231/249 92.8 (88.8, 95.7)	696/779 89.3 (87.0, 91.4)	3.43 (0.17, 6.68) (-0.45, 7.30)	Yes
Diphtheria (IU/mL)	≥0.1	286/287 99.7 (98.1, 100.0)	862/862 100.0 (99.6, 100.0)	-0.35 (-0.92, 0.22) (-1.03, 0.33)	Yes
	≥1.0	273/287 95.1 (92.0, 97.3)	823/862 95.5 (93.9,96.8)	ND	ND
Tetanus (IU/mL)	≥0.1	287/287 100.0 (98.7, 100.0)	861/861 100.0 (99.6, 100.0)	0.00 (NA)	Yes
	≥1.0	283/287 98.6 (96.5, 99.6)	804/861 93.4 (91.5, 94.9)	ND	ND
Polio 1 (1/dil)	≥1:8	285/285 100.0 (98.7, 100.0)	857/857 100.0 (99.6, 100.0)	0.00 (NA)	Yes
Polio 2 (1/dil)	≥1:8	284/284 100.0 (98.7, 100.0)	854/854 100.0 (99.6, 100.0)	0.00 (NA)	Yes
Polio 3 (1/dil)	≥1:8	287/287 100.0 (98.7, 100.0)	851/851 100.0 (99.6, 100.0)	0.00 (NA)	Yes

*anti-PT values generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.

[1] Non-inferiority is achieved when the upper limit of the 90% CI for the difference in seroresponse rates was <10% (<5% for Poliovirus). Additionally, in evaluating seroprotection against Poliovirus Types 1, 2, and 3, the lower limit of the 95% CI of the seroprotection rates had to be at least 90%.

[2] The fold-rise is calculated by post-Dose 4/pre-Dose 1 antibody level; pre-Dose 1 antibody levels were measured in Stage I of the study.

Source: 49401sii.pdf page 457 - 459

Stage II Non-inferiority analyses of pertussis and PRP GMTs following four doses of Pentacel or control vaccines administered at 15 months of age - Table 31 shows the results of the primary non-inferiority analyses for GMT response to the PRP and FHA, fimbriae and pertactin, post dose 4, based on the 90% CI for the ratio of GMTs. Non-inferiority criteria were not met for the response to PRP and pertactin, the control group had higher GMTs to both antigens. Non-inferiority of Pentacel relative to control vaccines was demonstrated for the response to FHA and fimbriae. Similar results were obtained with the ITT immunogenicity population.

Table 31: Study 494-01 Stage II: Post-dose 4 GMTs*, ratio of GMTs and non-inferiority analyses, PPI population

Antigen	Control N GMT (95% CI)	Pentacel. N GMT (95% CI)	Ratio of GMTs Control/Pentacel.	
			Non-Inferiority Comparison Control/Pentacel (90% CI) (95% CI)	Non-Inferiority [1] (Based on 90% CI)
PRP (µg/mL)	291 35.90 (31.01, 41.56)	874 24.12 (22.10, 26.33)	1.49 (1.29, 1.72) (1.25, 1.77)	**No**
FHA (EU/mL)	282 128.26 (116.77, 140.88)	853 134.59 (127.67, 141.89)	0.95 (0.87, 1.04) (0.86, 1.06)	Yes
FIM (EU/mL)	281 350.29 (306.46, 400.39)	854 514.19 (477.80, 553.35)	0.68 (0.60, 0.77) (0.59, 0.79)	Yes
PRN (EU/mL)	282 129.91 (114.13, 147.87)	853 94.91 (88.39, 101.90)	1.37 (1.21, 1.54) (1.19, 1.58)	**No**

[1] Non-inferiority is achieved when the upper limit of the 90% CI of the GMT ratio (Control/Pentacel) is <1.5.
Note: 'N' is the number of subjects with available data from the PP Immunogenicity Population.
*anti-PT values were generated in the ------ assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
Source: 49401sii.pdf page 90, Table 5.7 and page 453

Analyses of post-dose four GMT responses for diphtheria, tetanus and polio- AP has provided (49401sii.pdf page 100) descriptive analyses of the post dose 4 GMT response to the diphtheria, tetanus and polio components of Pentacel as compared to control vaccines. The GMT response to tetanus toxoid in subjects administered Pentacel appears diminished compared to those administered a fourth dose of HCPDT. The response to a fourth dose of Pentacel elicited a higher (non-overlapping 95% CI) response to poliovirus type 2 and 3 as compared to a fourth dose of POLIOVAX administered at 15 months of age (100% of subjects had seroprotective levels to each type). Non-inferiority criteria to these endpoints were not pre-specified in the protocol.

Table 32: Study 494-01 Stage II, Antibody GMTs to diphtheria, tetanus and polio antigens and descriptive non-inferiority analyses one month post- dose 4. PPI population

Antigen	Control N GMT (95% CI)	Pentacel. N GMT (95% CI)	Observational Comparison Control/Pentacel. (90% CI) [1] (95% CI)
Diphtheria (IU/mL)	287 5.50 (4.91, 6.17)	862 5.67 (5.32, 6.04)	0.97 (0.87, 1.08) (0.85, 1.10)
Tetanus (IU/mL)	287 6.98 (6.39, 7.62)	861 3.71 (3.51, 3.92)	1.88 (1.72, 2.06) (1.69, 2.09)
Polio 1 (1/dil)	285 2329.76 (2049.16, 2648.79)	857 2303.65 (2115.27, 2508.80)	1.01 (0.88, 1.16) (0.86, 1.19)
Polio 2 (1/dil)	284 2840.33 (2516.24, 3206.17)	854 4178.27 (3864.65, 4517.34)	0.68 (0.60, 0.77) (0.58, 0.79)
Polio 3 (1/dil)	287 3299.79 (2852.46, 3817.27)	851 4415.38 (4045.96, 4818.54)	0.75 (0.65, 0.86) (0.63, 0.89)

N = number of PPI subjects with available data.
[1] Non-inferiority criteria were not pre-specified.
Source: 49401sii.pdf page 100 and 454.

Stage II Observational Analyses

Effect of Prevnar administered concurrently with the first three doses of Pentacel or Control vaccines on the response to a fourth dose of Pentacel or control vaccines (HCPDT, ActHIB and POLIOVAX). These results should be interpreted with caution since these analyses were not pre-specified and few subjects received 0-1 dose of Prevnar co-administered with Pentacel (N = 61-62) or control vaccines (N = 17-20). Study M5A07 (Section 6.5) is designed to evaluate the immune response to Pentacel antigens after the third and fourth dose when Prevnar is co-administered at 2, 4 and 6 months of age. Post-dose 4 data from this study has not been provided in this BLA.

Table 33 presents the anti-PRP seroprotection and anti-FHA, fimbriae and pertactin seroresponse rates one month following a fourth dose of Pentacel or Control vaccines according to the number of doses of Prevnar co-administered at 2, 4 and 6 months of age. The anti-PRP seroprotection and anti-FHA, fimbriae and pertactin seroresponse rates are not significantly different (overlapping 95% CIs) in both groups.

Table 33: Study 494-01 Stage II. Anti-PRP seroprotective levels and seroresponse to pertussis antigens* (≥ 4x rise compared to pre-dose 1 level) one month following a fourth dose of Pentacel or control vaccines according to the number of doses of Prevnar co-administered with Pentacel at 2, 4 and 6 months of age. PPI population.

Antigen Number of concurrent Prevnar doses at 2, 4 and 6m of age	**Pentacel**		**Control (HCPDT + ActHIB + POLIOVAX)**	
	N	%(95% CI)	N	%(95% CI)
PRP % ≥1 ug/mL				
3	571	97.9 (96.4, 98.9)	183	98.4 (95.3, 99.7)
2	240	98.8 (96.4, 99.7)	88	100.0 (95.9, 100.0)
0-1	62	98.4 (91.3, 100.0)	20	100.0 (83.2, 100.0)
FHA % ≥4-fold rise				
3	507	91.7 (89.0, 94.0)	154	85.7 (79.2, 90.8)
2	212	90.1 (85.3, 93.8)	78	87.2 (77.7, 93.7)
0-1	59	78.0 (65.3, 87.7)	17	88.2 (63.6, 98.5)
FIM ≥4-fold rise				
3	507	91.5 (88.7, 93.8)	155	87.7 (81.5, 92.5)
2	212	90.6 (85.8, 94.1)	76	86.8 (77.1, 93.5)
0-1	58	93.1 (83.3, 98.1)	16	93.8 (69.8, 99.8)
Pertactin % ≥4-fold rise				
3	507	89.2 (86.1, 91.7)	154	91.6 (86.0, 95.4)
2	212	88.7 (83.6, 92.6)	78	93.6 (85.7, 97.9)
0-1	59	93.2 (83.5, 98.1)	17	100.0 (80.5, 100.0)

*anti-PT values were generated in the ----- assay performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.

[2] The fold-rise is calculated by post-Dose 4/pre-Dose 1 antibody level; pre-Dose 1 antibody levels were measured in Stage I of the study.

Source: 49401sii.pdf page 93 and 94

Table 34 shows PRP and FHA, fimbriae and pertactin GMTs one month following a fourth dose of Pentacel or Control vaccines according to the number of doses of Prevnar co-administered with these vaccines at 2, 4 and 6 months of age. The data are not definitive but suggest that co-administration of Prevnar with Pentacel or control vaccines during the infant series may diminish the post-dose 4 response to pertactin. The PT values were generated in the ----- performed in the sanofi pasteur, Canada laboratory which CBER has determined to be non-specific. Similar results were seen in the ITT for immunogenicity population.

Table 34: Study 494-01 Stage II: Anti-PRP and -pertussis GMTs* one month following the fourth dose of Pentacel or Control vaccines according to the number of doses of Prevnar co-administered with Pentacel at 2, 4 and 6 months of age. PPI population

Antigen Number of concurrent Prevnar doses at 2, 4 and 6m of age	**Pentacel**		**Control (HCPDT + ActHIB)**	
	N	GMT (95% CI)	N	GMT (95% CI)
PRP ug/mL				
3	571	23.61 (21.16, 26.35)	183	36.38 (30.00, 44.11)
2	240	24.94 (21.03, 29.56)	88	34.85 (27.18, 44.67)
0-1	62	25.87 (19.38, 34.54)	20	36.31 (20.40, 64.63)
FHA EU/mL				
3	553	129.85 (121.83, 138.39)	175	121.66 (107.52, 137.65)
2	238	150.59 (135.59, 167.25)	87	141.12 (119.34, 166.87)
0-1	61	120.74 (98.10, 148.61)	20	134.39 (102.44, 176.31)
FIM EU/mL				
3	554	506.57 (463.97, 553.08)	175	341.62 (288.64, 404.32)
2	238	533.73 (459.99, 619.29)	87	384.78 (297.99, 496.84)
0-1	61	529.50 (394.87, 710.04)	19	287.07 (183.30, 449.58)
Pertactin EU/mL				
3	553	90.82 (83.46, 98.83)	175	115.31 (97.41, 136.49)
2	238	100.67 (87.29, 116.10)	87	157.54 (125.06, 198.46)
0-1	61	115.34 (84.86, 156.76)	20	159.35 (107.93, 235.26)

*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER.
See *Section 5.5*
Source: 49401sii.pdf page 96 and 97,

Stage II - Comparison of anti-diphtheria and anti-tetanus levels post-dose 4 based on pre-dose 4 levels. - A descriptive analysis of the response of children to a fourth dose of tetanus or diphtheria toxoids based on pre-dose 4 antibody levels < 0.1, ≥ 0.1-< 0.2 and ≥ .0 IU/mL is shown in Table 35. The majority of subjects in both the Pentacel and control groups had pre-dose 4 levels ≥ 0.1 - < 2.0 IU/mL to both diphtheria and tetanus. Approximately 96% of these had a ≥ 4 fold rise in anti-diphtheria levels after the fourth dose. Among subjects with pre-dose 4 anti-tetanus levels ≥ 0.1-< 0.2 the proportion with ≥ 4 fold rise to a fourth dose of tetanus was lower (non-overlapping 95% CI) in the Pentacel group (92%) as compared to the control group (98%). Among subjects with pre-dose 4 diphtheria and tetanus levels < 0.1 IU/mL >95% achieved ≥ 0.4 IU/mL post dose 4. Similar results were obtained for the ITT for immunogenicity population.

Table 35. Study 494-01 Stage II Anti-diphtheria and anti-tetanus titers following the fourth dose of Pentacel or control vaccines according to pre-specified thresholds. PPI population.

Antigens	Criteria		Pentacel		HCPDT + POLIOVAX + ActHIB	
	Pre-dose 4	Post-dose 4	N	% (95% CI)	N	% (95% CI)
Diphtheria (IU/mL)	<0.1	≥0.4	51	96.1 (86.5, 99.5)	19	100 (82.4, 100.0)
	≥0.1- <2.0	≥4x rise	644	95.8 (94.0, 97.2)	221	95.5 (91.8, 97.8)
	≥2.0	≥2x rise	99	94.9 (88.6, 98.3)	27	96.3 (81.0, 99.9)
Tetanus (IU/mL)	<0.1	≥0.4	129	94.9 (89.7, 97.9)	23	100 (85,2, 100.0)
	≥0.1- <2.0	≥4x rise	592	92.4 (90.0, 94.3)	231	97.8 (95.0, 99.3)
	≥2.0	≥2x rise	11	68.8 (41.3, 89.0)	12	91.7 (61.5, 99.8)

Source: 494sii.pdf page 99, table 5.12.

Post-hoc analyses: Several analyses not specified in the protocol were presented in the final study report.

Anti-PRP levels pre-dose 4 and post dose 4 in those subjects with anti-PRP levels <0.15ug/mL and <1.0 ug/mL - APL presented (49401sii.pdf page 107-109) a comparison of post dose 4 anti-PRP response for Pentacel and control subjects with post dose three levels <0.15 ug/mL and <1.0 ug/mL and subjects with pre-dose 4 levels <0.15 ug/mL (Table 36). Following a fourth dose of either Pentacel or ActHIB >80% of these subjects had anti-PRP levels ⩾1.0ug/mL. The post-dose 4 GMT among these subjects appears generally lower following a fourth dose of Pentacel or ActHIB (3.25-11.83 ug/mL) as compared to the GMT of all subjects included the PPI population (24.12-35.90 ug/mL , see Table 31).

Among some subjects with post-dose 3 levels <0.15 and <1.0 ug/mL there was an apparent increase in anti-PRP levels prior to receipt of the fourth dose of PRP-T: Forty-six subjects had post dose 3 anti-PRP <0.15 ug/mL. Prior to dose 4, five of these subjects (2 in the control group and 3 in the Pentacel group) had ⩾ 0.15 ug/mL (one subject in the Pentacel group had seroprotective levels ⩾ 1.0 ug/mL). Following the third dose of either Pentacel or ActHIB 218 subjects had <1.0 ug/mL, at 15 months of age, prior to receipt of the fourth dose of Pentacel or ActHIB, 5 of these subjects has ⩾ 1.0 ug/mL. The narrative provided in the study report does not address whether the apparent increase in anti-PRP levels between receipt of the third and fourth dose is due to cross reactivity, natural boosting or variability of the immunological assay to measure antibodies to PRP. In response to a question from CBER (September 7, 2006 amendment, questions1_133.pdf page 63) sanofi state that these increased antibody levels prior to the fourth dose may be due to delayed immune response to PRP-T or sub-clinical infection with Hib. Although not noted by sanofi an alternative possibility is boosting, perhaps due to *E. coli* K100 polysaccharide which is cross reactive with PRP of *H. influenzae* type b.

Table 36: Study 494-01 Stage I and II. Anti-PRP levels pre- and post-dose 4 of Pentacel or ActHIB (+ HCPDT + POLIOVAX) for those subjects with post dose 3 levels <0.15 ug/mL and <1.0 ug/mL and pre-dose 4 <0.15ug/mL. PPI population.

	GMT		Seroprotection Rates	
Post-Dose 4 Outcome According to Post-Dose 3 Criteria	**Control GMT (n)**	**Pentacel. GMT (n)**	**Control % (n/N)**	**Pentacel. % (n/N)**
Post-Dose 3 [1] anti-PRP Level <0.15 µg/mL				
N	5	41	5	41
Anti-PRP (µg/mL) at Pre-Dose 4	0.14 (5)	0.04 (39)		
≥0.15 µg/mL			40.0 (2/5)	7.7 (3/39)
≥1.0 µg/mL			0.0 (0/5)	2.6 (1/39)
Anti-PRP (µg/mL) at Post-Dose 4	6.64 (5)	3.25 (41)		
≥0.15 µg/mL			100.0 (5/5)	97.6 (40/41)
≥1.0 µg/mL			80.0 (4/5)	85.4 (35/41)
Post-Dose 3 [1] anti-PRP Level <1.0 µg/mL				
N	32	186	32	186
Anti-PRP (µg/mL) at Pre-Dose 4	0.08 (29)	0.06 (175)		
≥0.15 µg/mL			31.0 (9/29)	22.3 (39/175)
≥1.0 µg/mL			3.4 (1/29)	2.3 (4/175)
Anti-PRP (µg/mL) at Post-Dose 4	8.60 (32)	7.82 (184)		
≥0.15 µg/mL			100.0 (32/32)	99.5 (183/184)
≥1.0 µg/mL			93.8 (30/32)	94.0 (173/184)
Pre-Dose 4 anti-PRP Level <0.15 µg/mL				
N	53	260	53	260
Anti-PRP (µg/mL) at Post-Dose 4	11.83 (53)	8.35 (259) 2		
≥0.15 µg/mL			100.0 (53/53)	99.2 (257/259)
≥1.0 µg/mL			96.2 (51/53)	94.6 (245/259)

Source: 49401sii.pdf page 107.

Analysis of seroconversion to the pertussis antigens using an alternative definition for anti-pertussis seroconversion: - Noting that another combination vaccine (Pediarix) has been licensed using an alternative definitions for seroresponse to the pertussis antigens APL provide an analysis of non-inferiority of seroresponse post-dose 4 relative to pre-dose 1 antibody levels using a revised definition for response to the pertussis antigens (Table 37). Neither the definition nor acceptance criteria for non-inferiority analyses were pre-specified in the protocol. It should be noted that the seroconversion definition used for evaluation of Pediarix was based on the pre-dose 1 levels compared to post-dose 3.

Table 37: Non-inferiority analyses of response to the pertussis antigens* based upon a revised definition for seroresponse following the fourth dose relative to the pre-vaccination levels (EU/mL). PPI population

Antigens	Seroresponse Pre-dose 1 EU/mL, post dose 4 EU/mL[1]	Control (n/N) % (95% CI)	Pentacel. (n/N) % (95% CI)	Non-Inferiority Comparison Control-Pentacel. (90% CI)[2]
FHA	Pre <5, post ≥5 Pre ≥ 5, post ≥pre-dose 1	247/249 99.2 (97.1, 99.9)	765/779 98.2 (97.0, 99.0)	0.99 (-0.22, 2.21)
FIM	Pre <17, post ≥17 Pre ≥17, post ≥pre-dose 1	241/247 97.6 (94.8, 99.1)	761/778 97.8 (96.5, 98.7)	-0.24 (-2.07, 1.58)
PRN	Pre <5, post ≥5 Pre ≥ 5, post ≥pre-dose 1	248/249 99.6 (97.8, 100.0)	768/779 98.6 (97.5, 99.3)	1.01 (0.05, 1.97)

[1]Seroreponse defined as: PT, FHA and pertactin: Pre-vaccination <5 EU/mL, post-dose 4 vaccination ⩾ 5 EU/mL; pre-vaccination ⩾5 EU/mL, post-dose 4 ⩾pre-dose 1
Fimbriae: Pre-vaccination <17 EU/mL, post-dose 4 vaccination ⩾ 17 EU/mL; pre-vaccination ⩾17 EU/mL, post-dose 4 ⩾ pre-dose 1
[2]Non-inferiority analyses and criteria were not pre-specified.
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: 49401sii.pdf page 109

Anti-pertussis response post-dose 4 stratified by post-dose 3 anti-pertactin levels. To assess how subjects with "low" post dose 3 antibody levels respond to a fourth dose of pertussis containing vaccine sanofi provided (September 7, 2006 submission questions1_133.pdf page 265 and Dec 8, 2006 page 24) post dose 4 GMTs stratified by post-dose 3 antipertactin levels (Table 38). Approximately 25% of subjects in each group had anti-pertactin levels ⩽ 20 EU/mL following the third dose of vaccine. These data suggest that in each group subjects with "lower" (⩽ 20 EU/mL) anti-pertactin levels following the third dose of vaccine do not respond as to a fourth dose of FIM or pertactin as well as subjects with "higher (>20 EU/mL) levels of anti-pertactin antibodies The PT ------ performed in the sanofi pasteur Canadian laboratory was non-specific, thus anti-PT levels stratified by post-dose 3 anti-pertactin levels are not presented.

Table 38: Study 494-01 Post dose 4 GMT to FHA fimbriae, and pertactin* based on post dose 3 anti-pertactin seroresponse levels. PPI population*

	HCPDT + ActHIB		Pentacel	
Post dose 3 anti-pertactin level	**N**	**GMT (95% CI)**	**N**	**GMT (95% CI)**
	Anti-FHA level post dose 4			
< 5 EU/mL	13	119.7 (84.0, 170.7)	28	103.7 (72.7, 148.0)
≥5-<10 EU/mL	14	100.2 (61.3, 163.8)	56	112.2 (88.5, 142.1)
≥10- ≤20 EU/mL	36	102.4 (78.6, 133.4)	130	120.1 (104.5, 138.1)
≤20 EU/mL	63	105.2 (87.0, 127.3)	214	115.7 (103.4, 129.6)
>20 EU/mL	196	139.4 (124.4, 156.2)	594	142.4 (134.1, 151.1)
	Anti-Fim 2 & 3 GMT post dose 4			
<5 EU/mL	13	208.4 (115.8, 375.2)	28	234.9 (137.6, 400.7)
≥5-<10 EU/mL	14	227.4 (118.3, 437.2)	56	345.1 (256.3, 464.7)
≥10-≤20 EU/mL	36	183.5 (129.8, 259.6)	130	377.8 (307.6, 463.9)
≤20 EU/mL	63	197.6 (152.6, 255.9)	214	346.7 (295.1, 407.4)
>20 EU/mL	195	403.6 (345.3, 471.7)	595	603.4 (557.3, 653.3)
	Anti-pertactin GMT post dose 4			
< 5 EU/mL	13	28.8 (17.5, 47.2)	28	18.5 (12.7, 27.0)
≥5-<10 EU/mL	14	57.4 (34.9, 94.4)	56	50.0 (37.2, 67.3)
≥10-≤20 EU/mL	36	58.2 (41.3, 82.1)	130	51.0 (43.0, 60.5)
≤20 EU/mL	63	50.2 (39.2, 64.2)	214	44.4 (38.5, 51.3)
>20 EU/mL	196	178.7 (156.5, 204.1)	594	130.0 (121.2, 139.5)

*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

Source: September 7, 2006 questions1_133.pdf page 265, Dec 8, 2007 response_fax09nov06.pdf page 24
PPI population with all 4 doses as per randomization*

6.1.3 Comments and Conclusions:

Study 494-01

Lot consistency of Pentacel

The pre-specified criteria to demonstrate consistency of manufacture of three lots of Pentacel were based on the post-dose 3 GMTs and seroconversion/seroprotection rates to each of the antigens in Pentacel. Anti-PT values were generated in the ----- performed at sanofi pasteur, Canada laboratory. CBER has determined this assay is non-specific thus, no conclusions can be drawn regarding lot consistency of the PT component of Pentacel. Lot consistency criteria were met for seroconversion/seroprotection rates for each antigen (except PT). Lot consistency criteria were also met for the GMT response to FHA, fimbriae, pertactin, diphtheria, and tetanus. Lot consistency criteria were not met for the GMT response to PRP-T and the polio virus serotypes 1, 2 and 3. During an April 29, 2003 telecon with AP "CBER acknowledged that the criteria were marginally missed for PRP GMTs… and that high polio GMTs and seroprotection rates were observed for all lots." At that time CBER said there were no major concerns despite the non-fulfillment of equivalence for these endpoints. ----------

Non-inferiority of Pentacel relative to separately administered "component equivalent" vaccines HCPDT, POLIOVAX and ActHIB.

Post dose 3: Study 494-01 failed to demonstrate non-inferiority of three doses of Pentacel compared to separately administered ActHIB for anti-PRP seroprotective levels ≥1.0 ug/mL and GMTs for PRP.

The pre-specified criteria to demonstrate non-inferiority of seroconversion/seroprotection rates following three doses of Pentacel (pooled lots) relative to separately administered control vaccines were met for FHA, fimbriae, pertactin, diphtheria, tetanus, and polio virus serotypes. Non-inferiority of post-dose 3 GMTs to FHA, fimbriae, pertactin, diphtheria, and tetanus was also demonstrated. No conclusion can be drawn regarding non-inferiority of response to the PT-antigen of Pentacel relative to separately administered HCPDT.

Control subjects received the same bulk lots of vaccine administered as HCPDT, POLIOVAX and ActHIB as those administered Pentacel lot #3. Following three doses of Pentacel lot #3 82% of subjects had seroprotective levels ≥ 1.0 ug/mL, the GMT was 3.64 ug/mL. When the PRP-T bulk was administered separately as ActHIB 89% of subjects had seroprotective levels ≥ 1.0ug/mL, the GMT was 6.23 ug/mL. Based on these data it appears that when ActHIB is reconstituted with DTaP-IPV and administered as Pentacel the response to PRP-T is diminished as compared to administration of ActHIB alone. The reason for this is unclear. Further discussion of these data and results from other pivotal and supportive immunogenicity studies is included in the Executive Summary Section 3.0.

Post dose 4: Non-inferiority was not demonstrated for PRP and pertactin GMT following four doses of Pentacel relative to three doses of separately administered HCPDT.

Non-inferiority was demonstrated for FHA, fimbriae, pertactin seroconversion rates and diphtheria, tetanus, polio and PRP seroprotection rates.

No conclusion can be drawn regarding non-inferiority of response to the PT-antigen of Pentacel relative to separately administered HCPDT.

Immune response to Prevnar

Prevnar was licensed and recommended for use after Study 494-01 was initiated. Consequently, subjects may have received Prevnar concurrently with one, two or three doses of Pentacel administered at 2, 4 and 6 months of age. Non-inferiority criteria were not pre-specified however, the GMT response and proportion of subjects with antibody levels ≥ 0.5 ug/mL to serotype 6B appears to be marginally lower when three doses of Prevnar were coadministered with three doses of Pentacel compared to separately administered vaccines. The proportion of subjects with antibody levels ≥ 0.15 ug/mL and ⩾ 0.5 ug/mL and the GMTs to each of the other serotypes were similar when Prevnar was administered with Pentacel or control vaccines. There is no assessment of response to Prevnar when administered with and without Pentacel.

Immune response to hepatitis b vaccine

RECOMBIVAX HB was administered to subjects at 2, and 6 months of age, following a birth dose of hepatitis B vaccine. Although non-inferiority criteria were not specified seroprotection rates and GMTs were similar following three dose of hepatitis B vaccine administered with Pentacel (98% ⩾10 mIU/mL, GMT 365mIU/mL) or control vaccines (98% ⩾10mIU/mL, GMT 303 mIU/mL) (Table 22).

The GMT response to RECOMBIVAX HB in 494-01 (administered at 2 and 6 months of age following a birth dose of hepatitis B vaccine) appears diminished as compared to the data presented in the Comvax package insert (Table 39). However, this result is difficult to interpret since the RECOMBIVAX HB package insert does not contain data on the response to RECOMBIVAX HB when the immunization schedule is three doses administered a birth, 2 and 6 months of age. It is unclear whether this diminished response in Study 494-01 is due to the vaccine, the schedule or co-administration.

The response to one, two and three doses of RECOMBIVAX HB or Comvax presented in the Comvax package inserts is presented in Table 39.

Table 39: Response to HBsAg one month or two months following administration of one, two and three doses of RECOMBIVAX HB (0.5ug HBsAg/0.5mL dose) or Comvax administered at 2, 4 and 14/15 months of age (data from the Comvax PI).

		2m post dose 1	**2m post dose 2**	**1m post dose 3**
Study 1* RECOMBIVAX HB (+ PedvaxHIB,) at 2, 4 and 12-15m (no birth dose HepB)* N = 221	% 10mIU/mL GMT	41.9 5.3	98.4 255.7	100 6943.9
Study 2** Comvax at 2, 4 and 14/15m (following birth dose of HepB) N= 126	% ≥10 mIU/mL GMT	ND	98.2 417.2	98.9 3500.7
				2m post dose 3
Study 3** Comvax at 2, 4 and 15 m (following birth dose of HepB) N = 19	% ≥10mIU/mL GMT	81.3 35.2	100 281.8	100 3913.4

*> 75% of infants also received DTP and OPV at 2 and 4m, ~ 1/3rd of subjects received MMR with 3rd HepB

** infants also received DTP and OPV/eIPV at 2 and 4m. Study 2 DTaP, OPV and MMR at 15m. Study 3 MMR at 15m.

6.1.4 Pertussis Serology Bridge to Sweden I

6.1.4.1 Applicants Study Title
Serology Bridging Study for the Pertussis Response in the Pentacel Clinical Trial 494-01 in the United States and the Sweden Efficacy Trials

6.1.4.2 Rationale
During the clinical development of Pentacel, it was decided that the primary effectiveness evaluation for the pertussis component would include a comparison of immune responses in US children to those observed following DAPTACEL in the Sweden I Efficacy Trial even though DAPTACEL had not yet been licensed in the US. (See Section 4.4.1 for description of Sweden I Efficacy Trial.) Although bridging to Swedish children who received HCPDT in the Sweden II efficacy trial also was considered, this was not feasible as a primary analysis due to an insufficient number of available serum samples from Sweden II. (See Section 4.4.3 for description of Sweden II Efficacy Trial.)

As discussed in Section 4.4.2, the immune responses to pertactin observed following three doses of DAPTACEL in US infants (historical US Bridging Study) were lower than those observed in the Sweden I Efficacy Trial. In view of these findings and the same amount of pertactin in Pentacel and DAPTACEL, CBER advised the sponsor to compare pertussis immune responses following four doses of Pentacel in US children to those observed following three doses of DAPTACEL in the Sweden I Efficacy Trial.

6.1.4.3 Objectives
Primary Immunogenicity Objectives

1. To compare the antibody response to the pertussis antigens (PT, FHA, FIM, and PRN) elicited by 4 doses of Pentacel in Study 494-01 Stage II performed in the United States with those elicited by 3 doses of DAPTACEL (CPDT Vaccine) in the Sweden I Efficacy Trial, based on seroconversion rates and using non-inferiority criteria.

2. To compare the antibody response to the pertussis antigens elicited by 4 doses of Pentacel in Study 494-01 Stage II performed in the United States with those elicited by 3 doses of DAPTACEL (CPDT Vaccine) in the Sweden I Efficacy Trial based on geometric mean titer (GMT) ratios and using non-inferiority criteria.

Observational Objective

To summarize and present the anti-pertussis antibody responses obtained at 16 months of age after 4 doses of Pentacel in a 2, 4, 6, and 15 months of age schedule in Study 494-01 Stage II and those obtained at 13 months of age after 3 doses of HCPDT Vaccine Adsorbed in a 3, 5, and 12 months of age schedule in the Sweden II Efficacy Trial.

6.1.4.4 Design overview
Available sera pairs from Study 494-01 Stages I and II and from the Sweden I and II Efficacy Trials were used in the Serology Bridging Study. The evaluation of the antibody responses to each of the pertussis antigens following Pentacel, DAPTACEL, or HCPDT was based on seroconversion rates and GMTs. All samples were tested during the same time period in the same laboratory.

Vaccines administered and schedule of administration

Refer to Section 3.0 Table 1 for a comparison of the antigenic composition of Pentacel, DAPTACEL and HCPDT. All vaccines contain diphtheria, tetanus and pertussis antigens manufactured by APL using the same process. HCPDT and Pentacel contain the same quantities of pertussis antigens, diphtheria toxoid and tetanus toxoid. DAPTACEL contains reduced quantities of PT and FHA as compared to Pentacel and HCPDT.

Table 40 presents a summary of the vaccination schedules used in Study 494-01 and the Sweden I and Sweden II Efficacy Trials.

Table 40: Serology bridge studies, vaccines and schedule

Study	Vaccine	Schedule
494-01	Pentacel, Prevnar [1], HepB[2]	2, 4, 6, and 15 months of age
Sweden I	DAPTACEL, HIB[3], OPV[3]	2, 4, and 6 months of age
Sweden II	HCPDT, HIB[3], IPV[2]	3, 5, and 12 months of age

[1]The fourth dose of Prevnar administered at 12m of age.
[2]Hepatitis B vaccine administered at 0, 2 and 6 months of age; manufacturer not specified for the first dose, the second and third dose were with RECOMBIVAX HB.
[3]Manufacturer not specified

Lot numbers of DTaP/DTaP-IPV administered in each study:
494-01 Stage I: DTaP-IPV # C0155A, C0154B and C0094A;
494-01 Stage II: DTaP-IPV #C0790BA
Sweden I: DAPTACEL lot # CPDT006
Sweden II: HCPDT lot # HCPDT003

6.1.4.5 Immunogenicity Endpoints and Evaluation Criteria

Antibody Assays
See Section 5.5 for details of assay methodology.

Revised assay procedures for reporting certain low values as less than the LOQ were used for these analyses as compared to the historical Sweden I-U.S. Bridging Study analyses (Section 4.4.2), resulting in a greater number of available serum pairs from Sweden I for analyses of four-fold rise in antibodies.

Primary endpoints and evaluation criteria

Non-inferiority of pertussis antibody responses to Pentacel in 494-01 relative to DAPTACEL in Sweden I –

Table 41 presents the primary immunogenicity endpoints and evaluation criteria.

Table 41: Primary non-inferiority evaluation of sera of US infants one month following a fourth dose of Pentacel (2, 4, 6, 15 month schedule; doses 1-3 administered with Prevnar) compared to sera obtained one month following a third dose of DAPTACEL administered to Swedish infants at 2, 4 and 6 months of age (Sweden I):

Antigens	Comparisons	Non-inferiority Criteria
PT, FHA FIM PRN	GMT ratio DAPTACEL/Pentacel	UL of 2-sided 90% CI for GMT ratios <1.5
	% ≥4-fold rise* (DAPTACEL– Pentacel)	UL of 2-sided 95% CI for difference in rates <10%

Observational Endpoints:

Presentation of seroconversion rates and GMTs to each pertussis antigen one month post dose 4 Pentacel (Study 494-01) compared to one month post dose 3 of HCPDT administered to Swedish infants at 3, 5 and 12 months of age (Sweden II). Non-inferiority criteria were not pre-specified.

Post-Hoc Analyses –

These following presentations of data were not prespecifed but were included in the study report:

- Anti-pertussis antigens post dose 4 Pentacel (Study 494-01 Stage II) Reverse Cumulative Distribution Curves (RCDCs, not presented in this review)
- Anti-pertussis antigens post dose 3 DAPTACEL (Sweden I) RCDC (not presented in this review)
- Anti-pertactin pre dose 1 Pentacel (Study 494-01) and DAPTACEL (Sweden I) – box plot (not presented in this review)
- Seroconversion rates and GMTs for pertussis antigens post dose 3 (Sweden I) and post-dose -4 (Study 494-01 Stage II) based on pre-dose 1 levels:
  PT, FHA and pertactin: <20 EU/mL and ≥20 EU/mL
  FIM: <68 EU/mL and ≥68 EU/mL
- "Exploratory matching analysis": Subjects with available sera from the Sweden I Efficacy Trial were sorted by pre-Dose 1 PRN levels. For each Sweden I subject, three Study 494-01 subjects with the same pre-Dose 1 PRN level were randomly selected for the matching analysis. The PRN seroconversion rate was calculated from this subset of subjects. Another randomly matched sample of subjects from Study 494-01 Stage II was generated, and the seroconversion rate was again calculated. This process was performed 10,000 times and the average seroconversion rate for Study 494-01 Stage II from those 10,000 samples was used in a non-inferiority analysis. (this approach is explained further in a Statistical review)
- Revised definition of seroresponse, percent of subjects: pre dose 1 anti-PT, FHA and pertactin <5 EU/mL, post dose 3 (Sweden I) or post dose 4 (Study 494-01 Stage II) ≥5 EU/mL. Pre dose 1 anti-FIM <17 EU/mL, post dose 3 (Sweden I) or post dose 4 (Study 494-01 Stage II) ≥17 EU/mL.
- Anti-pertactin post dose 4 (Study 494-01 Stage II) according to the number of doses of Prevnar co-administered at 2, 4 and 6 months of age compared to post dose 3 (Sweden I).

6.1.4.6 Statistical Considerations

Sample size and statistical power
Samples size and power estimates were based on 75 pairs of sera expected to be available from subjects that had received DAPTACEL and participated in Sweden I efficacy study. Sample size

for Pentacel sera was assumed to be 540 subjects who had received four doses, met the PPI definition and had received Prevnar concurrently at 2, 4 and 6 months of age. Overall power to conclude non-inferiority of seroconversion approximately 100%. Power to conclude non-inferiority of GMTs 98.52%.

Analysis populations:
The Intent to treat (ITT) and per protocol immunogenicity (PPI) populations pertain only to Study 494-01, for both Sweden I and Sweden II all available sera were used.

Sweden I: Post dose 3 sera were collected from 181 children (those enrolled at one site) one month after the third dose administered at 6 months of age. Of these, 80 serum sample pairs were available for testing. These sera were from the same set of 83 samples previously used to bridge the serologic response of US and Canadian infants administered DAPTACEL to responses of infants in Sweden I.

During review of the serology bridge proposal CBER requested the applicant compare the GMTs of the subset of available sera to the GMT of all sera. This data is shown in Table 42, all assays were performed at the Swedish Institute of Infectious Disease Control Laboratory thus, are not directly comparable to those performed by sanofi and presented in the Pentacel BLA. For each antigen the 95% CI on the GMTs of available and all sera overlap.

Table 42: Post-dose 3 GMT of available sera and all sera following three doses of DAPTACEL in Sweden I based on assays performed at the Swedish Institute of Infectious Disease Control Laboratory.

		GMT EU/mL (95% CI)			
	N	PT	FHA	Fim	Pertactin
Available sera	81	50 (43-58)	35 (30-41)	325 (256-412)	129 (109-153)
All sera	181	48 (43-53)	33 (29-37)	333 (282-393)	110 (95-127)

Source: IND 8502 amendment 46 submitted February 2, 2001.

Sweden II: Serum samples were collected from 58 children recruited in defined geographic regions one month post the third dose of HCPDT administered at 12 months of age. Seventeen pairs were available for the comparison to sera from 494-01.

Study 494-01 - ITT for immunogenicity population - included any subject who had received 4 doses of Pentacel, were bled after the fourth dose and had a valid post-dose 4 serology result regardless of whether they adhered to the study eligibility criteria or their immunization and bleeding visits were within the protocol specified windows or the number of concurrently administered Prevnar doses.

Study 494-01 –PPI population included all subjects who received 4 doses of Pentacel were bled within the age and vaccine interval windows specified in the protocol, and had a valid post-Dose 4 serology result for at least 1 pertussis antigen contained in Pentacel. All subjects had received Prevnar co-administered with Pentacel at 2, 4 and 6 months of age. All primary analyses were based on the PPI population.

Statistical criteria for equivalence and non-inferiority analyses:
The protocol specified statistical criteria for non-inferiority of GMTs were based on the 90% CI for the ratio of GMTs. While this was agreed upon with CBER, of note is that CBER currently recommends use of 2-sided 95% CIs for ratios of GMTs for non-inferiority analyses. The

protocol specified criteria for non-inferiority of seroresponse were based on the 95% CIs for the difference in rates between groups, as currently recommended by CBER.

6.1.4.7 Results

6.1.4.7.1 Populations and sera availability

Table 43 presents the number of sera available from Sweden I and II and the number of sera available for the 494-01 Stage II immunogenicity populations. From Study 494-01 paired sera (pre-dose 1 and post dose 4) were available from 508 subjects in the per-protocol for immunogenicity population who had also received three doses of Prevnar concomitantly with Pentacel at 2, 4 and 6 months of age. Paired sera (pre-dose 1 and post dose 3) were available from 80 subjects in Sweden I and from 17 in Sweden II.

Table 43: Sweden I and II and Study 494-01 Stage II available sera.

	Sweden I DAPTACEL	Sweden II HCPDT	494-01 4 Doses of Pentacel, with Concomitant Prevnar for Doses 1, 2, 3
At least 1 valid post-Dose 3 serology result [1]	80	17	-
At least 1 valid pre-Dose 1 / post-Dose 3 serology result [2]	80	17	-
ITT Immunogenicity Population [3]			
At least 1 valid post-Dose 4 serology result	-	-	610
At least 1 valid pre-Dose 1 / post-Dose 4 serology result	-	-	552
PP Immunogenicity Population [3]			
At least 1 valid post-Dose 4 serology result	-	-	554 [1]
At least 1 valid pre-Dose 1 / post-Dose 4 serology result	-	-	508 [2]

1 Used in GMT analyses; numbers by antigen may vary due to missing post-Dose 4 results
2 Used in seroconversion rate and supportive seroresponse rate analyses; numbers by antigen may vary due to missing post-Dose 4/pre-Dose 1 results
3 ITT and PP Immunogenicity Populations apply only to Study 494-01.
Study 494-01 Stage II ITT and PP population numbers
Source: 49401sii.pdf page 83

6.1.4.7.2 Immunogenicity Analyses

In this review, results of primary, secondary, observational and selected supportive analyses are presented. Also provided are selected FDA presentations of data and additional analyses. Because anti-PT levels were generated in the ------ performed in the laboratory at sanofi pasteur, Canada which CBER has determined to be non-specific this serology bridge analysis does not include an evaluation of response to PT.

Primary Non-inferiority Analyses

Seroconversion rates following four doses of Pentacel in 494-01 and three doses of DAPTACEL in Sweden I:

Table 44 presents the results of the primary non-inferiority analysis of seroconversion rates for the pertussis antigens. The non-inferiority criterion was not met for anti-pertactin seroconversion rates (UL 95% CI difference in rates 13.24). For FHA and FIM seroconversion rates, non-inferiority of four doses of Pentacel relative to three doses of DAPTACEL in Sweden I was demonstrated. Similar results were seen using the ITT for immunogenicity population. .

Table 44: Non-inferiority analyses of seroconversion rates to pertussis antigens* one month post dose 4 of Pentacel as compared to one month post dose 3 of DAPTACEL administered to Swedish infants (PPI population).

Pertussis Antigen and criteria	**Post dose 3 DAPTACEL Sweden I n/N % (95% CI)**	**Post dose 4 Pentacel n/N % (95% CI)**	**Non-Inferiority DAPTACEL minus - Pentacel. (95% CI)**	**Non-Inferiority [1] based on 95% CI Yes/No**
FHA (EU/mL) ≥4-fold rise	55/80 68.8 (57.4, 78.7)	465/507 91.7 (89.0, 94.0)	-22.97 (-33.40, -12.53)	Yes
FIM (EU/mL) ≥4-fold rise	69/80 86.3 (76.7, 92.9)	464/507 91.5 (88.7, 93.8)	-5.27 (-13.20, 2.66)	Yes
PRN (EU/mL) ≥4-fold rise	79/80 98.8 (93.2, 100.0)	452/507 89.2 (86.1, 91.7)	9.60 (5.96, 13.24)	No

'N' represents number of subjects with a valid sera pair (Sweden I Efficacy Trial: pre-Dose 1 and post-Dose 3; or Study 494-01: pre-Dose 1 and post-Dose 4) for each antigen; n represents the number of subjects who fulfill the specified criteria.
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Subjects in Study 494-01 had 3 concurrently administered doses of Prevnar® with Pentacel during the infant series.
Source bridge.pdf page 42

GMT antibody levels following four doses of Pentacel in 494-01 and three doses of DAPTACEL in Sweden I:

Table 45 presents the results of the primary non-inferiority analyses of pertussis antibody levels based on the 90% CI for the ratio of GMTs. For comparisons of response to FHA, FIM and pertactin non-inferiority of a fourth dose of Pentacel relative to three doses of DAPTACEL in Sweden I was demonstrated although the UL of the 90% CI for the ratio of GMTs to pertactin (UL 90% CI 1.49) approaches the pre-specified limit for non-inferiority (<1.5). An exploratory post-hoc analysis of non-inferiority using the 95% CI for the ratio of GMTs was provided at CBER's request.

Table 45: Non-inferiority analyses of anti-pertussis GMTs* post dose 4 Pentacel (PPI population) as compared to post dose 3 DAPTACEL in Sweden I.

Pertussis Antigen	Post dose 3 DAPTACEL Sweden I N GMT (95% CI)	Post dose 4 Pentacel N GMT (95% CI)	Non-inferiority Comparison DAPTACEL/Pentacel[1]		
				90% CI[1]	95% CI
FHA (EU/mL)	80 40.70 (34.99, 47.36)	553 129.85 (121.83, 138.39)	0.31	(0.27, 0.36)	(0.26, 0.37)
FIM (EU/mL)	80 339.31 (266.46, 432.08)	554 506.57 (463.97, 553.08)	0.67	(0.54, 0.82)	(0.52, 0.86)
PRN (EU/mL)	80 111.26 (94.19, 131.44)	553 90.82 (83.46, 98.83)	1.23	(1.01, 1.49)	(0.97, 1.54)

[1] Non-inferiority: the upper limit of the 2-sided 90% CI of CPDT Vaccine Adsorbed/Pentacel is <1.5
Note: 'N' represents number of subjects with a valid post-Dose 3 (Sweden I) or post-Dose 4 (Study 494-01) serum sample for each antigen.
*anti-PT values generated in the ------ performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: bridge.pdf page 43, September 7, 2006 questions1_133.pdf page 266

FDA exploratory data presentation:

Seroconversion rates and GMTs following three doses of Pentacel in 494-01 relative to three doses of DAPTACEL in Sweden I:

No comparison of the response of US-infants administered three doses of Pentacel to the response of infants administered DAPTACEL in Sweden I were prespecified in the serology bridge plan.

Table 46 presents an exploratory analysis of the post dose 3 seroconversion rates following Pentacel (coadministered with Prevnar) in Study 494-01 and DAPTACEL in Sweden I. Following three doses of Pentacel in Study 494-01 the responses to FHA and FIM, but not PRN, appear similar (overlapping 95% CIs) to the responses of infants in Sweden I. The pertactin seroconversion rate is lower than that following DAPTACEL in Sweden I.

Table 46: Pertussis seroconversion rates* one month following three doses of DAPTACEL administered to Swedish infants and one month following three doses of Pentacel administered in Study 494-01

Antigen	Post dose 3 DAPTACEL Sweden I n/N % ≥ 4 fold rise (95% CI)	Post dose 3 Pentacel Study 494-01 n/N % ≥4 fold rise (95% CI)	Difference DAPTACEL – Pentacel % (95% CI) †
FHA	55/80 68.8 (57.4, 78.7)	520/652 79.8 (76.5, 82.8)	-11.0 (-22.23, -1.32)
FIM	69/80 86.3 (76.7, 92.9)	563/651 86.5 (83.6, 89.0)	-0.23 (-9.75, 6.38)
Pertactin	79/80 98.8 (93.2, 100.0)	485/652 74.4 (70.9, 77.7)	24.36 (18.44, 28.20)

'N' represents number of subjects with a valid sera pair pre-Dose 1 and post-Dose 3 for each antigen; n represents the number of subjects who fulfill the specified criteria.
Subjects in Study 494-01 had 3 concurrently administered doses of Prevnar® with Pentacel
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
† CBER generated 95% CI (STAT EXACT)Source bridge.pdf page 42, 49401si.pdf page 105,

Table 47 below presents the post dose 3 GMTs following Pentacel coadministered with Prevnar in Study 494-01 compared to those following three doses of DAPTACEL in Sweden I. Of note is the markedly lower anti-PRN GMT (38 EU/mL) following three doses of Pentacel in Study 494-01 compared to DAPTACEL in Sweden I (111 EU/mL). The response to FIM also appears diminished following three doses of Pentacel as compared to three doses of DAPTACEL in Sweden I. Pentacel contains four times the FHA concentration as DAPTACEL therefore not unexpectedly the GMT to FHA is higher following three doses of Pentacel compared to three doses of DAPTACEL.

Table 47: Pertussis GMTs* one month following three doses of DAPTACEL administered to Swedish infants and one month following three doses of Pentacel administered in Study 494-01

Antigen	Post dose 3 DAPTACEL Sweden I N = 80 GMT (95% CI)	Post dose 3 Pentacel Study 494-01 N 730-731 GMT (95% CI)	Ratio DAPTACEL/Pentacel (90% CI) †
FHA (EU/mL)	40.70 (34.99, 47.36)	71.46 (67.83, 75.29)	0.57 (0.50, 0.65)
FIM (EU/mL)	339.31 (266.46, 432.08)	265.02 (249.30, 281.72)	1.28 (1.04, 1.58)
Pertactin (EU/mL)	111.26 (94.19, 131.44)	38.11 (35.35, 41.08)	2.92 (2.50, 3.40)

Note: 'N' represents number of subjects with a valid post-Dose 3 serum sample for each antigen.
Subjects in Study 494-01 had 3 concurrently administered doses of Prevnar® with Pentacel.
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
† CBER generated 90% CI (STAT EXACT)
Source: bridge.pdf page 43, 49401si.pdf page 104 and 106

Observational Analyses:

Seroconversion rates following four doses of Pentacel in 494-01 compared to three doses of HCPDT in Sweden II:

Table 48 presents the rates of seroconversion to FHA, FIM and pertactin one month following the fourth dose of Pentacel administered at 15 months of age in Study 494-01 (first three doses administered concomitantly with Prevnar) as compared to the rates one month following the third dose of HCPDT administered at 12 months of age to children in Sweden II. Non-inferiority criteria were not pre-specified. The 95% CIs for the rates overlap however, paired sera were available from only 17 of 58 subjects who were bled in Sweden II. Therefore, these data are of limited usefulness.

Table 48: Seroconversion rates* one month following the fourth dose of Pentacel in 494-01 Stage 4 (PPI population) and one month following the third dose of HCPDT in Sweden II

Pertussis Antigens	Criteria	Post dose 3 HCPDT Sweden II n/N % (95% CI)	Post dose 4 Pentacel n/N % (95% CI)
FHA (EU/mL)	≥4-fold	14/17 82.4 (56.6, 96.2)	465/507 91.7 (89.0, 94.0)
FIM (EU/mL)	≥4-fold	13/17 76.5 (50.1, 93.2)	464/507 91.5 (88.7, 93.8)
PRN (EU/mL)	≥4-fold	16/17 94.1 (71.3, 99.9)	452/507 89.2 (86.1, 91.7)

'N' represents number of subjects with a valid sera pair (Sweden II: pre-Dose 1 and post-Dose 3; or Study 494-01: pre-Dose 1 and post-Dose 4) for each antigen.
'n' represents the number of subjects who fulfill the specified criteria.
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source bridge.pdf page 44

Antibody levels following four doses of Pentacel in 494-01 compared to three doses of HCPDT in Sweden II:

Table 49 presents the GMT levels to FHA, fimbriae and pertactin one month following the fourth dose of Pentacel administered at 15 months of age in Study 494-01 (first three doses administered concomitantly with Prevnar) and one month following the third dose of HCPDT administered at 12 months of age to children in Sweden II. Non-inferiority criteria were not pre-specified. Of

note is the apparently lower anti-PRN GMT (based on non-overlapping CIs) following the fourth dose of Pentacel in Study 494-01 compared to the third dose of HCPDT in Sweden II. As noted above sera were available from only 17 subjects in Sweden II thus, these data are of limited usefulness.

Table 49: GMT levels* one month following the fourth dose of Pentacel in 494-01 and one month following the third dose of HCPDT in Sweden II (PPI population)

Pertussis Antigens	**Post dose 3 HCPDT Sweden II N GMT (95% CI)**	**Post dose 4 Pentacel N GMT (95% CI)**
FHA (EU/mL)	17 86.76 (69.18, 108.81)	553 129.85 (121.83, 138.39)
FIM (EU/mL)	17 299.36 (172.27, 520.19)	554 506.57 (463.97, 553.08)
PRN (EU/mL)	17 171.83 (100.79, 292.94)	553 90.82 (83.46, 98.83)

'N' represents number of subjects with a valid post-Dose 3 (Sweden II) or post-Dose 4 (Study 494-01) serum sample for each antigen.
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER.
See *Section 5.5*
Source bridge.pdf page 45

Selected Supportive analyses:

Anti-pertactin level prior to administration of Pentacel in Study 494-01and DAPTACEL in Sweden I:

Table 50 below was presented by sanofi pasteur to indicate that the pre-dose 1 anti-pertactin levels of US children enrolled in Study 494-01 who subsequently received three doses of Prevnar at 2, 4 and 6 months of age and were included in the PPI of the serology bridge study were higher than those of Swedish children enrolled in Sweden I. A box plot of the anti-pertactin levels pre-immunization is included in the BLA. As presented the pre-dose 1 anti-pertactin levels of US subjects enrolled in 494-01 (GMT 3.12) are higher than those of Swedish infants in Sweden I (GMT 2.17). The pre-immunization antibody levels to FHA and fimbriae were similar between groups. This data presentation was not pre-specified and had no pre-defined criteria for evaluation.

Table 50: Pre-dose 1 pertussis antibody levels* in Swedish and US infants enrolled in 494-01 who were included in the per-protocol immunogenicity population for the serology bridge

Specific Antigen	Pre-dose 1 Sweden I N GMT (95% CI)	Pre-dose 1 494-01 Stage II N GMT (95% CI)	GMT Ratio	Upper 90% CI	p-Value
FHA (EU/mL)	80 5.13 (4.13, 6.39)	507 5.03 (4.60, 5.50)	0.98	1.20	0.8679
FIM (EU/mL)	80 13.62 (11.45, 16.20)	507 13.10 (12.27, 13.98)	0.96	1.12	0.6661
PRN (EU/mL)	80 2.17 (1.87, 2.51)	507 3.12 (2.87, 3.40)	1.44	1.73	0.0012

Less than LOQ values, i.e., <X are analyzed as X/2.
'N' represents number of subjects with a valid sera pair (Sweden I Efficacy Trial: pre-Dose 1 and post-Dose 3; or Study 494-01: pre-Dose 1 and post-Dose 4) for each antigen.
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER.
See *Section 5.5*
Source: bridge.pdf page 46

Seroconversion and GMTs for pertussis antigens post dose 3 (Sweden) and 4 (494-01) based on pre-dose 1 levels:

Table 51 presents the GMTs and rates of seroconversion post dose 3 DAPTACEL in Sweden I and post dose 4 Pentacel in Study 494-01 for subjects with anti- FHA and -pertactin pre-titers <20 EU/mL and ≥ 20 EU/mL. This level was chosen because it is at least 4 times the assay LOQ for these antigens. Anti-FIM GMTs and seroconversion rates are presented for those subjects with pre-vaccination levels <68 EU/mL and ≥ 68 EU/mL (4x LOQ).

The data indicate that fewer subjects with "high" pre-vaccination levels had a four-fold rise in antibody level following DAPTACEL or Pentacel compared to those subjects with "low" levels of pre-existing antibodies. With the exception of the response to pertactin in Pentacel recipients, it appears that the level of pre-existing antibody affected the GMT response to vaccination: subjects with "high" pre-existing antibodies had a lower GMT following vaccination as compared to those subjects with "low" pre-existing antibody levels. Subjects with "high" pre-existing antibodies to pertactin did not have a diminished GMT following a fourth dose of Pentacel as compared to those with "low" preexisting antibody levels.

APL presented these data to support their argument that although the rate of 4-fold rise in pertactin antibody level is lower for subjects with pre-immunization levels >20 EU/mL the post-immunization antibody level of this group (144.43 EU/mL) is higher than observed for the overall PP population in that group (90.82 EU/mL) or in the Sweden I Efficacy Trial (111.26 EU/mL). However, it should also be noted that the majority of subjects in both studies had pre-vaccination pertactin levels <20 EU/mL. Among subjects with pre-vaccination anti-pertactin levels <20 EU/mL, the post dose 4 pertactin GMT in Study 494-01 (88.03 EU/mL) is lower than that post-dose 3 in Sweden I (111.41 EU/mL). Prevaccination GMTs stratified by pre-vaccination antibody level categories were requested by CBER and are included in the Table below.

Table 51: Anti-pertussis GMTs and seroconversion rates* based on pre-vaccination antibody levels of children enrolled in Sweden I and 494-01 PPI population.

		DAPTACEL Sweden I N = 80				Pentacel 494-01 Stage II N = 507-508			
		Pre-dose 1		Post-dose 3		Pre-dose 1		Post-dose 4	
Pertussis Antigens	**Pre-Dose 1 Criteria**	**n (%)**	GMT	**GMT†**	**% 4x rise**	**n (%)**	GMT	**GMT†**	**% 4x rise**
FHA (EU/mL)	<20	73 (91.3%)	4.33	42.32	75.3	453 (89.3)	4.02	129.46	97.1
	≥20	7 (8.8%)	30.58	27.15	0.0	54 (10.7)	33.02	112.61	46.3
FIM (EU/mL)	<68	76 (95.0%)	12.21	341.40	88.2	483 (95.5)	11.85	503.72	94.0
	≥68	4 (5.0%)	108.81	302.07	50.0	23 (4.5)	106.80	315.61	39.1
PRN (EU/mL)	<20	79 (98.8)	2.11‡	111.41	98.7	479 (94.5)	2.72‡	88.03	90.8
	≥20	1 (1.3)	20.00	100.00	100.0	28 (5.5)	32.23	144.43	60.7

'n' represents number of subjects who fulfill the specified criteria.
'N' represents number of subjects with a valid sera pair (Sweden II: pre-Dose 1 and post-Dose 3; or Study 494-01: pre-Dose 1 and post-Dose 4) for each antigen.
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
† 95% CI not provided.
‡Sanofi note that among subjects with pre-vaccination anti-pertactin levels <20 EU/mL the GMT of US infants (2.72, 95% CI 2.53, 2.93) are higher than those of Sweden I subjects (2.11, 95% CI 1.84, 2.41).
Source: bridge.pdf page 49, September 7, 2006 questions1_133.pdf page 267.

Post hoc exploratory matching analysis to assess whether subjects with equivalent anti-pertactin pre-immunization levels would have similar post-immunization seroconversion rates after immunization with 4 doses of Pentacel in the US or three doses of DAPTACEL in Sweden I. Sweden I subjects were sorted according to their pre-Dose 1 PRN antibody levels and a subset of Study 494-01 subjects was identified by matching their pre-immunization antibody levels to those of the subjects in Sweden I. For each Sweden I subject, three 494-01 subjects with the same pre-Dose 1 PRN value were randomly selected and included in the new subset. The total number of 494-01 subjects in the subset was 240. The PRN seroconversion rate was calculated. Another randomly matched sample of subjects from Study 494-01 was generated, and the seroconversion rate was again calculated. This process was performed 10,000 times and the average seroconversion rate for Study 494-01 from those 10,000 samples was compared to the Sweden I seroconversion rate in a non-inferiority analysis. APL conclude non-inferiority since the UL 95% CI <10%. This analysis is presented in Table 52, of note using this approach the UL of the 95% CI approaches 10%.

During the pre-BLA meeting of December 14, 2004 CBER told AP that these post-hoc analyses were of limited usefulness in making regulatory decisions. See the statistical review for details.

Table 52: Exploratory analysis of pertactin seroconversion rates based on 3:1 matching by pre-vaccination anti-PRN level[1]

Probability of a ≥4-fold rise		Non-inferiority comparison
Sweden I Post dose 3 DAPTACEL N= 80	494-01 Stage II Post dose 4 Pentacel[2] N = 240	CPDT minus Pentacel (95% CI)
98.8%	93.2%	5.55 (1.54, 9.56)

[1]See text for methods of matching analysis
[2]Average seroconversion rate based on 10,000 calculations. See text for methods.
*Non-inferiority analysis not pre-specified.
Source: bridge.pdf page 51

New (not-pre-specified) definition of seroresponse: Sanofi note that a DTaP combination vaccine, Pediarix, manufactured by GSK, has been licensed using a definition of seroresponse to each pertussis antigen rather than a fold-rise. The definition of seroresponse to PT, FHA and pertactin used by GSK and presented in the Pediarix package insert is as follows: in initially seronegative infants the appearance of antibodies (concentration $\geqslant$ 5 EU/mL); in initially seropositive infants, at least the maintenance of pre-vaccination concentration. It should be noted that the definition used by GSK pertains antibody levels one month following the third dose of pertussis containing vaccine and antibody levels as measured in their ------. AP present the rate of seroresponse to pertussis antigens following a fourth dose of Pentacel administered at 15 months of age in Study 494-01 relative to the rate following three doses of DAPTACEL in Sweden I (Table 53). AP have defined seroresponse as follows: pre dose 1 anti- FHA and pertactin <5 EU/mL, post dose 3 (Sweden I) or post dose 4 (494-01) $\geqslant$ 5 EU/mL. Pre dose 1 anti-FIM <17 EU/mL, post dose 3 (Sweden I) or post dose 4 (494-01) $\geqslant$ 17 EU/mL. APL conclude non-inferiority however, this analysis is post-hoc. While these definitions were not pre-specified for the Pentacel bridging analyses, they were proposed by the sponsor and considered by CBER for Study M5A07. However, CBER has not concurred with the use of these definitions for Study M5A07 due to concerns about assay precision.

Table 53: Post-hoc analysis of vaccine response rates to the pertussis antigens* one month following the third dose of DAPTACEL in Sweden II and one month following the fourth dose of Pentacel in 494-01 (PPI population)

Antigens	**Post dose 3 DAPTACEL Sweden I n/N % VR (95% CI)**	**Post dose 4 Pentacel 494-01 Stage II n/N % VR (95% CI)**	**Non-Inferiority Comparison DAPTACEL minus Pentacel (90% CI)[1]**
FHA	74/80 92.5 (84.4, 97.2)	501/507 98.8 (97.4/99.6)	-6.32 (-11.22, -1.41)
FIM	76/80 95.0 (87.7, 98.6)	494/507 97.4 (95.7, 98.6)	-2.44 (-6.61, 1.74)
PRN	80/80 100.0 (95.5, 100.0)	499/507 98.4 (96.9, 99.3)	1.58 (0.67, 2.49)

VR= Vaccine Response (Not predefined): PT, FHA, Pertactin:
pre-Dose 1 antibody level <5 EU/mL: post-Dose 4 (post-Dose 3 for Sweden I) ≥5 EU/mL
pre-Dose 1 antibody level ≥5 EU/mL: post-Dose 4 (post-Dose 3 for Sweden I) ≥ pre-dose 1
FIM:

pre-Dose 1 antibody level <17 EU/mL: post-Dose 4 (post-Dose 3 for Sweden I) ≥17 EU/mL
pre-Dose 1 antibody level ≥ 17 EU/mL: post-dose 4 (post-Dose 3 for Sweden I) ≥ pre-dose 1.
[1] Non-inferiority criteria were not-prespecified
'N' represents number of subjects with a valid sera pair, 'n' represents number of subjects who fulfill specified criteria.
*anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*.
Source: bridge.pdf page 52.

Anti-pertactin post dose 4 (494-01) according to the number of doses of Prevnar co-administered at 2, 4 and 6 months of age compared to post dose 3 (Sweden I). An analysis of the post-dose 4 response to pertactin based on the number of doses of Prevnar co-administered at 2, 4 and 6 months of age in Study 494-01 had suggested that the post-dose 4 response to pertactin was inversely related to the number of doses of Prevnar coadministered at these ages (See this review Table 34).

In view of these findings, APL provided comparative analyses (without pre-specified non-inferiority criteria) of the GMT post-dose 4 Pentacel in Study 494-01 compared to post-dose 3 DAPTACEL in Sweden I, stratified by the number of doses of Prevnar co-administered with Pentacel at 2, 4 and 6 months of age in Study 494-01. These data, shown in Table 54, are consistent with the analyses previously presented in Table 34.

Study, M5A07, is designed to evaluate whether the post-dose 3 and 4 response to pertussis antigens of Pentacel is affected by Prevnar co-administered at 2, 4 and 6 months of age. Post dose 3 results have been provided to this BLA and are summarized in Section 6.5.

Table 54: Analyses of anti-pertactin GMTs following DAPTACEL administered in Sweden I compared to Pentacel based on the number of doses of Prevnar co-administered with Pentacel (ITT population).

Number of Concurrent Prevnar® Doses with Pentacel. During the Infant Series in Study 494-01 [1]	DAPTACEL Sweden I (Prevnar was not administered) N GMT (95% CI)	Pentacel 494-01 Stage II N GMT (95% CI)	Ratio of GMTs CPDT/Pentacel (90% CI)
3	80 111.26 (94.19, 131.44)	609 89.75 (82.80, 97.29)	1.24 (1.02, 1.50)
2	80 111.26 (94.19, 131.44)	260 98.24 (85.41, 113.00)	1.13 (0.90, 1.42)
1	80 111.26 (94.19, 131.44)	62 108.32 (79.93, 146.80)	1.03 (0.78, 1.35)
Any: All Pentacel Subjects [2]	80 111.26 (94.19, 131.44)	932 93.39 (87.21, 100.02)	1.19 (0.98, 1.46)

[1]Number of Prevnar® refers only to Study 494-01 Stage II subjects, Subjects in Sweden I did not receive Prevnar®.
[2] Pentacel subjects received 0-3 doses of Prevnar administered concurrently.
'N' represents number of subjects with a valid post-Dose 3 (Sweden I) or post-Dose 4 (Study 494-01) serum sample.
Source: bridge.pdf page 53

6.1.4.8 Comments and Conclusions

As discussed in Section 4.4.2, for pertussis, a primary series of DAPTACEL consists of four doses, based on lower responses to pertactin following three doses in US infants relative to Swedish infants who participated in the Sweden I Efficacy Trial. The responses to each of the pertussis antigens following four doses of DAPTACEL in Canadian children were at least as high as those observed following three doses in Sweden I. However, following four doses of Pentacel in Study 494-01, the pertactin seroconversion rate was inferior to that observed following three doses of DAPTACEL in Sweden I (UL of 95% CI for Sweden I minus 494-01 13.24) (Table 44). Non-inferiority was demonstrated for FHA, and FIM seroconversion rates and GMTs for FHA, fimbriae and pertactin following four doses of Pentacel (Study 494-01) relative to three doses of DAPTACEL (Sweden I) (Table 44 and 45). With the notable exception of pertactin, the anti-FHA and anti-FIM GMTs and seroresponse rates following three doses of Pentacel in Study 494-01 appeared to be at least as high as those observed following three doses of DAPTACEL in Sweden I, although non-inferiority analyses were not performed (Table 46 and 47). Anti-PT levels were generated in a non-specific assay thus, a comparison of anti-PT levels following three and four doses of Pentacel in Study 494-01 and three doses of DAPTACEL in Sweden I is not available.

A higher proportion of subjects with relatively high pre-vaccination anti-PRN levels in Study 494-01 relative to Sweden I may have contributed to the findings observed in the bridging analyses. However, of note is that among subjects with relatively low pre-vaccination anti-PRN levels, the anti-PRN GMT following four doses of Pentacel in Study 494-01 also appears to be lower than that observed following three doses of DAPTACEL in Sweden I (Table 51).

The failure to bridge to Sweden I with regard to pertactin seroconversion rates following a fourth dose of Pentacel administered at 15-18 months of age is of concern. However, in the absence of a well accepted serological correlate of protection for pertussis it is unclear whether this difference is clinically meaningful.

Data from Study 494-01 suggest that the response to a fourth dose of Pentacel may be affected by the number of doses of Prevnar co-administered at 2, 4 and 6 months of age. Study M5A07 was designed to address whether co-administered Prevnar interferes with the immune responses to Pentacel. Post dose 4 data from Study M5A07 have not been submitted to the BLA.

6.2 Trial #2

6.2.1 Applicants Protocol # and Protocol Title

Study 494-03 Safety and Immunogenicity of PENTACEL when Co-administered with Other Recommended Vaccines at 2, 4, 6 and 15 Months of Age

6.2.1.1 Rationale/Objectives

Study 494-03 was designed as a two stage study to assess the safety and immunogenicity of Pentacel when coadministered with other recommended vaccines in infants and children 2, 4, 6 and 15 months of age. Stage I assessed safety and immunogenicity of Pentacel when co-administered with RECOMBIVAX HB and Prevnar during the infant series (2, 4 and 6 months of age). RECOMBIVAX HB was either administered at 2, 4 and 6 months of age or at 2 and 6 months following a birth dose of hepatitis B vaccine.

Stage II was designed to assess the effect of co-administration of MMR_{II}, VARIVAX, and Prevnar on the safety and immunogenicity of Pentacel. The Stage II design also allowed assessment of the effect of co-administration of Pentacel on the immunogenicity of Prevnar, VARIVAX, and MMR_{II}

Specific objectives relevant to the immunological evaluation of Pentacel and co-administered vaccines are listed below for Stages I and II of Study 494-01.

Primary immunogenicity objectives

Stage I - none

Stage II

1. To compare the relative frequencies of seroconversion and seroprotection against the antigens in PENTACEL when the 4th dose is administered alone or co-administered with varicella vaccine and measles, mumps and rubella (MMR) vaccine at 15 months of age.

2. To compare the relative frequencies of seroconversion and seroprotection against the antigens in PENTACEL when the 4th dose is administered alone or co-administered with pneumococcal conjugate vaccine at 15 months of age.

Secondary Immunogenicity Objectives

Stage I

1. To describe the relative frequencies of seroprotection and antibody GMTs against the antigens in PENTACEL (PT, FHA, FIM 2 & 3, PRN, diphtheria toxoid, tetanus toxoid, poliovirus types 1, 2 and 3, and PRP) at 7 months of age, when co-administered with other recommended vaccines at 2, 4 and 6 months of age.

2. To describe the relative frequencies of seroresponse and antibody GMTs against the antigens in the pneumococcal conjugate vaccine when co-administered with PENTACEL at 2, 4 and 6 months of age.

Stage II

1. To compare the antibody responses against the antigens in PENTACEL when the 4th dose is administered alone or co-administered with a varicella vaccine and MMR vaccine at 15 months of age.

2. To compare the antibody responses against the antigens in PENTACEL when the 4th dose is administered alone or co-administered with pneumococcal conjugate vaccine at 15 months of age.

3. To compare the relative frequencies of seroresponse against the antigens in a varicella and an MMR vaccine when co-administered or not with PENTACEL at 15 months of age.

4. To compare the relative frequencies of seroresponse against the antigens in pneumococcal conjugate vaccine when co-administered or not with PENTACEL at 15 months of age.

Observational Immunogenicity Objectives

Stage I

To present the relative frequencies of seroprotection elicited by a hepatitis B vaccine when coadministered with PENTACEL at either 2, 4 and 6 months or 2 and 6 months of age (subjects were not randomized into these schedules).

Stage II

To present an anti-PT, anti-FHA, anti-FIM 2 & 3 and anti-PRN antibody decay curve from 7 months (post-infant series), 12 months, 15 months (pre-4th dose), and 16 months (post-4th dose) from a subset of subjects.

6.2.1.2 Design Overview

Study 494-03 was a two-staged, randomized, multicenter study. In Stage I all subjects received Pentacel and Prevnar administered at 2, 4 and 6 months of age. If subjects had received a dose of hepatitis B vaccine before study entry (birth to 28 days of age) RECOMBIVAX HB was administered at 2 and 6 months of age. Subjects who had not received a previous dose of hepatitis B vaccine received RECOMBIVAX HB at 2, 4 and 6 months of age. In Stage I serum samples were obtained at 7 months from the first 348 subjects enrolled. Stage II vaccines were administered at 12, 15 and 16 months of age. Subjects bled at 7 months of age were asked to donate a serum sample at 12 months of age. These subjects were also bled at 15 and 16 months of age.

Subjects were randomized at recruitment (approx. 2 months of age). Subjects were assigned a random number from a list generated by AP Inc. During Stage I this number served only as an identifier. In Stage II the randomization number allocated subjects into one of four study groups.

6.2.1.3 Population

Healthy infants 2 months of age were enrolled. Inclusion and Exclusion criteria are detailed in the clinical review.

The Study period from the beginning of Stage I to the end of Stage II was July 10, 2000-December 26, 2002. Subjects were enrolled at 11 centers in the US.

6.2.1.4 Products mandated by the Protocol

Study vaccines – schedule of administration

Tables 55 and 56 present the vaccines administered, schedule and vaccination groups during Stage I and II of the Study 494-03.

Table 55: Study 494-03 Schedule of vaccine administration during Stage I

Group	2, 4 and 6 months of age	0, 2, 6 months or 2, 4, 6m*
All subjects	Pentacel and Prevnar	Hepatitis B vaccine (RECOMBIVAX HB)

Subjects who had not received a birth dose of hepatitis b vaccine (at 0-28 days of age) received RECOMBIVAX HB at 4 months of age. The birth dose of hepatitis B vaccine (manufacturer not specified) was administered outside of the study.

Table 56 Study 494-03 Schedule of vaccine administration during Stage II

Study Group	Months of age	Vaccines
1	12	MMR_{II}, VARIVAX, Prevnar
	15	Pentacel
2	12	Prevnar
	15	MMR_{II}, VARIVAX, Pentacel
3	12	MMR_{II}, VARIVAX,
	15	Pentacel, Prevnar
4	15	MMR_{II}, VARIVAX, Prevnar
	16	Pentacel

Study vaccines – formulation and lot numbers:
All study vaccines except Pentacel are licensed in the US.

- Pentacel (DTaP-IPV used to reconstitute ActHIB)

The formulation of Pentacel per 0.5mL dose is described in **Section 1.2.3**

Lot number for Stage I: DTaP-IPV C0155AA and ActHIB UA480AD (bulk R0181)
Lot number for Stage II: DTaP-IPV C0790BA and ActHIB UA480AE (bulk R0181) (Note: This is the same bulk lot of PRP-T administered to Study 494-01 Group 3 (as Pentacel) and separately as ActHIB to the control group.

Other Study vaccines:

- Prevnar, [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), Wyeth]: Each 0.5 ml dose of Prevnar contains 2 μg of each polysaccharide for *Streptococcus pneumoniae* serotypes 4, 9V, 14, 18C, 19F, and 23F and 4 μg of serotype 6B (16 μg total polysaccharide); approximately 20 μg of CRM_{197} protein; and 0.125 mg of aluminum as aluminum phosphate adjuvant.

  Stage I and II: Lots 471-212, 474-723 and 477-171

- RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant), Merck & Co., Inc]: Each 0.5 ml dose contains 5 μg of purified HBsAg without preservative.

Lot 0581K

- MMR_{II} (Measles, Mumps, and Rubella Virus Vaccine Live, Merck & Co., Inc.): Each 0.5 ml dose contains not less than 1,000 TCID50 (tissue culture infectious doses) of measles virus; -------TCID50 of mumps virus; and 1,000 TCID50 of rubella virus. Each dose of the vaccine contains approximately 25 µg of neomycin; sorbitol and hydrolyzed gelatin as stabilizers. The product contains no preservative.

  Lot MMR 1179K, diluent 1013K

- VARIVAX [Varicella Virus Vaccine Live (Oka/Merck); Merck & Co., Inc.]: Each 0.5 ml dose contains a minimum of 1350 plaque forming units of Oka/Merck varicella virus. The product contains no preservative.
  Lot numbers were identified and recorded at time of use.

6.2.1.5 Immunogenicity Endpoints and Evaluation Criteria

Antibody Assays
Section 5.5 contains a summary of the immunogenicity assay methods and laboratories. Assays have been reviewed by other members of the Pentacel BLA committee.

Prioritization
If the volume of serum obtained was limited, assays were to be prioritized as follows:
- Stage I: PRP, pertussis antigens, diphtheria, tetanus, poliovirus antigens, pneumococcal antigens, and Hepatitis B.
- Stage II: PRP, pertussis antigens, diphtheria, tetanus, pneumococcal antigens, poliovirus antigens, measles, mumps, rubella, and varicella.

Primary Endpoints and Evaluation Criteria

Stage I – no primary endpoints.

Stage II – Non-inferiority of immune response to dose 4 of Pentacel concurrently administered with varicella and MMR vaccines at 15 months of age (Group 2) relative to Pentacel administered alone at 15months of age (Group 1)

Table 57 presents the primary endpoints and non-inferiority criteria for evaluation of immune response following the fourth dose of Pentacel administered alone at 15 months of age (Group 1) compared to the response to Pentacel co-administered with MMR and VARIVAX at 15 months of age (Group 2).

Table 57: Study 494-03 Stage II Primary immunogenicity endpoints and non-inferiority criteria for evaluation of seroconversion/seroprotection rates in Group 1 relative to Group 2

Antigen	Endpoint	Evaluation Criteria
PT FHA FIM Pertactin	% ≥4x rise (post-dose 4 vs. pre-dose 4)	UL 2-sided 90% CI Group 1 minus group 2 <10%
PRP	% ≥ 1ug/mL	UL 2-sided 90% CI Group 1 minus Group 2 <10%
Diphtheria	% ≥0.1 IU/mL	UL 2-sided 90% CI Group 1 minus Group 2 <10%
Tetanus	% ≥0.1 IU/mL	UL 2-sided 90% CI Group 1 minus Group 2 <10%
Polio virus type 1 Polio virus type 2 Polio virus type 3	% ≥1:8 % ≥1:8 % ≥1:8	UL 2-sided 90% CI Group 1 minus Group 2 <5% LL 90% CI >90%

⩾ 4x rise (post dose 4/pre-dose4 titer (pre-dose 1 sera were not collected)
Group 1: MMR, Varicella and Prevnar at 12m, Pentacel at 15m
Group 2: Prevnar at 12m, MMR, Varicella and Pentacel at 15m
Source: 49401si.pdf page 956 and 964

Stage II – Non-inferiority of immune response to dose 4 of Pentacel concurrently administered with Prevnar at 15 months of age (Group 3) relative to Pentacel administered alone at 15 months of age (Group 1)

Table 58 presents the primary endpoints and non-inferiority criteria for evaluation of immune response following the fourth dose of Pentacel administered alone (Group 1) compared to the response to Pentacel co-administered with Prevnar at 15 months of age (Group 3).

Table 58: Study 494-01 Stage II: Primary Immunogenicity endpoints and non-inferiority criteria for evaluation of seroconversion/seroprotection rates in Group 1 relative to Group 3.

Antigen	Endpoint	Evaluation Criteria
PT FHA FIM Pertactin	% ≥4x rise (post-dose 4 vs. pre-dose 4)	UL 2-sided 90% CI Group 1 minus group 2 <10%
PRP	% ≥ 1ug/mL	UL 2-sided 90% CI Group 1 minus Group 2 <10%
Diphtheria	% ≥0.1 IU/mL	UL 2-sided 90% CI Group 1 minus Group 2 <10%
Tetanus	% ≥0.1 IU/mL	UL 2-sided 90% CI Group 1 minus Group 2 <10%
Polio virus type 1 Polio virus type 2 Polio virus type 3	% ≥1:8 % ≥1:8 % ≥1:8	UL 2-sided 90% CI Group 1 minus Group 2 <5%

⩾ 4x rise (post dose 4/pre-dose4 titer (pre-dose 1 sera were not collected)
Group 1: MMR, Varicella and Prevnar at 12m, Pentacel at 15m
Group 3: MMR and Varicella at 12m and Pentacel + Prevnar at 15m
Source: 49401si.pdf page 957 and 965

Secondary Immunogenicity Endpoints and Evaluation Criteria

Stage I – Presentation of anti-PRP, tetanus, diphtheria, and poliovirus seroprotection rates and anti-pertussis GMTs following a third dose of Pentacel.

Stage I - Presentation of seroresponse rates and GMTs following the third dose of Prevnar

Table 59 presents the Stage I immunogenicity endpoints and descriptive evaluation criteria.

Table 59: Study 494-03 Stage I Secondary Immunogenicity endpoints and descriptive analyses following a third dose of Pentacel and Prevnar

Antigen	Endpoint	Descriptive Analyses
PRP	≥0.15 ug/mL ≥1.0 ug/mL	Rate 95% CI
Diphtheria	≥0.01 IU/mL ≥0.1 IU/mL	Rate 95% CI
Tetanus	≥0.01 IU/mL ≥0.1 IU/mL	Rate 95% CI
Polio virus 1 Poliovirus 2 Poliovirus 3	≥1:8 ≥1:8 ≥1:8	Rate 95% CI
PT FHA Fim Pertactin	GMT	GMT 95% CI
Pneumococcal serotype 4, 6B, 9V, 14, 18C, 19F and 23F	≥0.15 ug/mL ≥0.5 ug/mL GMT	Rate 95% CI Rate 95% CI GMT 95% CI

Source: 49403si.pdf page 960

Stage II – Non-inferiority of immune response to Dose 4 Pentacel concurrently administered with varicella and MMR at 15 months of age (Group 2) relative to Pentacel alone at 15 months (Group 1)

Table 60 presents the non-inferiority criteria for evaluation of immune response post-dose 4 Pentacel for Stage II Group 1 relative to Group 2.

Table 60: Study 494-03 Stage II Non-inferiority of immune response post dose 4 Pentacel concurrently administered with varicella and MMR at 15 months of age compared to Pentacel alone at 15 months

Antigen	Endpoint	Non-inferiority criteria
PRP	GMT ratio (Group 2/Group 1)	LL 2-sided 90% CI GMT ratio >2/3 (Study report presents UL <1.5)
PT, FHA, FIM, pertactin		
Diphtheria		
Tetanus		
Polio virus 1 Polio virus 2 Polio virus 3		

Source: 49401.pdf page 961 and 965

Stage II- Non-inferiority of immune response to Dose 4 Pentacel concurrently administered with Prevnar (Group 3) relative to Pentacel alone at 15 months of age (Group 1)

Table 61 presents the non-inferiority criteria for evaluation of immune response post-dose 4 Pentacel for Stage II Study group 3 relative to Stage II Study Group 3.

Table 61: Study 494-03 Stage II Non-inferiority of immune response post dose 4 Pentacel concurrently administered with Prevnar at 15 months of age compared to Pentacel alone at 15 months.

Antigen	Endpoint	Non-inferiority criteria
PRP	GMT ratio (Group 3/Group 1)	LL 2-sided 90% CI GMT ratio >2/3 (Study report presents UL <1.5)
PT, FHA, FIM, pertactin		
Diphtheria		
Tetanus		
Polio virus 1 Polio virus 2 Polio virus 3		

Source: 49401si.pdf page 961 and 966

Stage II – Non-inferiority of the immune response to MMR and varicella when concurrently administered with Pentacel (Group 2) relative to MMR and varicella co-administered with Prevnar (Group 4).

Table 62 presents the non-inferiority criteria for evaluation of immune response to measles, mumps, rubella and varicella when co-administered with Pentacel as compared to co-administration with Prevnar.

Table 62: Study 494-03 Stage II non-inferiority testing of immune response to MMR and varicella when co-administered with Pentacel or Prevnar.

Antigen	Endpoint	Non-inferiority criteria
Measles	% >300 mIU/mL (Group 4 – Group 2)	UL 90% CI difference in seroresponse/seroprotection <5%
Mumps	% >500 mIU/mL (Group 4 – Group 2)	
Rubella	% >10 IU/mL (Group 4 – Group 2)	
Varicella	% ≥300 mIU/mL by ELISA or positive by FAMA (Group 4 – Group 2)	UL 90% CI difference in seroresponse/seroprotection <10%

Source 49401si.pdf page 962 and 966
Note: the power calculations for response to measles and mumps presented in Section 9.6.4.3 of the protocol refer to expected seroresponse rates, the protocol description of the assays Section 8.2.3.81-notes the "measure of interest" as described in this table.

Stage II – Non-inferiority of immune response to a fourth dose of Prevnar when concurrently administered with Pentacel (Group 3) relative to Prevnar co- administered with varicella and MMR (Group 4)

Table 63 presents the non-inferiority criteria for evaluation of immune response to pneumococcal serotypes when co-administered with Pentacel or varicella and MMR.

Table 63: Study 494-01 Stage II Non-inferiority testing of immune response to a fourth dose of Prevnar when co-administered with Pentacel or MMR and varicella

Antigen	Endpoint	Non-inferiority
Pnc 7 serotypes	% ≥0.15 ug/mL (Group 4 – Group 3) % ≥1.0 ug/mL (Group 4 – group 3)	UL 90% CI for difference in seroresponse rates <10%
	*GMT ratio (Group 4/group 3)	UL 90% CI GMT ratio <2.0

Source 49401si.pdf page 962

*The objectives of the protocol (49401si.pdf page 927) refer only to measurement of seroresponse levels ($\geqslant$ 0.15 ug/mL and $\geqslant$ 0.5 ug/mL). The data analysis section however, indicates that both seroresponse and GMTs were to be assessed using non-inferiority criteria.

Observational Immunogenicity Endpoints and Evaluation criteria

Stage I – presentation of anti-HBsAg seroprotection rates post dose 3 when co-administered with Pentacel at 2, 4 and 6 months of age or 2 and 6 months of age.

Table 64: Study 494-03 Stage I Evaluation criteria for assessment of response to hepatitis B vaccine given at 2, 4 and 6 months of age or 0, 2, and 6 months of age.

Antigen	Endpoint	Descriptive Analysis
HBsAg	% ≥10mIU/mL	2,4,6 month vs. 0, 2, 6 month schedule

Stage II – presentation of pertussis antibody decay curves for 7 months, 12 months, 15 months and 16 months bleeds.

Results for antibody to each pertussis antigen presented graphically.

6.2.1.6 Surveillance/Monitoring

Immunogenicity

In Stage I and II serum samples were collected from the first (at least) 348 enrolled subjects 21-48 days after the third dose of study vaccines administered and from all vaccinated subjects at 15 months of age. In the study reports AP acknowledge an error in the protocol: samples were intended to be taken 28-48 days following vaccination (49403si.pdf page 33, 49403sii page 42). AP note that subjects who provided a blood sample 21 to 27 days after vaccines administered at 6 and 15 months of age were not considered protocol violators. In response to a question from CBER sanofi stated that despite this error all subjects included in the PPI provided blood samples 28-48 days post-vaccination. Subjects bled at 7 months were asked to donate another sample at 12 months of age. The immune response to vaccines administered at 12 months of age was not assessed. In Stage II immune responses were assessed only for vaccines administered at 15 months of age. Immune responses were not assessed for vaccines administered at 12 months of age (i.e. MMR_{II}, VARIVAX, and Prevnar for Group 1, Prevnar for Group 2, MMR_{II}, VARIVAX for Group 3) and following Pentacel administered at 16 months of age (Group 4).

6.2.1.7 Statistical Considerations

Samples Size and Statistical Power

The planned enrollment was 1200 subjects in Stage I. An attrition rate of 10% to the end of Stage I and an additional 10% to the end of Stage II was considered for all statistical power calculations. Power calculations presented for Stage I secondary immunogenicity endpoints and

Stage II primary and secondary immunogenicity endpoints are based on 243 subjects per group, and indicated at least 88% power for each endpoint..

Analysis populations

Intent to Treat Immunogenicity population

Stage I and II - The ITT population included subjects who received three or four doses of Pentacel, a post-vaccination blood draw and serology test result for at least one Pentacel antigen (Stage I) or any antigen (Stage II) regardless of whether they adhered to the study eligibility criteria or their immunization and blood draws were within the protocol specified windows.

Per Protocol population

Stage I - The PPI population included all eligible subjects who received three doses of Pentacel, had all doses and a post dose 3 blood draw within windows as specified in the protocol and had a valid serology result for at least one Pentacel antigen.

Stage II – The PPI population included all eligible subjects who received four doses of Pentacel, and had post dose 4 blood sample within window as specified in the protocol, and had a valid serology result for at least one antigen.

Statistical criteria for equivalence and non-inferiority analyses

The protocol-specified statistical criteria for non-inferiority of immune response between Stage II study groups were based on the 90% CIs for the ratios of GMTs and 90% CI for the difference in seroconversion/seroresponse rates. Currently, CBER recommends use of 2-sided 95% CIs for ratios of GMTs for non-inferiority analyses, as well as 2-sided 95% CIs for rate differences for non-inferiority analyses.

6.2.2 Results

6.2.2.1 Populations enrolled/analyzed

Table 65 presents a summary of the ITT and PPI populations in Stage I and II of Study 494-03. The percent of subjects included in the analyses populations relative to the number of sera planned is also noted. The study report notes that due to an audit based on non-conformance of Good Clinical Practices 62 subjects at one of the study centers were excluded from all analyses. During Stage I, 5 of these had received three doses of Pentacel and provided a blood sample post dose 3 (49403si_a.pdf page 244). During Stage II of the study 53 of these subjects were vaccinated, pre-bleed and post bleed samples were obtained from 46 subjects. Subjects enrolled at this center were not included in the table below.

Table 65: Study 494-03 Subject disposition – number of subjects randomized, immunized, bled and included in the immunogenicity populations relative to the number of sera planned.

Stage I*					
Randomized					
and received one dose of Pentacel	1207				
..and received 3 doses of Pentacel	1077				
Number of sera planned	*348 (100%)*				
Received 3 doses of Pentacel and bled post dose 3	**309 (88.8%)**				
Insufficient blood volume	2				
ITT immunogenicity	**307 (88.2%)**				
Protocol violations					
visit out of window interval	33				
PP Immunogenicity Population	**274 (78.7%)**				
Stage II**					
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Pooled Pentacel**
Number of sera planned (based on expected 10% attrition to the end of Stage I and an additional 10% to the end of Stage II)					982 (100%)
Bled pre-dose4	238	244	232	221	935
Received all 4 doses of Pentacel by randomization group[1]	245	247	239	227	958 (97.5%)
Received four doses and bled post dose 4	237	239	229	219	924 (94%)
Invalid test results for all antigens	0	0	0	36	36
ITT immunogenicity[1]	**237**	**239**	**229**	**183**	**888 (90.4%)**
Protocol violations:					
Did not satisfy eligibility criteria	1	1	1	0	3
Tx error	0	2	0	3	5
Visit out of time interval	18	14	13	15	60
other	0	0	1	0	1
PP Immunogenicity Population[2]	**218**	**222**	**214**	**165**	**819 (83.4%)**

*excludes 62 subjects due to site audit (5 of these subjects were bled and excluded from Stage I immunogenicity analyses)

** excludes 53 subjects due to site audit

Percentages are based on the planned number of blood samples during Stage I and Stage II

[1] Stage II ITT immunogenicity population classified by randomized treatment

2 Stage II PP immunogenicity population defined as all eligible subjects who had 4 doses of Pentacel and their 4th dose and post-Dose 4 blood draw were within windows and 15-month vaccination per randomization schedule and had a valid serology test result for at least 1 antigen at post-Dose 4. PP population was used only in the immunogenicity analyses.

Group 1: MMR_{II}, VARIVAX, Prevnar at 12m, Pentacel at 15m
Group 2: Prevnar 12m, MMR_{II}, VARIVAX, Pentacel at 15m
Group 3: MMR_{II}, VARIVAX at 12m, Pentacel and Prevnar at 15m
Group 4: MMR_{II}, VARIVAX, Prevnar at 15m, Pentacel at 16m
Source: 49403si.pdf page 62-63 and 49403sii.pdf page 79-80, September 7, 2006 questions1_133.pdf page 279.

6.2.2.2 Immunogenicity Analyses and Data Presentation

In this review results of the primary and secondary immunogenicity analyses and selected other immunogenicity analyses will be presented. The results of the per-protocol for immunogenicity population will be presented. For all analyses the results for the ITT for immunogenicity population were similar to those obtained for the per-protocol population.

PT antibody levels were generated in the ----- performed in the sanofi pasteur, Canada, laboratory. Because this assay has been determined to be non-specific these data are not acceptable to CBER and are not presented in this review.

Pre-dose 1 blood samples were not obtained in this study.

Stage I – Secondary Immunogenicity Endpoints

Presentation of seroprotection rates following a third dose of Pentacel - Table 66 presents the results of the Stage I secondary immunogenicity analysis of seroprotection rates to PRP, diphtheria, tetanus and polio antigens one month post dose 3 using the PPI population. Over 95% of subjects had seroprotective levels to diphtheria, tetanus and poliovirus serotypes. Approximately 76% of subjects had anti-PRP levels ≥1.0 ug/mL. Seroconversion rates to the pertussis antigens are not presented because no per-vaccination blood sample was available.

Table 66: Study 494-03 Stage I Seroprotection rates to PRP, diphtheria and tetanus and polio virus serotypes one month after three doses of Pentacel administered with Prevnar and hepatitis B vaccine*.

Antigens	Criteria	N	n	Rate %	95% CI
PRP	≥0.15 ug/mL ≥1.0 ug/mL	270 270	255 204	94.4 75.6	(91.0, 96.9) (70.0, 80.6)
Diphtheria	≥0.01 IU/mL ≥0.1 IU/mL	266 266	266 254	100.0 95.5	(98.6, 100) (92.3, 97.6)
Tetanus	≥0.01 IU/mL ≥0.1 IU/mL	264 264	264 262	100.0 99.2	(98.6, 100) (97.3, 99.9)
Polio 1	≥1:8	262	262	100.0	(98.6, 100)
Polio 2	≥1:8	259	259	100.0	(98.6, 100)
Polio 3	≥1:8	255	255	100.0	(98.6, 100)

*Subjects received hepatitis b vaccine at birth, 2 and 6 moths of age or at 2, 4 and 6 months of age.
'N': Number of subjects with available data for the specific test from the PP Immunogenicity Population.
'n ' Number of subjects achieving seroresponse.
Source: 49403si.pdf page 94 and 474

Presentation of anti-PRP, pertussis and poliovirus GMTs following a third dose of Pentacel - The following Table presents the results of the Stage I secondary analyses of GMTs one month post-dose 3 using the PPI population. Following the third dose of Pentacel the GMT for PRP was 2.8 ug/mL. Of note, the bulk lot of ActHIB used in this study was the same as that administered in Study 494-01 as Pentacel lot 3 and also as ActHIB. In Study 494-01 when bulk lot R0181 was administered as ActHIB the anti-PRP GMT was 6.23, % ≥1.0ug/mL 89%, when reconstituted with DTaP-IPV and administered as Pentacel the anti-PRP GMT was 3.64, % ≥1.0 ug/mL 82%.

Table 67: Study 494-03 GMT to PRP, pertussis†, diphtheria, tetanus and polio antigens of Pentacel when co-administered with Prevnar and hepatitis B vaccine* one month post dose 3. PPI population

Antigens	N	GMT	95% CI
PRP (µg/mL)	270	2.80	(2.30, 3.41)
FHA (EU/mL)	270	85.52	(79.02, 92.55)
FIM (EU/mL)	269	243.25	(214.92, 275.32)
PRN (EU/mL)	268	37.84	(33.24, 43.08)
Diphtheria (IU/mL)	266	0.81	(0.71, 0.92)
Tetanus (IU/mL)	264	1.08	(0.96, 1.21)
Polio 1 (1/dil)	262	477.33	(409.08, 556.98)
Polio 2 (1/dil)	259	1090.47	(947.66, 1254.79)
Polio 3 (1/dil)	255	816.07	(696.88, 955.63)

†anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
*Subjects received hepatitis b vaccine at birth, 2 and 6 moths of age or at 2, 4 and 6 months of age.
'N': Number of subjects with available data for the specific test from the PP Immunogenicity Population. Source: 49403si.pdf page 95

Presentation of anti-pneumococcal seroresponse rates one month after a third dose of Prevnar
The following table presents the results of the Stage I secondary objective to describe the anti-pneumococcal seroresponse rate and GMT one month following the third dose of Prevnar. Over 90% of subjects had anti-pneumococcal levels to each serotype ≥0.15 ug/ml. Over 90% of subjects had anti-pneumococcal levels ≥0.5 ug/mL to each serotype with the exception of type 6B. To type 6B 79% of subjects had levels ≥0.5 ug/mL.

Table 68: Study 494-01 Stage I. Anti-pneumococcal seroresponse rates and GMTs one month following the third dose of Prevnar. PPI population.

Pneumococcal Polysaccharide	N	% ≥0.15 ug/mL	%≥0.5 ug/mL	GMT
Serotype 4 (µg/mL)	245	100.0 (98.5, 100)	97.1 (94.2, 98.8)	2.52 (2.27, 2.79)
Serotype 6B (µg/mL)	248	90.7 (86.4, 94.0)	79.0 (73.4, 83.9)	1.83 (1.50, 2.23)
Serotype 9V (µg/mL)	248	100.0 (98.5, 100)	96.8 (93.7, 98.6)	2.17 (1.96, 2.39)
Serotype 14 (µg/mL)	248	99.6 (97.8, 100)	96.4 (93.2, 98.3)	4.83 (4.25, 5.50)
Serotype 18C (µg/mL)	247	99.2 (97.1, 99.9)	97.2 (94.2, 98.9)	3.42 (3.05, 3.83)
Serotype 19F (µg/mL)	248	98.0 (95.4, 99.3)	95.2 (91.7, 97.5)	2.93 (2.57, 3.32)
Serotype 23F (µg/mL)	248	96.4 (93.2, 98.3)	90.3 (85.9, 93.7)	2.23 (1.90, 2.62)

N = number of subjects with available data.
Source: 49401si.pdf page 96, 97 and 475

Stage I – Observational Objective

Presentation of seroprotection rates when hepatitis B vaccine was administered at 2, 4 and 6 months of age or 0, 2, and 6 months of age.

Table 69 presents the seroprotection rates and GMT to HBsAg following the third dose when hepatitis b vaccine was administered at 0, 2 and 6 months of age or at 2, 4, and 6 months of age. Over 98% of subjects had seroprotective levels (≥10 mIU/mL) one month following the third dose irrespective of schedule. When hepatitis b vaccine was administered at 2, 4 and 6 months of age the GMT was 424 mIU/mL compared to 292 mIU/mL when administered at 0, 2 and 6 months of age although the 95% CIs overlap. These data should be interpreted with caution since children were not randomized to the groups and the vaccine administered at birth is not noted. These GMTs appear diminished compared to the response following RECOMBIVAX HB and presented in the Comvax package insert(PI). However, immune response to three doses of RECOMBIVAX HB administered at 0, 2, 6 month or 2, 4 and 6 months is not presented in this PI.

Table 69: Study 494-03 Stage I Anti-hepatitis B seroprotection rates and GMTs one month following the third dose, PPI population.

	0, 2, 6 months schedule*	2, 4, 6 months schedule	All schedules
N	169	83	252
% ≥10m IU/mL (95% CI)	98.2 (94.9, 99.6)	100 (95.7, 100)	98.8 (96.6, 99.8)
GMT mIU/mL (95% CI)	292.01 (232.71, 366.40)	424.31 (317.53, 566.98)	330.25 (275.89, 395.33)

*Hepatitis B vaccine administered at birth is not provided, RECOMBIVAX HB was administered at the other doses

N = number of subjects with available data from the PPI population

Source: 49401si.pdf page 98

Response to PRP: Sanofi pasteur have presented post-hoc analyses of the response to the PRP component of Pentacel based on ethnicity. The results for the PPI population are presented in the Table below. The number of black and Asian subjects is small and while the data suggest race and ethnicity may play a role in the response to PRP, the 95% CI provided for GMT are overlapping and thus the data are too limited to draw a conclusion.

Table 70: Anti-PRP seroprotective levels and GMTs one month post dose 3, PPI population

Race	N	%≥0.15 ug/mL	% ≥1.0 ug/mL	GMT ug/mL (95% CI)
Caucasian	168	91.7	71.4	2.1 (1.64, 2.79)
Black	16	100	75	3.1 (1.41, 6.64)
Hispanic	58	100	84.5	5.5 (3.85, 7.83)
Asian	6	100	100	6.1 (2.49, 14.99)
Other	22	95.5	77.3	2.8 (1.56, 5.20)

95% CI were not provided for the % seroprotected at 0.15 ug/mL or 1.0 ug/mL

Source: 49403si.pdf page 488 and 490

Sanofi pasteur have also analyzed the response to PRP based upon study site. These data are not presented in this review.

Stage II:

Prevaccination antibody levels - Table 71 presents the anti-PRP antibody levels at the time of administration of a fourth dose of Pentacel for study Groups 1, 2 and 3. This information was not provided for subjects enrolled in Group 4 (these subjects received 1st Dose of M-M-R®II and VARIVAX® and 4th Dose of Prevnar® at 15 months, and 4th Dose of Pentacel at 16 months).

Table 71: Study 494-03 Stage II. Anti-PRP levels prior to receipt of the fourth dose of Pentacel for Groups 1, 2 and 3. PPI population

	Group 1 N = 210	**Group 2 N= 215**	**Group 3 N = 209**
PRP % ≥0.15 (95% CI)	83.8 (78.1, 88.5)	74.4 (68.0, 80.1)	75.1 (68.7, 80.8)

Group is defined as per randomization.
Group 1: Received 4th Dose of Pentacel at 15 months (MMR, VARIVAX and Prevnar at 12m).
Group 2: Received 4th Dose of Pentacel concomitantly with the 1st Dose of MMR®II and VARIVAX® at 15 months (Prevnar at 12m).
Group 3: Received 4th Dose of Pentacel concomitantly with the 4th Dose of Prevnar® at 15 months (MMR and varicella at 12 months of age)
Source: 49403sii.pdf page 658

Stage II – Primary Immunogenicity Endpoints

Non-inferiority of seroconversion/seroprotection rates elicited by Pentacel concurrently administered with varicella and MMR vaccines at 15 months compared to Pentacel alone at 15 months - Table 72 presents the results of the primary non-inferiority analyses of response to a fourth dose of Pentacel coadministered with varicella and MMR at 15 months of age (Group 2) relative to Pentacel administered alone at 15 months (Group 1). Using 2-sided 90% CI for the difference in seroconversion/seroprotection rates the statistical criteria for non-inferiority between groups (UL <10% for diphtheria, tetanus, PRP, FHA, fimbriae and pertactin, UL <5% for polio) were met for all antigens. Anti-PT ----- values were generated in a non-specific assay thus, anti-PT seroconversion rates are not presented. Note that the definition for seroresponse to the pertussis antigens used in this study differs from that used in the other pivotal immunogenicity studies, because pre-dose 1 sera were not available seroresponse is defined as post-dose 4 relative to pre-dose 4. Analyses using the 95% CI for the difference in rates were not prespecified in the protocol however, these analyses were provided and are shown in the table. Non-inferiority criteria were not pre-specified in the protocol for anti-PRP levels ≥0.15 ug/mL, anti-diphtheria and anti-tetanus levels ≥1.0 IU/mL.

Table 72: Study 494-03 Stage II Seroconversion/seroprotection rates† and non-inferiority analyses one month following a fourth dose of Pentacel administered alone or concurrently with MMR and VARIVAX at 15 months of age, PPI population.

Antigen	Group 1 (Pentacel alone at 15m)			Group 2 (Pentacel + MMR + VARIVAX at 15m)			Group 1 minus group 2		
	n/N	%	95% CI	n/N	%	95% CI		(90% CI)[2]	(95% CI)
PRP (µg/mL)									
≥ 0.15 ug/mL*	218/218	100.0	(98.3, 100.0)	219/221	99.1	(96.8, 99.9)	0.90	(-0.14, 1.95)	(-0.34, 2.15)
≥ 1.0 ug/mL	216/218	99.1	(96.7, 99.9)	214/221	96.8	(93.6, 98.7)	2.25	(0.04, 4.46)	(-0.38, 4.88)
FHA (EU/mL)									
≥ 4 fold-rise[1]	157/180	87.2	(81.4, 91.7)	160/188	85.1	(79.2, 89.9)	2.12	(-3.80, 8.03)	(-4.93, 9.16)
FIM (EU/mL)									
≥4 fold-rise[1]	157/180	87.2	(81.4, 91.7)	166/188	88.3	(82.8, 92.5)	-1.08	(-6.70, 4.55)	(-7.78, 5.62)
PRN (EU/mL)									
≥4 fold-rise[1]	152/180	84.4	(78.3, 89.4)	166/188	88.3	(82.8, 92.5)	-3.85	(-9.74, 2.03)	(-10.86, 3.16)
Diphtheria									
≥0.1 IU/mL	217/217	100.0	(98.3, 100.0)	221/221	100.0	(98.3, 100.0)	0.00	NA	NA
≥ 1.0 IU/mL*	214/217	98.6	(96.0, 99.7)	217/221	98.2	(95.4, 99.5)	0.43	(-1.54, 2.40)	(-1.92, 2.77)
Tetanus									
≥ 0.1 IU/mL	215/215	100.0	(98.3, 100.0)	222/222	100.0	(98.4, 100.0)	0.00	NA	NA
≥ 1.0 IU/mL*	202/215	94.0	(89.9, 96.7)	198/222	89.2	(84.3, 92.9)	4.76	(0.42, 9.11)	(-0.42, 9.94)
Polio 1 (1/dil)≥1:8	218/218	100.0	(98.3, 100.0)	222/222	100.0	(98.4, 100.0)	0.00	NA	NA
Polio 2 (1/dil) ≥1:8	218/218	100.0	(98.3, 100.0)	222/222	100.0	(98.4, 100.0)	0.00	NA	NA
Polio 3 (1/dil) ≥1:8	218/218	100.0	(98.3, 100.0)	220/220	100.0	(98.3, 100.0)	0.00	NA	NA

†anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

[1] The fold-rise is calculated by post-Dose 4/pre-Dose 4 titer (pre-Dose 1 samples were not collected).

[2] Non-inferiority: Upper limit of the two-sided 90% CI of Group 1–Group 2 <10% (or 5% for Polio 1, Polio 2 and Polio 3).

*Criteria for non-inferiority were not pre-specified in the protocol.

Groups are defined as per randomization. Group 1 received Pentacel at 15 months of age (Prevnar, MMR and varicella at 12m), Group 2 received Pentacel, MMR and varicella at 15 months of age (Prevnar at 12m)

Source: 49403sii.pdf page 83 and 84

Non-inferiority of seroconversion/seroprotection rates elicited by Pentacel concurrently administered with Prevnar at 15 months of age compared to Pentacel alone at 15 months – Table 73 presents the results of the primary non-inferiority analyses of response to a fourth dose of Pentacel coadministered with Prevnar at 15 months of age (Group 3) relative to Pentacel administered alone at 15 months (Group 1). Anti-PT ----- values were generated in a non-specific assay thus anti-PT seroconversion rates are not presented. Using 2-sided 90% CI for the difference in seroconversion/seroprotection rates the statistical criteria for non-inferiority between groups (UL <10% for diphtheria, tetanus, PRP, and pertussis antigens, UL <5% for polio) was met for all antigens except fimbriae. The UL of the 90% CI on the difference between seroresponse of group 1 subjects minus group 3 was 13.1%. Non-inferiority criteria were not pre-specified in the protocol for anti-PRP levels ≥ 0.15 ug/mL, anti-diphtheria and anti-tetanus levels ≥ 1.0 IU/mL. Analyses using the 2-sided 95% CI for the difference in rates were not specified in the protocol however, these were provided and are included in the table below.

Table 73: Study 494-03 Stage II. Seroconversion/seroprotection rates† and non-inferiority analyses one month following a fourth dose of Pentacel administered alone or concurrently with Prevnar at 15 months, PPI population.

Antigen	Group 1 (Pentacel alone at 15m)			Group 3 (Pentacel + Prevnar at 15m)			Group 1 minus Group 3 (90% CI)[2]		
	n/N	%	(95% CI)	N/n	%	(95% CI)		(90% CI)	(95% CI))
PRP (µg/mL) ≥0.15 ug/mL*	218/218	100.0	(98.3, 100.0)	211/213	99.1	(96.6, 99.9)	0.94	(-0.15, 2.03)	(-0.36, 2.23)
≥1.0 ug/mL	216/218	99.1	(96.7, 99.9)	208/213	97.7	(94.6, 99.2)	1.43	(-0.58, 3.44)	(-0.97, 3.82)
FHA (EU/mL) ≥4 fold-rise[1]	157/180	87.2	(81.4, 91.7)	159/184	86.4	(80.6, 91.0)	0.81	(-5.02, 6.64)	(-6.14, 7.76)
FIM (EU/mL) ≥4 fold-rise[1]	157/180	87.2	(81.4, 91.7)	148/184	80.4	(74.0, 85.9)	6.79	(0.47, 13.10)	(-0.74, 14.31)
PRN (EU/mL) ≥4 fold-rise[1]	152/180	84.4	(78.3, 89.4)	150/184	81.5	(75.1, 86.9)	2.92	(-3.55, 9.40)	(-4.79, 10.64)
Diphtheria									
≥0.1 IU/mL	217/217	100.0	(98.3, 100.0)	212/212	100.0	(98.3, 100.0)	0.00	NA	NA
≥1.0 IU/mL*	214/217	98.6	(96.0, 99.7)	203/212	95.8	(92.1, 98.0)	2.86	(0.24, 5.49)	(-0.26, 5.99)
Tetanus									
≥0.1 IU/mL	215/215	100.0	(98.3, 100.0)	210/210	100.0	(98.3, 100.0)	0.00	NA	NA
≥1.0 IU/mL*	202/215	94.0	(89.9, 96.7)	191/210	91.0	(86.2, 94.5)	3.00	(-1.21, 7.21)	(-2.02, 8.02)
Polio 1 (1/dil)≥1:8	218/218	100.0	(98.3, 100.0)	211/211	100.0	(98.3, 100.0)	0.00	NA	NA
Polio 2 (1/dil) ≥1:8	218/218	100.0	(98.3, 100.0)	210/210	100.0	(98.3, 100.0)	0.00	NA	NA
Polio 3 (1/dil) ≥1:8	218/218	100.0	(98.3, 100.0)	209/210	99.5	(97.4, 100.0)	0.48	(-0.31, 1.26)	(-0.45, 1.41)

†anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, these anti-PT values are not acceptable to CBER. See *Section 5.5*

[1] The fold-rise is calculated by post-Dose 4/pre-Dose 4 titer (pre-Dose 1 results were not collected).

[2] Non-inferiority: Upper limit of the two-sided 90% CI of Group 1–Group 3 <10% (or 5% for Polio 1, Polio 2 and Polio 3).

Group is defined as per randomization. **Group 1:** Received 4th Dose of Pentacel at 15 months (MMR, varicella and Prevnar at 12m). **Group 3**: Received 4th Dose of Pentacel concomitantly with the 4th Dose of Prevnar® at 15 months (MMR and varicella at 12 months of age)

'n' is the number of subjects who met the criteria of the test indicated.

'N' is the total number of subjects with available serology data from the PP Immunogenicity Population.

Shaded cell: pre-defined non-inferiority criterion not met.

*Non-inferiority criteria were not prespecified for this endpoint.

Source: 49403sii.pdf page 86, 87, 681 and 683

Stage II Secondary Immunogenicity Endpoints

Non-inferiority of immune response elicited by Pentacel concurrently administered with MMR and varicella vaccine at 15 months of age compared to Pentacel alone at 15 months. Table 74 presents the secondary non-inferiority analyses comparing the GMTs elicited by Pentacel when the 4th dose was co-administered with varicella and MMR (Stage II, Group 2) or administered alone at 15 months (Stage II Group 1). Anti-PT ----- values were generated in a non-specific assay thus, PT GMTs are not presented.

For all comparisons except GMT to PRP and polio serotype 1 non-inferiority of Group 2 relative to Group 1 was demonstrated. Following co-administration of MMR_{II} and VARIVAX with a fourth dose of Pentacel the GMT to PRP and polio did not meet the pre-defined criteria for non-inferiority using the 2-sided 90% CI for the ratio. Although the 90% CI on the GMT ratio was prespecified in the protocol the manufacturer has also supplied the 95% CI on the ratio which is provided in the table below. Over 95% of subjects in both groups had anti-PRP seroprotective levels $\geqslant$ 1.0 ug/mL thus it is likely that the lower GMT response is not clinically relevant. Over 99% of subjects in both groups had protective levels of antibodies to polio types 1, 2 and 3 thus the difference in GMT levels is not likely to be clinically relevant.

Table 74: Study 494-03 Stage II: GMT response† to a fourth dose of Pentacel when administered alone or concurrently with MMR and Varicella at 15 months of age. PPI population.

Antigen	Group 1 (Pentacel at 15m)			Group 2 (Pentacel + MMR + VARIVAX at 15m)			Group 1/ Group 2[1]		
	N	GMT	(95% CI)	N	GMT	(95% CI)		(90% CI)	(95% CI)
PRP (µg/mL)	218	36.69	(30.99, 43.42)	221	30.26	(24.80, 36.93)	1.21	(0.97, 1.51)	(0.93, 1.57)
FHA (EU/mL)	203	134.47	(120.76, 149.74)	205	138.95	(124.42, 155.19)	0.97	(0.85, 1.10)	(0.83, 1.13)
FIM (EU/mL)	203	434.35	(372.93, 505.89)	205	439.30	(377.33, 511.45)	0.99	(0.83, 1.18)	(0.80, 1.23)
PRN (EU/mL)	203	76.44	(66.01, 88.52)	205	91.54	(79.14, 105.87)	0.84	(0.70, 0.99)	(0.68, 1.03)
Diphtheria (IU/mL)	217	7.83	(6.98, 8.78)	221	6.44	(5.71, 7.26)	1.22	(1.06, 1.40)	(1.03, 1.44)
Tetanus (IU/mL)	215	3.37	(3.01, 3.78)	222	2.89	(2.59, 3.21)	1.17	(1.02, 1.33)	(1.00, 1.37)
Polio 1 (1/dil)	218	3155.96	(2622.89, 3797.38)	222	2508.81	(2092.54, 3007.90)	1.26	(1.01, 1.56)	(0.97, 1.63)
Polio 2 (1/dil)	218	5052.42	(4260.81, 5991.09)	222	4108.87	(3507.46, 4813.40)	1.23	(1.01, 1.49)	(0.98, 1.55)
Polio 3 (1/dil)	218	4878.75	(4001.79, 5947.88)	220	6356.88	(5000.22, 8081.64)	0.77	(0.59, 1.00)	(0.56, 1.05)

†anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

[1] Non-inferiority: Upper limit of the two-sided 90% CI of the GMT ratio is <1.5.

Shaded cells: Pre-defined non-inferiority criteria not met.

Group is defined as per randomization.

Group 1: Received 4th Dose of Pentacel at 15 months (MMR, VARIVAX and Prevnar at 12m).

Group 2: Received 4th Dose of Pentacel concomitantly with the 1st Dose of MMR®II and VARIVAX® at 15 months (Prevnar at 12m).

GMTs are based on the number of subjects with available serology data from the PP Immunogenicity Population.

Source: 49403sii.pdf page 89 and 689,

Non-inferiority of immune response to Pentacel concurrently administered with Prevnar at 15 months of age compared to Pentacel alone at 15 months of age. Table 75 presents the secondary non-inferiority analyses comparing the GMTs elicited by Pentacel when the fourth dose was co-administered with Prevnar (Group 3) or administered alone at 15 months of age (Group 1). Using the protocol specified 2-sided 90% CI on the ratio of GMTs the response to PRP, fimbriae, diphtheria and the polio antigens when Pentacel was coadministered with Prevnar did not meet the prespecified criteria for non-inferiority. Anti-PT ----- values were generated in a non-specific assay thus, neither anti-PT GMTs nor an assessment of non-inferiority of response to PT are presented. CBER currently requests analyses of non-inferiority using a 2-sided 95% CI on the ratio of the difference, this information was provided by the manufacturer and is included in the table below.

Table 75: Study 494-03 Stage II GMT response† to a fourth dose of Pentacel when administered alone or concurrently with Prevnar at 15 months of age. PPI population.

Antigen	Group 1 (Pentacel at 15m)			Group 3 (Pentacel + Prevnar at 15m)			Group 1/Group 3[1]		
	N	GMT	(95% CI)	N	GMT	(95% CI)		90% CI	95% CI
PRP (µg/mL)	218	36.69	(30.99, 43.42)	213	26.40	(21.66, 32.18)	1.39	(1.12, 1.73)	(1.07, 1.80)
FHA (EU/mL)	203	134.47	(120.76, 149.74)	202	128.12	(113.79, 144.24)	1.05	(0.92, 1.20)	(0.89, 1.23)
FIM (EU/mL)	203	434.35	(372.93, 505.89)	202	324.96	(273.72, 385.78)	1.34	(1.10, 1.62)	(1.06, 1.68)
PRN (EU/mL)	203	76.44	(66.01, 88.52)	202	69.63	(59.81, 81.06)	1.10	(0.92, 1.31)	(0.89, 1.36)
Diphtheria (IU/mL)	217	7.83	(6.98, 8.78)	212	5.36	(4.67, 6.15)	1.46	(1.26, 1.70)	(1.22, 1.74)
Tetanus (IU/mL)	215	3.37	(3.01, 3.78)	210	3.19	(2.86, 3.56)	1.06	(0.93, 1.21)	(0.90, 1.24)
Polio 1 (1/dil)	218	3155.96	(2622.89, 3797.38)	211	2212.37	(1874.77, 2610.76)	1.43	(1.16, 1.76)	(1.11, 1.83)
Polio 2 (1/dil)	218	5052.42	(4260.81, 5991.09)	210	3685.45	(3165.29, 4291.08)	1.37	(1.13, 1.66)	(1.09, 1.72)
Polio 3 (1/dil)	218	4878.75	(4001.79, 5947.88)	210	3571.79	(2967.39, 4299.31)	1.37	(1.09, 1.71)	(1.04, 1.79)

†anti-PT values generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

[1] Non-inferiority: Upper limit of the two-sided 90% CI of the GMT ratio is <1.5.

Shaded cells: per-defined non-inferiority criteria not met.

Group is defined as per randomization.

Group 1: Received 4th Dose of Pentacel at 15 months (MMR, VARIVAX and Prevnar at 12m).

Group 3: Received 4th Dose of Pentacel concomitantly with the 4th Dose of Prevnar® at 15 months (MMR and VARIVAX at 12m).

GMTs are based on the number of subjects with available serology data from the PP Immunogenicity Population. Source: 49403sii.pdf page 689

Non-inferiority of immune response to MMR and VARIVAX when concurrently administered with Pentacel (Group 2) relative to MMR and VARIVAX co-administered with Prevnar at 15 months (Group 4). Table 76 presents the secondary non-inferiority analyses comparing the response to measles, mumps, rubella and varicella antigens when Pentacel is coadministered with MMR and VARIVAX to the response when MMR and VARIVAX are administered with Prevnar at 15 months of age.

For measles and mumps, Table 76 includes analyses of seroconversion rates based on ELISA only, as specified in the protocol, as well as analyses of seroconversion rates based on ELISA or neutralization assay. In the latter analyses, sera with an ELISA antibody level <300 mIU/mL for measles and <500 EU/mL for mumps were re-tested in a neutralization assay, and the definitions for seroconversion were based on the results of either assay, as indicated in Table 76. The final study report indicates that the criteria for non-inferiority for measles and mumps seroresponse rates were based on definitions of seroconversion by either ELISA or neutralization assay. However, these definitions and analyses were not pre-specified in the protocol although an amendment to the IND indicated sanofi pasteur's intention to perform these assays for neutralizing antibodies.

In the protocol, for measles, mumps, and rubella, the definitions of seroresponse were based on the proportion of subjects with antibody titers greater than pre-specified thresholds, as specified earlier in Table 62. According to the protocol, subjects with antibody titers lower than or equal to these thresholds were to be considered seronegative. However, in the analyses of seroresponse rates for measles, mumps, and rubella (Table 76), subjects with antibody titers greater than or equal to the specified thresholds were considered seropositive. In response to a query by CBER sanofi state that the appropriate definition of seroresponse rate was subjects with antibody titers greater than or equal to the specified thresholds (September 7, 2006 questions1_133.pdf page 91-93).

The expected mumps seroconversion rate (by ELISA) used in the protocol for statistical power calculations was 98.4%. Of note were the lower than expected mumps seroconversion rates (by ELISA) observed in both study groups (i.e., 71.4% in Stage II Group 2 and 69.4% in Stage II Group 4) and the missed non-inferiority criterion for Group 2 (Pentacel, MMR_{II} and VARIVAX concomitantly) relative to Group 4 (Prevnar, MMR_{II} and VARIVAX concomitantly) (Table 76). Using a criterion (not pre-specified) for mumps seroresponse based on either ELISA or neutralization assay, the observed seroresponse rates (i.e., 98.1% in Stage II Group 2 and 97.2% in Stage II Group 2) the upper limits of the confidence intervals (90% or 95%) for the difference between groups (Group 4 minus Group 2) were < 5% (Table 76).

The analyses indicated that co-administration of MMR and VARIVAX with Pentacel did not adversely affect the seroresponse rates for measles, rubella and varicella (Table 76), although the thresholds used for seroresponse differed from those specified in the protocol, as discussed above.

Table 76: Study 494-03 Stage II Seroresponse to measles, mumps, rubella and varicella one month following vaccination at 15 months of age. PPI population.

Antigen and Criteria for seroresponse	Group 2 (Pentacel + MMR + VARIVAX at 15m)			Group 4 (MMR + VARIVAX + Prevnar at 15m)			Group 4 – Group 2[1]		
	n/N	%	(95% CI)	n/N	%	(95% CI)		90% CI	95% CI
Measles									
ELISA ≥150 mIU/mL	152/154	98.7	(95.4, 99.8)	140/144	97.2	(93.0, 99.2)	-1.48	(-4.19, 1.23)	(-4.70, 1.75)
ELISA ≥300 mIU/mL[2]	152/154	98.7	(95.4, 99.8)	140/144	97.2	(93.0, 99.2)	-1.48	(-4.19, 1.23)	(-4.70, 1.75)
Neutralization ≥120 mIU/mL	0/2	0.0	NA	1/4	25.0	(0.6, 80.6)	NA		
ELISA ≥150 mIU/mL or neutralization ≥120 mIU/mL	152/154	98.7	(95.4, 99.8)	141/144	97.9	(94.0, 99.6)	-0.78	(-3.25, 1.68)	(-3.72, 2.15)
ELISA ≥300 or Neutralization ≥120 mIU/mL[3]	152/154	98.7	(95.4, 99.8)	141/144	97.9	(94.0, 99.6)	-0.78	(-3.25, 1.68)	(-3.72, 2.15)
Mumps									
ELISA ≥500 EU/mL[2]	110/154	71.4	(63.6, 78.4)	100/144	69.4	(61.2, 76.8)	-1.98	(-10.69, 6.72)	(-12.35, 8.38)
Neutralization ≥60 1/dil	41/44	93.2	(81.3, 98.6)	40/44	90.9	(78.3, 97.5)	NA		
ELISA ≥500 U/mL or Neutralization ≥60 (1/dil)[3]	151/154	98.1	(94.4, 99.6)	140/144	97.2	(93.0, 99.2)	-0.83	(-3.73, 2.07)	(-4.29, 2.63)
Rubella									
≥10 IU/mL[2]	149/154	96.8	(92.6, 98.9)	140/144	97.2	(93.0, 99.2)	0.47	(-2.79, 3.72)	(-3.41, 4.35)
Varicella									
ELISA ≥ 300 mIU/mL	49/154	31.8	(24.6, 39.8)	43/144	29.9	(22.5, 38.0)	-1.96	(-10.76, 6.84)	(-12.44, 8.53)
FAMA ≥4 1/dil	94/103	91.3	(84.1, 95.9)	92/100	92.0	(84.8, 96.5)			
ELISA ≥300 mIU/mL or FAMA ≥4(1/dil) [2]	143/154	92.9	(87.6, 96.4)	135/144	93.8	(88.5, 97.1)	0.89	(-3.87, 5.65)	(-4.78, 6.57)

[1] Non-inferiority: Upper limit of the two-sided 90% CI of Group 4–Group 2 <5% (except <10% for Varicella).
[2] Protocol defined criteria for seroresponse except Measles, mumps and rubella seroresponse defined as >300 mIU/mL, >500 EU/mL and >10 mIU/mL respectively.
[3] Non-inferiority analyses presented in the study report.
Group is defined as per randomization. **Group 2:** Received 4th Dose of Pentacel concomitantly with the 1st Dose of MMR_{II} and VARIVAX at 15 months.
Group 4: Received 1st Dose of MMR_{II} and VARIVAX and 4th Dose of Prevnar® at 15 months, and 4th Dose of Pentacel at 16 months.
'n' is the number of subjects who met the criteria of the test indicated.
'N' is the total number of subjects with available serology data from the PP Immunogenicity Population.
NA – not available
Source 49403sii.pdf page 93, 664, 665, 692, 693

A presentation of GMTs pre and post vaccination is included in the Statistical Tables and Figures section of the study report. The post vaccination GMTs to mumps, measles, rubella and varicella were similar following receipt of MMR and VARIVAX administered with Pentacel or Prevnar (overlapping 95% CI of the GMT) (Table 77). No analyses of GMTs were prespecified.

Table 77: Study 494-03 Stage II GMTs of mumps, measles, rubella and varicella antigens pre and post the first dose administered at 15 months of age in group 2 and 3

Antigen	Per-vaccination (15m)		Post-vaccination (16m)	
	N	GMT (95% CI)	N	GMT (95% CI)
Measles mIU/mL				
Group 2	157	75.00 (75.00, 75.00)	154	2744.15 (2462.46, 3058.05)
Group 4	122	75.89 (74.14, 77.68)	144	2514.61 (2193.65, 2882.52)
Mumps EU/mL				
Group 2	157	125.70 (124.32, 127.11)	154	802.49 (689.37, 934.17)
Group 4	122	125.00 (125.00, 125.00)	144	738.16 (633.08, 860.68)
Rubella IU/mL				
Group 2	157	4.00 (4.00, 4.00)	154	55.03 (47.73, 63.45)
Group 4	122	4.00 (4.00, 4.00)	144	62.38 (54.57, 71.29)
Varicella mIU/mL				
Group 2	157	25.00 (25.00, 25.00)	154	217.80 (194.32, 244.12)
Group 4	122	25.00 (25.00, 25.00)	144	204.64 (180.30, 232.26)

Group is defined as per randomization.
Group 2: Received 4th Dose of Pentacel concomitantly with the 1st Dose of M-M-R® and VARIVAX® at 15 months.
Group 4: Received 1st Dose of M-M-R® and VARIVAX® and 4th Dose of Prevnar® at 15 months, and 4th Dose of Pentacel at 16 months.
GMTs are based on the number of subjects with available serology data from PP Immunogenicity Population.
Source 49403sii.pdf page 677

Non-inferiority of immune response to a fourth dose of Pnuemococcal conjugate vaccine when concurrently administered with Pentacel (Group 3) relative to pneumococcal conjugate vaccine concurrently administered with varicella and MMR (Group 4). The minimum serum antibody level necessary for protection against pneumococcal disease for any serotype has not been determined. However, antibody levels $\geqslant$ 0.15ug/mL and $\geqslant$0.5 ug/mL were prespecified for the analysis of seroresponse to the serotypes contained in US-licensed vaccine Prevnar.

Table 78 presents the secondary non-inferiority analyses of seroresponse rates for the pneumococcal serotypes following a fourth dose of Prevnar administered with Pentacel relative to a fourth dose of Prevnar concurrently administered with varicella and MMR at 15 months of age. The protocol specified that non-inferiority be based on the UL of the 2-sided 90% CI of the difference in rates. For each pneumococcal serotype the non-inferiority criterion were met. Although not specified in the protocol the manufacturer also provided the 95% CI on the difference in rates. Approximately 30% of subjects were excluded from these analyses (Group 3 PPI = 214), fewer subjects were excluded from group 4 (Group 4 PPI = 165), no explanation or assessment of the characteristics of this population have been provided.

Table 78: Study 494-03 Stage II Anti-pneumococcal seroresponse rates following the fourth dose of Prevnar and non-inferiority analyses, PPI population.

Antigen	Group 3 (Pentacel + Prevnar at 15m)			Group 4 (MMR + VARIVAX + Prevnar at 15m)			Group 4- Group 3[1]		
	n/N	%	(95% CI)	n/N	%	(95% CI)		90% CI	95% CI
Serotype 4									
≥ 0.15 ug/mL	155/155	100.0	(97.6, 100.0)	158/158	100.0	(97.7, 100.0)	0.0	NA	NA
≥ 0.5 ug/mL	153/155	98.7	(95.4, 99.8)	157/158	99.4	(96.5, 100.0)	0.66	(-1.16, 2.47)	(-1.51, 2.82)
Serotype 6B									
≥0.15 ug/mL	151/155	97.4	(93.5, 99.3)	157/158	99.4	(96.5, 100.0)	1.95	(-0.39, 4.29)	(-0.84, 4.73)
≥0.5 ug/mL	148/155	95.5	(90.9, 98.2)	154/158	97.5	(93.6, 99.3)	1.98	(-1.44, 5.41)	(-2.10, 6.07)
Serotype 9V									
≥0.15 ug/mL	155/155	100.0	(97.6, 100.0)	158/158	100.0	(97.7, 100.0)	0.0	NA	NA
≥0.5 ug/mL	153/155	98.7	(95.4, 99.8)	157/158	99.4	(96.5, 100.0)	0.66	(-1.16, 2.47)	(-1.51, 2.82)
Serotype 14									
≥0.15 ug/mL	155/155	100.0	(97.6, 100.0)	158/158	100.0	(97.7, 100.0)	0.0	NA	NA
≥0.5 ug/mL	154/155	99.4	(96.5, 100.0)	158/158	100.0	(97.7, 100.0)	0.65	(-0.41, 1.70)	(-0.62, 1.91)
Serotype 18C									
≥0.15 ug/mL	155/155	100.0	(97.6, 100.0)	157/158	99.4	(96.5, 100.0)	-0.63	(-1.67, 0.40)	(-1.87, 0.60)
≥0.5 ug/mL	153/155	98.7	(95.4, 99.8)	156/158	98.7	(95.5, 99.8)	0.02	(-2.06, 2.11)	(-2.46, 2.51)
Serotype 19F									
≥0.15 ug/mL	155/155	100.0	(97.6, 100.0)	157/158	99.4	(96.5, 100.0)	-0.63	(-1.67, 0.40)	(-1.87, 0.60)
≥0.5 ug/mL	151/155	97.4	(93.5, 99.3)	152/158	96.2	(91.9, 98.6)	-1.22	(-4.48, 2.05)	(-5.10, 2.67)
Serotype 23F									
≥0.15 ug/mL	153/155	98.7	(95.4, 99.8)	156/158	98.7	(95.5, 99.8)	0.02	(-2.06, 2.11)	(-2.46, 2.51)
≥0.5 ug/mL	148/155	95.5	(90.9, 98.2)	151/158	95.6	(91.1, 98.2)	0.09	(-3.76, 3.93)	(-4.49, 4.67)

[1] Non-inferiority: Upper limit of the two-sided 90% CI of Group 4–Group 3 <10%. Bold protocol specified 90% CI on difference in rates.
Group is defined as per randomization.
Group 3: Received 4th Dose of Pentacel concomitantly with the 4th Dose of Prevnar® at 15 months.
Group 4: Received 1st Dose of M-M-R®II and VARIVAX® and 4th Dose of Prevnar® at 15 months, and 4th Dose of Pentacel at 16 months.
'n' is the number of subjects who met the criteria of the test indicated.
'N' is the total number of subjects with available serology data from the PP Immunogenicity Population. NA = Not Applicable.
Source 49403sii.pdf page 95, 697, 699

Table 79 presents the GMTs to each pnuemococcal serotype one month following a fourth dose of Prevnar administered with Pentacel relative to a fourth dose of Prevnar concurrently administered with varicella and MMR at 15 months of age. Although not noted as a study objective the protocol included non-inferiority of pneumococcal serotypes based on the UL of the 2-sided 90% CI of the ratio of GMTs $\leq$ 2.0. For each pneumococcal serotype these non-inferiority criteria were met. The manufacturer also provided the 95% CI on the difference in ratio of GMTs. Approximately 30% of subjects were excluded from these analyses (Group 3 PPI = 214), fewer subjects were excluded from group 4 (Group 4 PPI = 165), no explanation or assessment of the characteristics of this population have been provided.

Table 79: Study 494-03 Stage II Anti-pneumococcal GMTs following the fourth dose of Prevnar and non-inferiority analyses, PPI population.

Antigen	Group 3			Group 4			Group 4/Group 3		
	N	GMT	(95% CI)	N	GMT	(95% C)	ratio	(90% CI)	(95% CI)
Serotype 4	155	5.11	(4.44, 5.88)	158	6.55	(5.69, 7.54)	1.28	(1.09, 1.51)	(1.05, 1.56)
Serotype 6B	155	9.46	(7.67, 11.66)	158	11.93	(9.92, 14.35)	1.26	(1.00, 1.59)	(0.96, 1.67)
Serotype 9V	155	5.45	(4.76, 6.24)	158	7.01	(6.19, 7.93)	1.29	(1.10, 1.50)	(1.07, 1.54)
Serotype 14	155	13.92	(12.02, 16.13)	158	15.43	(13.23, 17.99)	1.11	(0.93, 1.32)	(0.90, 1.37)
Serotype 18C	155	5.26	(4.54, 6.09)	158	6.24	(5.38, 7.24)	1.19	(1.00, 1.41)	(0.96, 1.46)
Serotype 19F	155	5.44	(4.62, 6.40)	158	6.96	(5.73, 8.46)	1.28	(1.04, 1.58)	(0.99, 1.65)
Serotype 23F	155	6.16	(5.02, 7.55)	158	7.40	(6.16, 8.89)	1.20	(0.96, 1.51)	(0.91, 1.58)

[1] Non-inferiority: Upper limit of the two-sided 90% CI of the GMT ratio is <2.0
Notes: Group is defined as per randomization.
Group 3: Received 4th Dose of Pentacel concomitantly with the 4th Dose of Prevnar® at 15 months.
Group 4: Received 1st Dose of M-M-R®II and VARIVAX® and 4th Dose of Prevnar® at 15 months, and 4th Dose of Pentacel at 16 months.
GMTs are based on the number of subjects with available serology data from the PP Immunogenicity Population.
Source 49403sii.pdf page 98 and 705

Stage II Observational Endpoints

Presentation of antibody decay curves for each pertussis antigen. The BLA contains a graphical presentation of the GMTs to each pertussis antigen at 7 months, 12 months 15 months and 16 months of age.
This data for group 1, 2 and 3 together with the PRP GMTs is presented below in tabular form (Table 80). Table 80 also summarizes the post-dose 3, pre-dose 4 and post-dose 4 GMT to diphtheria toxoid, tetanus toxoid and polio antigens.

The GMT to PRP, FHA, fimbriae and pertactin decreases following vaccination at 6 months until 12 months of age, there is a further decease until revaccination. Anti-PT ----- values were generated in a non-specific assay thus, anti-PT values are not presented.

Table 80: Study 494-03 Antibody levels to each of the antigens* of Pentacel at 7 months, 12 months, 15 months and 16 months of age for subjects in the PPI population

Antigen	7months		12 months		15 months		16 months	
	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
PRP ug/mL								
Group 1	60	2.89 (1.93, 4.32)	56	0.62 (0.42, 0.92)	210	0.56 (0.46, 0.69)	218	36.69
Group 2	65	3.09 (2.03, 4.70)	55	0.53 (0.35, 0.81)	215	0.44 (0.35, 0.55)	221	30.26
Group 3	64	3.06 (1.97, 4.75)	52	0.70 (0.45, 1.09)	209	0.45 (0.36, 0.56)	213	26.40
FHA EU/mL								
Group 1	60	90.42 (77.92, 104.92)	56	26.50 (21.69, 32.38)	193	12.34 (10.88, 13.99)	203	134.47 (120.76, 149.74)
Group 2	56	90.26 (78.50, 103.78)	55	26.50 (21.69, 32.38)	202	14.20 (12.43, 16.21)	205	138.95 (124.42, 155.19)
Group 3	193	86.54 (75.02, 99.83)	53	23.86 (18.40, 30.95)	191	11.85 (10.20, 13.78)	202	128.12 (113.79, 144.24)
FIM EU/mL								
Group 1	60	251.22 (201.67, 312.94)	55	58.49 (47.55, 71.94)	193	31.76 (27.50, 36.68)	203	434.35 (372.93, 505.89)
Group 2	66	256.66 (205.64, 320.35)	55	52.54 (41.74, 66.13)	202	35.07 (30.27, 40.63)	205	439.30 (377.33, 511.45)
Group 3	64	207.74 (155.22, 278.05)	53	59.74 (44.38, 80.41)	191	32.02 (27.50, 37.28)	202	324.96 (273.72, 385.78)
Pertactin EU/mL								
Group 1	60	39.07 (30.29, 50.40)	56	10.79 (7.95, 14.63)	193	6.61 (5.70, 7.66)	203	76.44 (66.01, 88.52)
Group 2	66	39.49 (30.47, 51.19)	55	9.24 (6.92, 12.33)	202	7.42 (6.35, 8.67)	205	91.54 (79.14, 105.87)
Group 3	63	28.96 (21.99, 38.16)	53	8.36 (6.02, 11.61)	191	5.91 (5.03, 6.93)	202	69.63 (59.81, 81.06)
Dip Toxoid IU/mL								
Group 1	59	0.89 (0.66, 1.21)		NA	212	0.59 (0.51, 0.67)	217	7.83 (6.98, 8.78)
Group 2	65	0.70 (0.53, 0.93)		NA	213	0.49 (0.42, 0.57)	221	6.44 (5.71, 7.26)
Group 3	64	0.70 (0.57, 0.86)		NA	0.49	0.12 (0.11, 0.14)	212	5.36 (4.67, 6.15)
Tet toxoid IU/mL								
Group 1	58	1.04 (0.84, 1.28)		NA	204	0.24 (0.21, 0.27)	215	3.37 (3.01, 3.78)
Group 2	65	1.00 (0.79, 1.27)		NA	209	0.23 (0.20, 0.26)	222	2.89 (2.59, 3.21)
Group 3	62	1.02 (0.79, 1.32)		NA	200	0.23 (0.20, 0.26)	210	3.19 (2.86, 3.56)
Polio 1								
Group 1	57	416.37 (288.24, 601.46)		NA	212	90.81 (74.56, 110.61)	218	3155.96 (2622.89, 3797.38)
Group 2	65	409.29 (292.14, 573.43)		NA	218	72.68 (59.91, 88.18)	222	2508.81 (2092.54, 3007.90)
Group 3	62	395.91 (291.51, 537.69)		NA	208	60.68 (48.65, 75.69)	210	2212.37 (1874.77, 2610.76)
Polio 2								
Group 1	56	1049.66 (744.45, 1480.02)		NA	212	182.79 (152.37, 219.29)	218	5052.42 (4260.81, 5991.09)
Group 2	64	975.32 (733.93, 1296.09)		NA	218	152.96 (128.09, 182.65)	222	4108.87 (3507.46, 4813.40)
Group 3	61	1121.44 (824.27, 1525.74)		NA	206	175.32 (145.06, 211.89)	210	3685.45 (3165.29, 4291.08)
Polio 3								
Group 1	55	795.84 (553.04, 1145.24)		NA	209	129.07 (102.23, 162.96)	218	4878.75 (4001.79, 5947.88)
Group 2	63	600.55 (431.80, 835.26)		NA	216	74.80 (60.89, 91.90)	220	6356.88 (5000.22, 8081.64)
Group 3	61	797.49 (589.91, 1078.12)		NA	205	104.16 (83.45, 130.00)	210	3571.79 (2967.39, 4299.31)

*anti-PT values were generated in the ------ performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

Group is defined as per randomization.

Group 1: Received 4th Dose of Pentacel at 15 months (MMR, VARIVAX and Prevnar at 12m).

Group 2: Received 4th Dose of Pentacel concomitantly with the 1st Dose of MMR and VARIVAX at 15 months.
Group 3: Received 4th Dose of Pentacel concomitantly with the 4th Dose of Prevnar at 15 months.
Group 4: Received 1st Dose of MMR and VARIVAX and 4th Dose of Prevnar at 15 months, and 4th Dose of Pentacel at 16 months.
Source 49403sii.pdf page 670-672

A presentation of the GMTs for pnuemococcal serotypes is provided in Table 81. Although not an objective of the study this information is presented to show antibody decay following the third dose of Prevnar administered at 6 months of age and response to the fourth dose.

Table 81: Study 494-03 Stage II GMTs of Pneumococcal serotypes pre and post dose 4 for group 3 and 4. PPI population

Antigen	15m		16m	
	N	GMT (95% CI)	N	GMT (95% CI)
Serotype 4				
Group 3	164	0.56 (0.49, 0.63)	155	5.11 (4.44, 5.88)
Group 4	135	0.54 (0.47, 0.61)	158	6.55 (5.69, 7.54)
Serotype 6B				
Group 3	164	0.83 (0.68, 1.01)	155	9.46 (7.67, 11.66)
Group 4	135	0.77 (0.63, 0.94)	158	11.93 (9.92, 14.35)
Serotype 9V				
Group 3	164	0.60 (0.53, 0.68)	155	5.45 (4.76, 6.24)
Group 4	135	0.65 (0.56, 0.74)	158	7.01 (6.19, 7.93)
Serotype 14				
Group 3	164	1.76 (1.51, 2.05)	155	13.92 (12.02, 16.13)
Group 4	135	1.92 (1.63, 2.27)	158	15.43 (13.23, 17.99)
Serotype 18C				
Group 3	164	0.59 (0.52, 0.65)	155	5.26 (4.54, 6.09)
Group 4	135	0.57 (0.51, 0.65)	158	6.24 (5.38, 7.24)
Serotype 19F				
Group 3	164	0.94 (0.79, 1.13)	155	5.44 (4.62, 6.40)
Group 4	135	0.81 (0.68, 0.96)	158	6.96 (5.73, 8.46)
Serotype 23F				
Group 3	164	0.56 (0.47, 0.66)	155	6.16 (5.02, 7.55)
Group 4	135	0.49 (0.41, 0.58)	158	7.40 (6.16, 8.89)

Notes: Group is defined as per randomization.
Group 3: Received 4th Dose of Pentacel concomitantly with the 4th Dose of Prevnar® at 15 months.
Group 4: Received 1st Dose of M-M-R® and VARIVAX® and 4th Dose of Prevnar® at 15 months, and 4th Dose of Pentacel at 16 months.
GMTs are based on the number of subjects with available serology data from PP Immunogenicity Population.
Source 49403sii.pdf page 676-677

6.2.3 Comments and Conclusions

No primary hypotheses were tested during 494-03 Stage I. Secondary and observational objectives evaluated the response to Pentacel and co-administered vaccines (Prevnar and hepatitis B vaccine). The response to PRP was not comparative however, the seroprotective rate (75.6%, 95% CI 70.0-80.6, ≥1.0 ug/mL) and GMT (2.8 ug/mL, 95% CI 2.30-3.41) are similar to that observed in 494-01 among subjects administered the same lot of ActHIB reconstituted as Pentacel in Study 494-01 (81.7%, 95% CI 77.4-85.6 ≥1.0 ug/mL and GMT 3.64 ug/mL 95% CI 3.12-4.25).

Stage II of Study 494-03 evaluated the immune response to Pentacel administered alone or co-administered with Prevnar or MMR and VARIVAX in the second year of life.

The primary objective of Study 494-03 was non-inferiority of seroresponse/seroprotection rates to Pentacel when administered alone or co-administered with Prevnar or MMR and VARIVAX.

With the exception of seroresponse to FIM, which did not meet the criteria for non-inferiority when Pentacel was coadministered with Prevnar as compared to the rate when Pentacel was administered alone at 15 months of age, all Stage II primary immunogenicity analyses met the criteria for non-inferiority (Tables 72 and 73). The PT ----- performed at the sanofi pasteur, Canada, laboratory was non-specific thus, an assessment of non-inferiority of seroresponse to PT is not available.

When Pentacel was co-administered with MMR and VARIVAX the PRP and polio 1 GMT levels did not meet the pre-specified criteria for non-inferiority relative to antibody levels when Pentacel was administered alone (Table 74). However, 97% of subjects co-administered Pentacel with MMR and VARIVAX had seroprotective levels of antibodies to PRP (≥1.0 ug/mL) and 100% had anti-polio 1 titers ≥1:8 (Table 72). Thus, the failure to show non-inferiority for these antigens at this time point is likely not clinically relevant. The response to all other antigens met the criteria for non-inferiority.

When Pentacel was co-administered with Prevnar the GMT response to PRP, diphtheria and polio types 1, 2 and 3 and did not meet the prespecified criteria for non-inferiority relative to the levels when Pentacel was administered alone for the fourth dose (Table 75). However, over 97% of subjects who received Pentacel coadministered with Prevnar had seroprotective levels of antibodies to each antigen (Table 73; PRP ≥1.0 ug/mL, diphtheria ≥0.1 IU/mL, polio 1, 2 and 3 ≥1:8). Subjects administered Pentacel alone had received Prevnar at 12m of age thus, the higher GMT response to diphtheria toxoid in these subjects may be due to the administration of the CRM197 diphtheria protein contained in Prevnar. The failure to show non-inferiority for these antigens is likely not clinically relevant. The anti-fimbriae GMT level was inferior following administration of Pentacel with Prevnar as compared to the response following Pentacel administered alone (Table 75). The clinical significance of this, and the failure to meet non-inferiority criteria of seroresponse to FIM (Table 73), is unclear because there is no well accepted correlate of protection for pertussis. The GMT to all other Pentacel antigens (except PT) met the criteria for non-inferiority. The PT ----- performed at the sanofi pasteur, Canada, laboratory was non-specific thus, an assessment of non-inferiority of response to PT is not available.

Using a definition of seroresponse that encompasses both ELISA and neutralizing antibodies co-administration of the fourth dose of Pentacel with MMR and VARIVAX did not adversely affect the seroresponse rates for measles, mumps and varicella. The seroresponse to rubella also met the pre-defined criteria for non-inferiority (Table 84). Following input from the Division of Viral Products the PRNT evaluates functional response thus this two tiered approach to testing should correctly identify subjects who have seroconverted post-vaccination.

When the fourth dose of Prevnar was administered with Pentacel anti-pneumococcal seroresponse rates (⩾ 0.15ug/mL and ≥ 0.5 ug/mL) to each serotype were non-inferior to those following administration of Prevnar co-administered with MMR or varicella vaccine. In both groups >95% of subjects had anti-pnuemococcal levels ⩾ 0.5ug/mL to each serotype. Prevnar was co-administered with Pentacel for the first three doses thus, non-inferiority was not evaluated although seroresponse rates and GMTs were presented following three doses. With the exception of type 6B over 90% of subjects had anti-pnuemococcal levels ⩾ 0.5ug/mL to each serotype, 79% of subjects had anti-6B levels ⩾ 0.5ug/mL. However, it should be noted that currently ----- cut-off values of 0.35ug/mL post-dose 3 using ------ are considered the appropriate endpoint for evaluation of seroresponse levels.

6.3 Trial #3

6.3.1 Applicants Protocol # and Protocol Title

Study P3T06 Safety, Immunogenicity and Lot Comparability of DAPTACEL (Aventis Pasteur Classic Five-component Pertussis Vaccine in Combination with Tetanus and Diphtheria Toxoids Adsorbed) when Administered with Other Recommended Vaccines at 2, 4, 6, and 15 to 16 Months of Age

6.3.1.1 Objective/Rationale

Study P3T06 was designed to assess lot consistency of DAPTACEL as well as the safety and immunogenicity of DAPTACEL when co-administered with IPV, Hib vaccine, hepatitis B vaccine, pneumococcal conjugate vaccine, varicella vaccine, and MMR at the recommended schedules. The study was also designed to assess the immune responses to vaccines administered concomitantly with DAPTACEL. The study was also designed to compare the safety and immunogenicity of DAPTACEL co-administered with other recommended vaccines and Pentacel co-administered with other recommended vaccines.

Specific objectives relevant to the immunological evaluation of PENTACEL and co-administered vaccines are listed below for Stages I and II of Study P3T06. The other aspects of the study pertaining to evaluation of DAPTACEL lot consistency and co-administration of DAPTACEL with other recommended vaccines have been reviewed in DAPTACEL supplement 103666/5071 and will not be addressed in this review. Study P3T06 was a two-staged study, with Stage I vaccines administered at 2, 4, and 6 months of age, and Stage II vaccines administered between 12 and 17 months of age.

<u>Primary immunogenicity objectives</u>

Stage I

1. To compare the frequencies of seroconversion and seroprotection and the GMTs elicited by the pertussis, tetanus and diphtheria antigens in Pentacel with those of three lots of DAPTACEL when these vaccines are co-administered with other recommended vaccines, after the infant series.

2. To compare the frequencies of seroprotection elicited by the PRP-T antigen in Pentacel with that of ActHIB concurrently administered in a different injection site with DAPTACEL when these vaccines are co-administered with other recommended vaccines, after the infant series.

Stage II

1. To compare the frequencies of seroconversion and seroprotection and the GMTs elicited in toddlers after the 4$_{th}$ dose of the pertussis, tetanus and diphtheria, in Pentacel with those elicited by DAPTACEL co-administered with ActHIB.

2. To compare the frequencies of seroprotection to Hib elicited in toddlers by the 4th dose of Pentacel with that elicited by ActHIB concurrently administered with DAPTACEL.

<u>Secondary immunogenicity objectives</u>

Stage I – none

Stage II – none pertinent to the evaluation of Pentacel

Observational immunogenicity Objectives

Stage I

1. To present the immune responses of DAPTACEL (pooled responses from three vaccine lots) and Pentacel in Group #4 and the concomitant vaccines when DAPTACEL and Pentacel are co-administered with other recommended vaccines for the infant series.

2. To present the percentage of infants that have pertussis (PT, FHA, FIM 2&3 and PRN) antibody concentrations less than LOQ and appropriate low titer categories after the third dose in the infant series. Data and analysis assessing the antibody responses to the other pertussis antigens in infants who did not respond (<LOQ) to one of the pertussis antigens will also be presented. The pertussis antibody levels post third dose of DAPTACEL at 7 months of age will be presented with the pre-immunization levels at 2 months of age.

3. To calculate the anti-PRP GMT ratio of responses elicited by Pentacel with those elicited by separately administered DAPTACEL™, IPV and ActHIB® after the infant series.

Stage II

1. To present the antibody responses as expressed in GMTs, rates of seroprotection/seroconversion and RCFD (where applicable) for all vaccines administered at 15 to 16 months of age.
   Anti-pertussis antibody responses pre and post 4th dose will also be presented by a stratification of the 7 months PRN antibody level (5, 10, 20 EU/mL).
   The antibody GMTs, rates of seroprotection/seroconversion and the RCFD for all antigens tested for all Stage II Groups will be presented.

2. To calculate the anti-PRP GMT ratio of responses elicited by Pentacel with those elicited by separately administered DAPTACEL™, IPV and ActHIB® after the 4th dose.

6.3.1.2 Design Overview

Study P3T06 was a two-staged, randomized, multicenter study, with Stage I vaccines administered at 2, 4, and 6 months of age, and Stage II vaccines administered between 12 and 17 months of age. Assessments of immunogenicity of PENTACEL compared to DAPTACEL and concomitantly administered vaccines were based on an open-label design.

Subjects were randomized at recruitment. For each study site, randomization was provided in blocks of 12 (3 subjects for each of 3 DAPTACEL lots and 3 subjects to receive Pentacel). Subjects who received a particular lot of DAPTACEL in Stage I were randomized to one of the Stage II DAPTACEL groups. Subjects who received Pentacel in Stage I received Pentacel in Stage II. Randomization for Stages I and II was determined prior to initiation of the study.

The planned duration of the study, per subject, was 21-23 months.

6.3.1.3 Population

The study period from the beginning of Stage I to the end of Stage II was May 4, 2001 through January 21, 2004. Subjects were enrolled from 31 U.S. centers.

6.3.1.4 Products mandated by the protocol

Study vaccines—schedule of administration

Table 82: Study P3T06: Schedule of vaccine administration during Stage I

Group	2, 4, and 6 months	0, 2 and 6 months*
1	DAPTACEL Lot 1, IPOL, ActHIB, and Prevnar	Hepatitis B vaccine
2	DAPTACEL Lot 2, IPOL, ActHIB, and Prevnar	Hepatitis B vaccine
3	DAPTACEL Lot 3, IPOL, ActHIB, and Prevnar	Hepatitis B vaccine
4	Pentacel and Prevnar	Hepatitis B vaccine

* All subjects received hepatitis B vaccine at 0, 2, and 6 months; the first dose (manufacturer not specified) was administered outside of the study; the second and third doses were with RECOMBIVAX HB, administered as part of the study.

A primary endpoint for this study was assessment of DAPTACEL lot consistency, this aspect of the study was reviewed under DAPTACEL supplement 103666/5071 and will not be addressed in this review. Pooled DAPTACEL data will be presented.

Table 83: Study P3T06: Schedule of vaccine administration during Stage II

Study Group	Months of Age	Vaccines
1	12	MMR_{II}, VARIVAX, Prevnar
	15 to 16	DAPTACEL Lot 1, ActHIB
2	15 to 16	DAPTACEL Lot 1, ActHIB, MMR_{II}, VARIVAX, Prevnar
3	15 to 16	ActHIB, MMR_{II}, VARIVAX, Prevnar
	16 to 17	DAPTACEL Lot 1
4	12	MMR_{II}, VARIVAX, Prevnar
	15 to 16	Pentacel

This review will present the Stage II data from Group 1 and Group 4. An evaluation of the immunogenicity of DAPTACEL when administered with other vaccines routinely administered at 12-16 months of age has been reviewed in DAPTACEL Supplement **103666/5071**.

The protocol-specified interval between doses 1 and 2 of DAPTACEL or Pentacel was 60 days +/- 10 days. The protocol-specified interval between doses 2 and 3 of DAPTACEL or Pentacel was 60-90 days. The fourth dose of DAPTACEL or Pentacel was administered at $\geq$15 months to $\leq$17 months of age.

Study vaccines—formulation and lot numbers: All study vaccines except for Pentacel are licensed in the U.S.

- Pentacel (DTaP-IPV used to reconstitute ActHIB).

The formulation of Pentacel per 0.5mL dose is described in **Section 1.2.3**

DTaP-IPV Lot numbers for Stage I: C0790BA
DTaP-IPV Lot number for Stage II: C1362A

ActHIB Lot number for Stage I: UA596AB

ActHIB Lot number for Stage II: UA685AA

- DAPTACEL

  DAPTACEL, composition per 0.5 ml dose:
  Active Ingredients:
  10 µg Pertussis Toxoid (PT)
  5 µg Filamentous hemagglutinin (FHA)
  5 µg Fimbriae (FIM) 2 & 3
  3 µg Pertactin (PRN)
  15 LF Diphtheria toxoid
  5 LF Tetanus toxoid
  Adjuvant: 0.33 mg aluminum
  Excipient: 0.6% 2-phenoxyethanol

  Lot numbers for Stage I: C0239A (lot 1), C0314A (lot 2), and C0191A (lot 3);
  Lot number for Stage II: C0950AA

- ActHIB, Haemophilus b Conjugate Vaccine produced by Aventis Pasteur SA, is a lyophilized powder reconstituted with saline diluent. Each 0.5 ml dose is formulated to contain 10 µg of purified capsular polysaccharide conjugated to 24 µg of inactivated tetanus toxoid.
  Lot UA596AB was used in Stage I.
  Lot UA685AA was used in Stage II.

- IPOL is poliovirus vaccine, inactivated, and produced by Aventis Pasteur SA. Each 0.5 ml dose is formulated to contain 40 D antigen units of Type 1 (Mahoney), 8 D antigen units of Type 2 (MEF-1), and 32 D antigen units of Type 3 (Saukett) poliovirus. Also present are 0.5% 2-phenoxyethanol and a maximum of 0.02% formaldehyde per dose as preservatives. Neomycin (< 5 ng), streptomycin (< 200 ng) and polymyxin B (< 25 ng) may be present. Residual calf serum protein is less than 1 ppm in the final vaccine.
  IPOL lot T1189-2 was used.

For the following vaccines, lots available at individual study sites were used:

- Prevnar, [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), Wyeth]: Each 0.5 ml dose of Prevnar contains 2 µg of each polysaccharide for *Streptococcus pneumoniae* serotypes 4, 9V, 14, 18C, 19F, and 23F and 4 µg of serotype 6B (16 µg total polysaccharide); approximately 20 µg of CRM_{197} protein; and 0.125 mg of aluminum as aluminum phosphate adjuvant.

- RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant), Merck & Co., Inc]: Each 0.5 ml dose contains 5 µg of purified HBsAg without preservative.

- MMR_{II} (Measles, Mumps, and Rubella Virus Vaccine Live, Merck & Co., Inc.): Each 0.5 ml dose contains not less than 1,000 TCID50 (tissue culture infectious doses) of measles virus; ------ TCID50 of mumps virus; and 1,000 TCID50 of rubella virus. Each dose of the vaccine contains approximately 25 µg of neomycin; sorbitol and hydrolyzed gelatin as stabilizers. The product contains no preservative.

- VARIVAX [Varicella Virus Vaccine Live (Oka/Merck); Merck & Co., Inc.]: Each 0.5 ml dose contains a minimum of 1350 plaque forming units of Oka/Merck varicella virus. The product contains no preservative.

Study vaccines: route of administration

Pentacel, DAPTACEL, ActHIB, Prevnar, and RECOMBIVAX HB were injected intramuscularly. IPOL, MMR_{II}, and VARIVAX were injected subcutaneously.

6.3.1.5 Immunogenicity Endpoints and Evaluation Criteria

Antibody Assays

See **Section 5.5** for an overview of serology assays.

Primary endpoints and evaluation criteria

Stage I—Non-Inferiority Pentacel relative to DAPTACEL + ActHIB

Table 84 presents the criteria for evaluation of seroconversion/seroprotection and GMTs following three doses of Pentacel or DAPTACEL co-administered with other recommended vaccines.

Table 84. Study P3T06: Primary Immunogenicity Endpoints and Non-inferiority criteria for evaluation of sero-conversion/seroprotection rates and GMTs following Pentacel or DAPTACEL (pooled), post-dose 3

Antigen	Endpoint	Non-inferiority Criteria
PT FHA FIM Pertactin	≥4-fold rise (post dose 3 vs. pre-dose1) GMT	UL 90% CI difference DAPTACEL minus Pentacel < 10% UL 90% CI ratio DAPTACEL/Pentacel < 1.5
Diphtheria	≥0.01 IU/mL GMT	UL 90% CI difference DAPTACEL minus Pentacel < 10% UL 90% CI ratio DAPTACEL/Pentacel < 1.5
Tetanus	≥0.01 IU/mL GMT	UL 90% CI difference DAPTACEL minus Pentacel < 10% UL 90% CI ratio DAPTACEL/Pentacel < 1.5

Source p3t06si.pdf page 4060 and 4107

Table 85 presents the endpoints and non-inferiority criteria for comparison of the anti-PRP response following three doses of Pentacel or ActHIB

Table 85: Study P3T06 Primary Immunogenicity endpoints and non-inferiority criteria for evaluation of anti-PRP seroprotection

Antigen	Endpoint	Non-inferiority criteria
PRP	% ≥0.15 ug/mL % ≥1.0 ug/mL	UL 90% CI difference DAPTACEL minus Pentacel < 10%

Source p3t06si.pdf page 4060 and 4108

Stage II –Non-inferiority of Pentacel relative to DAPTACEL + ActHIB

Table 86 presents the primary endpoints and non-inferiority criteria for evaluation of the response to pertussis, diphtheria, tetanus and PRP-T following a fourth dose of Pentacel compared to DAPTACEL administered with ActHIB.

Table 86: Study P3T06: Primary Immunogenicity Endpoints and Non-inferiority criteria for evaluation of sero-conversion/seroprotection rates and GMTs following Pentacel (Group 4) or DAPTACEL concurrently administered with ActHIB (Group 1), post-dose 4

Antigens	Endpoint	Non-inferiority Criteria
PT FHA FIM Pertactin	≥4-fold rise (post dose 4 vs. pre-dose1) GMT	UL 90% CI difference DAPTACEL minus Pentacel < 10% UL 90% CI ratio DAPTACEL/Pentacel < 1.5
Diphtheria	≥0.1 IU/mL GMT	UL 90% CI difference DAPTACEL minus Pentacel < 10% UL 90% CI ratio DAPTACEL/Pentacel < 1.5
Tetanus	≥0.1 IU/mL GMT	UL 90% CI difference DAPTACEL minus Pentacel < 10% UL 90% CI ratio DAPTACEL/Pentacel < 1.5
PRP	⩾1.0 ug/mL	UL 90% CI difference DAPTACEL minus Pentacel < 10%

Observational Endpoints

Stage I –observational endpoints

Table 87 presents the observational immunogenicity endpoints as specified in the protocol.

Table 87: Study P3T06 Immunogenicity Endpoints to be presented following three doses of DAPTACEL or Pentacel co-administered with other recommended vaccines.

Antigen	Endpoint
PRP	GMT %≥0.15ug/mL %≥1.0 ug/mL
Diphtheria	GMT %≥0.01 IU/mL % ≥0.1 IU/mL
Tetanus	GMT % ≥0.01 IU/mL % ≥0.1 IU/mL
PT, FHA, Fim, pertactin	GMT % ≥4-fold rise (post dose 3 vs. pre dose 1
Polio type 1 Polio type 2 Polio type 3	GMT % ≥1:8
HBsAg	GMT % ≥10mIU/mL
Pneumococcal (4, 6B, 9V, 14, 18C, 19F, 23F0	GMT % ≥0.15 ug/mL % ≥0.5 ug/mL % > 2-fold rise (post dose 3 vs. pre-dose1)

Source p3t06si.pdf page 4063

Table 88 presents the observational endpoints to be presented for those infants with post-vaccination levels less than the Limit of Quantitation (LOQ) and other arbitrary cut-off values following three doses of DAPTACEL or Pentacel. For infants with post-dose 3 levels <LOQ for any antigen the antibody response to the other pertussis antigens will be presented.

Table 88: Study P3T06 Post dose 3 pertussis antibody levels

Antigen	post-vaccination cut-off values
PT	% < 5 EU/mL (LOQ) % <30 EU/mL % < 60 EU/mL
FHA	%<3 EU/mL (LOQ) %< 20 EU/mL %< 50 EU/mL
FIM	%< 17 EU/mL (LOQ) %<50 EU/mL %< 100 EU/mL
Pertactin	%< 3 EU/mL (LOQ) %< 20 EU/mL %< 50 EU/mL

Source p3t06si.pdf page 4064

Table 89 presents the additional observational endpoint to evaluate the response to PRP following three doses of Pentacel relative to three doses of DAPTACEL.

Table 89: Study P3T06 Endpoints and evaluation criteria for non-inferiority of response to PRP following three doses of Pentacel as compared to ActHIB

Antigen	Endpoint	Non-inferiority
PRP	GMT ug/mL	Ratio, criteria not specified

Stage II Observational endpoints

Table 90 and 91 indicate the Stage II observational endpoints to be presented for antigens administered at 15-16 months of age.

Table 90: Study P3T06 Immunogenicity Endpoints to be presented following four doses of DAPTACEL coadministered with ActHIB (Group 1) or Pentacel (Group 4).

Antigen	Endpoint
PRP	GMT %≥1.0 ug/mL
Diphtheria	GMT % ≥ 0.1 IU/mL % ≥ 1.0 IU/mL Pre-dose 4 ≤ 0.1, post ≥0.4 Pre- dose 4 ≥ 0.1-2 IU/mL, post ≥4 fold rise Pre-dose 4 ≥ 2.0 IU/mL, post ≥2-fold rise
Tetanus	GMT % ≥ 0.1 IU/mL % ≥ 1.0 IU/mL Pre-dose 4 ≤ 0.1, post ≥0.4 Pre- dose 4 ≥ 0.1-2 IU/mL, post ≥4 fold rise Pre-dose 4 ≥ 2.0 IU/mL, post ≥2-fold rise
PT, FHA, Fim, pertactin	GMT % ≥4-fold rise (post dose 4 vs. pre dose 1)
Polio type 1 Polio type 2 Polio type 3	GMT, ≥1:8

Source p3t06si.pdf page 4065

Table 91: Study P3T06 Observational non-inferiority analyses of the response to PRP following four doses of Pentacel as compared to four doses of ActHIB administered with DAPTACEL.

Antigen	Endpoint	Non-inferiority
PRP	GMT ug/mL	Ratio, criteria not specified

6.3.1.6 Surveillance/Monitoring

Immunogenicity

In Stage I, serum samples were collected prior to vaccination at Visit 1 (42-84 days of age) and 28-48 days after the third dose of DAPTACEL or Pentacel at 7 months of age. In Stage II, serum samples were collected prior to vaccination at 15-16 months of age and 28-48 days later. In Stage II, immune responses were assessed only for vaccines administered at 15 to 16 months of age. Immune responses were not assessed following vaccines administered at 12 months of age (i.e., MMR_{II}, VARIVAX, and Prevnar for Study Groups 1 and 4) and following DAPTACEL administered at 16-17 months of age (Study Group 3).

6.3.1.7 Statistical Considerations

Sample size and statistical power
The planned total sample size was 2,000 subjects randomized equally to one of the Stage I vaccine groups. An attrition rate of 15% to the end of Stage I and an additional 15% to the end of Stage II was considered for statistical power calculations. In addition, in Stage I, a 15% allowance was made to account for unsuccessful attempts at obtaining blood or insufficient blood volume. Power calculations presented for each of the primary and secondary endpoints for Stages I and II were based on 360 subjects per group, and indicated at least 90% power for each endpoint. The overall power of the study considering all endpoints for Stage I and Stage II combined was 89%.

Analysis populations
Intent to treat safety population The intent to treat (ITT) safety population included any subject who received a DAPTACEL or Pentacel dose. Analyses at each dose were based on the actual treatment received. Analyses of safety outcomes at any dose were based on the original randomization.

Intent to treat immunogenicity population The ITT population for immunogenicity included any subject who received all three doses of DAPTACEL or Pentacel (for Stage I) or who received the fourth dose of DAPTACEL or Pentacel (for Stage II) regardless of whether they adhered to the study eligibility criteria or their immunization and bleeding visits were within the protocol-specified windows, and had a valid serology test post-dose 3 (for Stage I) or post-dose 4 (for Stage II) for at least one DAPTACEL or Pentacel antigen. Analyses were based on the original randomization.

Per-protocol immunogenicity population The per-protocol population for immunogenicity included all eligible subjects who received the correct vaccines (according to the assigned treatment) for all doses (three doses for Stage I analyses and fourth dose for Stage II analyses), had all doses and blood draws within windows as specified in the protocol, and had a valid serology test result post-dose 3 (for Stage I) or post-dose 4 (for Stage II) for at least one DAPTACEL or Pentacel antigen.

Statistical criteria for non-inferiority analyses
The protocol-specified statistical criteria for non-inferiority of GMTs between study groups were based on the 90% CIs for the ratios of GMTs. Likewise, the protocol-specified statistical criteria for non-inferiority of seroprotection or seroconversion rates between study groups were based on the 90% CIs for differences in rates between groups. However, CBER currently recommends use of 2-sided 95% CIs for ratios of GMTs for both lot consistency and non-inferiority analyses, as well as 2-sided 95% CIs for rate differences for non-inferiority analyses. To be consistent with current policy, CBER requested analyses of lot consistency and non-inferiority using 95% CIs for GMT ratios and for rate differences, in addition to the protocol-specified analyses using 90% CIs.

6.3.2 Results
Only results that are relevant to the evaluation of Pentacel are included in this review. PT antibody levels were generated in the ----- performed in the sanofi pasteur, Canada, laboratory. Because this assay has been determined to be non-specific these data are not acceptable to CBER and are not presented in this review.

6.3.2.1 Populations enrolled/analyzed

Table 92 presents a summary of the immunogenicity populations in Stage I and II of P3T06. The Stage I DAPTACEL groups have been pooled. Stage II Groups 2 and 3 are not shown in this table since no analyses are presented using subjects from these groups.

Table 92: Summary of Subject Disposition – number of subjects randomized, immunized, bled and included in the immunogenicity populations

Immunogenicity disposition		
Stage I	**Pooled DAPTACEL (%)**	**Pentacel (%)**
Randomized	1457	484
And received one dose of Pentacel or DAPTACEL[1]	1454	485
And received three doses of Pentacel or DAPTACEL[1]	1376	461
Bled pre dose 1	1399	465
Received three doses of DAPTACEL or Pentacel[2]	**1375 (100.0)**	**462 (100.0)**
Missed, unable or refused to bleed post –dose 3*	115	55
Invalid test result (QNS, NS, , NR) for all antigens*	3	1
Missing test result for all antigens*	14	2
ITT immunogenicity[3]	**1243 (90.4)**	**404 (87.4)**
Protocol violations[4]		
Did not satisfy eligibility criteria	18	9
Treatment error	6	0
Visit out of time interval	52	21
PP Immunogenicity Population[5]	**1167 (84.9)**	**374 (92.6)**
Stage II	**DAPTACEL (group 1)**	**Pentacel (Group 4)**
Bled pre dose 4	385	414
Received all four doses of DAPTACEL or Pentacel (by actual tx at dose 4)	**418 (100)**	**431 (100)**
Received all four doses of DAPTACEL or Pentacel and bled post dose 4[2]	**390 (93.3)**	**405 (93.4)**
Invalid test result (QNS, NS, NR) for all antigens	0	0
Missing test result for all antigens	1	0
ITT for Immunogenicity population[6]	**389 (93.0)**	**405 (93.4)**
Protocol violations		
Did not satisfy eligibility criteria	6	8
Tx assignment error	6	4
Visit out of time or age window	28	22
PP Immunogenicity Population[7]	**349 (83.5)**	**371 (91.6)**

NA not available

[1] subjects classified by actual treatment received at dose 1 or 3

[2] table 5.1 in P3T06 Stage I (p3t06si.pdf page 80) study report and table 5.2 P3T06 Stage II study report (p3t06sii.pdf page 86) do not indicate whether subjects are classified by treatment or randomization

* Only the primary reason for exclusion per subject is selected in the order listed; QNS=bled, but serum quantity not sufficient to perform assay, NS=bled, but serum sample not available in laboratory (broken/spilled/lost in transit), NR=Non-reportable.

[3] ITT Immunogenicity Population: Defined as those who had 3 doses of DAPTACEL or Pentacel and a valid serology test result for at least 1 DAPTACEL or Pentacel antigen at post-Dose 3; Percentages of the sub-categories are based on the number of subjects in the ITT Immunogenicity Population.

[4] Only the primary reason for termination per subject is selected in the order listed.

[5] Stage I PP Immunogenicity Population: Defined as all eligible subjects who received the correct dosage for all doses, had all doses and blood draw within windows and had a valid serology test result for at least 1 DAPTACEL or Pentacel antigen at post-Dose 3; The PP Immunogenicity Population was used only in the Immunogenicity analyses

[6] Stage II TT immunogenicity population included all subjects who received 4 doses of DAPTACEL® or Pentacel and had a valid serology result for at least 1 DAPTACEL or Pentacel antigens at post Dose 4.

[7]Stage II PP immunogenicity population included all subjects who received the correct dosage for all doses, had all doses and blood draw within windows, and had valid serology result for at least one DAPTACEL® or Pentacel antigen at post Dose 4.
DAPTACEL (Group 1): Received the 4th doses of DAPTACEL and ActHIB at 15-16 months of age;
Pentacel (Group 4): Received the 4th Dose of Pentacel at 15-16 months of age.
Source; p3t06si.pdf page 80 and p3t06sii.pdf page 86. September 7, 2006 questions1_133.pdf page 318

6.3.2.1. Immunogenicity Analyses and Data Presentation

In this review results of primary analyses and selected additional analyses are presented (no secondary immunogenicity analyses were specified in the protocol). Results are presented for the PPI population. Results for the ITT immunogenicity population were similar.

Prevaccination antibody levels:
Prevaccination antibody levels were determined for the pertussis antigens. Anti-PT ----- values were generated in a non-specific assay thus, PT GMTs are not presented.

Table 93: Study P3T06: Pre-dose 1 GMTs for antibodies to the pertussis antigens* (Stage I PPI population)

Antigen	DAPTACEL (pooled groups)			Pentacel group		
	N	GMT	(95% CI)	N	GMT	(95% CI)
FHA (EU/mL)	791	4.88	(4.52, 5.26)	247	4.69	(4.12, 5.35)
FIM (EU/mL)	782	12.16	(11.57, 12.78)	244	11.66	(10.74, 12.65)
Pertactin (EU/mL)	784	3.14	(2.93, 3.36)	247	3.07	(2.72, 3.47)
PRP, D, T, polio		NA			NA	

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source; p3t06.pdf page 94
NA = not available

Stage I

Stage I Non-inferiority of Pentacel relative to DAPTACEL. Using 90% CI for difference in seroconversion/seroprotection rates the statistical criteria for non-inferiority between the response to FHA, fimbriae, pertactin, diphtheria and tetanus toxoids following three doses of DAPTACEL (pooled groups) or Pentacel were met. These data are presented in Table 101. Anti-PT ----- values were generated in a non-specific assay thus, anti-PT seroconversion rates are not presented. Also, shown in Table 94 are the 95% CIs for the difference in seroprotection/seroconversion which, although not pre-specified in the protocol, were provided following CBER's request. The protocol specified anti-tetanus levels of 0.01 IU/mL as seroprotective. However, review of the ---------- data does not support this as a seroprotective level. Based on this data the minimum seroprotective level as assessed by ELISA is 0.1 IU/mL. Over 99% of subjects in both groups had anti-tetanus levels $\geqslant$ 0.1 IU/mL following three doses of vaccine. An exploratory analysis of non-inferiority of three doses of DAPTACEL as compared to Pentacel with regard to anti-tetanus levels $\geqslant$ 0.1 IU/mL is also shown in this Table.

Table 94: Study P3T06 Stage I Seroconversion/seroprotection rates* and non-inferiority analyses following three doses of DAPTACEL or Pentacel. PPI population

Antigen and criteria	Pooled DAPTACEL n/N % (95%CI)	Pentacel. n/N % (95%CI)	Non-inferiority Comparison DAPTACEL®-Pentacel[1]		
				90% CI difference[1]	95% CI difference
FHA (EU/mL) ≥4-fold rise[2]	441/724 60.9 (57.2, 64.5)	181/221 81.9 (76.2, 86.7)	-20.99	(-26.19, -15.79)	(-27.18, -14.79)
FIM (EU/mL) ≥4-fold rise[2]	616/714 86.3 (83.5, 88.7)	200/218 91.7 (87.3, 95.0)	-5.47	(-9.19, -1.74)	(-9.91, -1.03)
PRN (EU/mL) ≥4-fold rise [2]	540/716 75.4 (72.1, 78.5)	164/221 74.2 (67.9, 79.8)	1.21	(-4.31, 6.73)	(-5.36, 7.78)
Diphtheria ≥0.01 IU/mL	1099/1099 100.0 (99.7, 100.0)	345/345 100.0 (98.9, 100.0)	0.00	(NA)	(NA)
Tetanus ≥0.01 IU/mL	1037/1037 100.0 (99.6, 100.0)	331/331 100.0 (98.9, 100.0)	0.00	(NA)	(NA)
Tetanus ⩾0.1 IU/mL	1037/1037 100.0 (99.6, 100.0)	330/331 99.7 (98.3, 100.0)	0.30	NP	(-0.29, 0.89)

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

[1] Non-Inferiority is achieved when the upper limit of the 90% CI of the rate difference (DAPTACEL®-Pentacel) is <10%.

[2] The fold rise is calculated by Post-Dose 3/Pre-Dose 1.

Note: 'n' is the number of subjects who achieved the criteria specified.

'N' is the number of subjects with a valid serology result Post-Dose 3 and Pre-Dose 1.

NA: not applicable, NP: Not Provided.

Source: p3t06si.pdf page 86, September 7, 2006 questions1_133.pdf page 319.

Stage I Non-inferiority of Pentacel relative to DAPTACEL. Using 90% CI for the ratio of GMTs the statistical criteria for non-inferiority for the response to FHA, fimbriae, pertactin, tetanus and diphtheria antigens were met. These data are presented in Table 95. Also shown in Table 95 are the 95% CI for the ratios of GMTs, provided at CBER's request. Anti-PT ----- values were generated in a non-specific assay thus, neither PT GMTs nor an evaluation of non-inferiority of response to PT are presented.

Table 95: Study P3T06 Stage I GMTs* and non-inferiority analyses following three dose of DAPTACEL or Pentacel. PPI population.

Antigen	Pooled DAPTACEL N GMT (95%CI)	Pentacel N GMT (95%CI)	Non-inferiority Comparison DAPTACEL/Pentacel[1]		
				90% CI ratio[1]	95% CI ratio
FHA (EU/mL)	1016 29.22 (27.91, 30.60)	318 73.68 (68.52, 79.23)	0.40	(0.37, 0.43)	(0.36, 0.43)
FIM (EU/mL)	1015 267.18 (253.15, 282.00)	318 268.15 (247.21, 290.87)	1.00	(0.91, 1.09)	(0.90, 1.11)
PRN (EU/mL)	1016 43.25 (40.68, 45.99)	318 36.05 (32.27, 40.27)	1.20	(1.08, 1.33)	(1.06, 1.36)
Diphtheria (IU/mL)	1099 0.94 (0.89, 0.99)	345 0.95 (0.86, 1.04)	0.99	(0.91, 1.08)	(0.89, 1.10)
Tetanus (IU/mL)	1037 1.24 (1.18, 1.29)	331 1.10 (1.01, 1.19)	1.12	(1.04, 1.21)	(1.03, 1.23)

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

[1]Non-Inferiority is achieved when the upper 90% CI of the GMT Ratio (DAPTACEL/Pentacel) is <1.5.
N' is the number of subjects with a valid Post-Dose 3 bleed value.
Source: p3t06si.pdf page 88 and 3322

Stage I Non-inferiority of Pentacel relative to ActHIB- Using 90% CIs the statistical criteria for non-inferiority of response to PRP component of Pentacel relative to ActHIB were met. These data are presented in Table 96. Also, shown in Table 96 are the 95% CIs for the difference in rates of seroprotection, provided at CBER's request.

Table 96: Study P3T06 Stage I Seroprotection rates following three doses of Pentacel or ActHIB. PPI population.

PRP	ActHIB (Groups 1-3 combined) n/N % (95%CI)	Pentacel. n/N % (95%CI)	Non-inferiority Comparison ActHIB- Pentacel[1]		
				90% CI	95% CI
≥ 0.15 ug/mL	1052/1128 93.3 (91.6, 94.7)	337/365 92.3 (89.1, 94.8)	0.93	(-1.67, 3.53)	(-2.16, 4.03)
≥ 1.0 ug/mL	799/1128 70.8 (68.1, 73.5)	263/365 72.1 (67.1, 76.6)	-1.22	(-5.68, 3.24)	(-6.53, 4.09)

Non-Inferiority is achieved when the upper limit of the 90% CI of the rate difference (ActHIB®-Pentacel) is <10%.
Note: 'n' is the number of subjects who achieved the criteria specified.

'N' is the number of subjects with a valid serology result Post-Dose 3
Source: p3t06si.pdf page 90 and 3324

Stage I Additional Analyses:

Response to polio antigens, hepatitis B vaccine, PRP-T and co-administered Prevnar: Seroprotection/seroconversion rates to the 7 pneumococcal serotypes, polioviruses and hepatitis b following DAPTACEL co-administered with ActHIB, IPOL, Prevnar and hepatitis B vaccine as compared to Pentacel co-administered with Prevnar and hepatitis B vaccine are presented in Table 97. The GMT response to these antigens and to PRP-T is presented in Table 98. Seroprotection/seroconversion rates and GMTs to all antigens were similar (overlapping 95% CI) for both groups.

Table 97: Study P3T06 Stage I Seroprotection and seroconversion rates to pnuemococcal serotypes, polio and hepatitis B following three doses of DAPTACEL or Pentacel PPI population.

Antigen and criteria	Pooled DAPTACEL Lots + ActHIB + IPOL + Prevnar + Hepatitis B* n/N % (95%CI)	Pentacel + Prevnar + Hepatitis B * n/N % (95%CI)
Serotype 4 ≥ 0.15 ug/mL	1027/1027 100 (99.6, 100)	321/321 100 (98.9, 100)
Serotype 4 ≥ 0.5 ug/mL	1016/1027 98.9 (98.1, 99.5)	315/321 98.1 (96.0, 99.3)
Serotype 6B ≥ 0.15 ug/mL	939/1027 91.4 (89.5, 93.1)	297/321 92.5 (89.1, 95.2)
Serotype 6B ≥ 0.5 ug/mL	829/1027 80.7 (78.2, 83.1)	260/321 81.0 (76.3, 85.1)
Serotype 9V ≥ 0.15 ug/mL	1021/1028 99.3 (98.6, 99.7)	320/321 99.7 (98.3, 100.0)
Serotype 9V ≥ 0.5 ug/mL	994/1028 96.7 (95.4, 97.7)	303/321 94.4 (91.3, 96.6)
Serotype 14 ≥ 0.15 ug/mL	1022/1029 99.3 (98.6, 99.7)	321/321 100.0 (98.9, 100.0)
Serotype 14 ≥ 0.5 ug/mL	1002/1029 97.4 (96.2, 98.3)	309/321 96.3 (93.6, 98.1)
Serotype 18C ≥ 0.15 ug/mL	1024/1029 99.5 (98.9, 99.8)	321/321 100.0 (98.9, 100.0)
Serotype 18C ≥ 0.5 ug/mL	1006/1029 97.8 (96.7, 98.6)	315/321 98.1 (96.0, 99.3)
Serotype 19F ≥ 0.15 ug/mL	1007/1029 97.9 (96.8, 98.7)	313/321 97.5 (95.1, 98.9)

Serotype 19F ≥ 0.5 ug/mL	984/1029 95.6 (94.2, 96.8)	304/321 94.7 (91.7, 96.9)
Serotype 23F ≥ 0.15 ug/mL	997/1029 96.9 (95.6, 97.9)	315/321 98.1 (96.0, 99.3)
Serotype 23F ≥ 0.5 ug/mL	939/1029 91.3 (89.4, 92.9)	298/321 92.8 (89.4, 95.4)
Polio type 1 ≥ 1:8[1]	1097/1097 100.0 (99.7, 100.0)	348/350 99.4 (98.0, 99.9)
Polio type 2 ≥ 1:8[1]	1073/1073 100.0 (99.7, 100.0)	348/348 100.0 (98.9, 100.0)
Polio type 3 ≥ 1:8[1]	1050/1050 100.0 (99.6, 100.0)	338/338 100.0 (98.9, 100.0)
HBsAg ≥ 10 mIU/mL	922/998 92.4 (90.6, 94.0)	292/325 89.8 (86.0, 92.9)

*Hepatitis B vaccine was administered at 0, 2 and 6 months of age, the first dose was not administered during the study, the second and third dose were with RECOMBIVAX HBHB

[1]Non-inferioirty was not prespecified but analyses were provided using 90 and 95% CI p3t06si.pdf page 3360

Source p3t06si.pdf page 3327, 3329,3360

Table 98: Study P3T06 Stage I GMTs to pnuemococcal serotypes, polio and hepatitis B following three doses administered with DAPTACEL or Pentacel PPI population.

Antigen	Pooled: DAPTACEL + ActHIB + IPOL + Prevnar + HepatitisB* N GMT (95%CI)	Pentacel + Prevnar + HepatitisB*. N GMT (95%CI)
PRP ug/mL	1128 2.29 (2.08, 2.53)	365 2.31 (1.94, 2.75)
Serotype 4 ug/mL	1027 3.23 (3.07, 3.39)	321 3.09 (2.82, 3.39)
Serotype 6B ug/mL	1027 1.75 (1.59, 1.93)	321 1.84 (1.55, 2.18)
Serotype 9V ug/mL	1028 2.35 (2.23, 2.47)	321 2.26 (2.06, 2.49)
Serotype 14 ug/mL	1029 6.03 (5.66, 6.43)	321 5.19 (4.63, 5.83)
Serotype 18C ug/mL	1029 3.75 (3.56, 3.96)	321 3.72 (3.37, 4.10)
Serotype 19F ug/mL	1029 3.40 (3.19, 3.62)	321 3.32 (2.95, 3.74)
Serotype 23F ug/mL	1029 2.48 (2.30, 2.67)	321 2.65 (2.33, 3.01)
Polio type 1 (1/dil)[1]	1097 463.49 (436.93, 491.67)	350 398.13 (343.10, 461.99)
Polio type 2 (1/dil)[1]	1073 913.35 (858.19, 972.06)	348 1032.20 (905.86, 1176.15)
Polio type 3 (1/dil)[1]	1050 902.12 (847.82, 959.89)	338 969.82 (852.28, 1103.57)
HBsAg mIU/mL	998 126.97 (113.19, 142.44)	325 120.98 (97.05, 150.81)

*Hepatitis B vaccine was administered at 0, 2 and 6 months of age, the first dose was not administered during the study, the second and third dose were with Recombivax HB

[1]Non-inferioirty was not prespecified but analyses were provided using 90 and 95% CI p3t06si.pdf page 3360

Source: p3t06si.pdf page 3335, 3337 and 3360

Descriptive presentation of immunogenicity results for those subjects with pertussis antibody levels < LOQ, and < other specified cut-off levels following the third immunization with either DAPTACEL (pooled) or Pentacel.

The number of subjects in the PPI population with pertussis antibody levels below arbitrary cut-off levels is shown in Table 99. Sixteen subjects who had received DAPTACEL (pooled) had post dose three antibody levels less than the limit of quantiation to at least one pertussis antigen (10 subjects anti-fimbriae levels < 17 EU/mL and 6 subjects anti-pertactin levels < 3 EU/mL). Three subjects administered Pentacel had post dose three levels less than the LOQ to at least one pertussis antigen (1 subject anti-fimbriae < 17 EU/mL and two subjects anti-pertactin < 3 EU/mL). No subjects in either group (PPI or ITT populations, p3t06.pdf page 3344-3347) had post-dose 3 anti-FHA levels less than the LOQ. Because the anti-PT levels were generated in a non-specific assay the values are not acceptable to CBER and it is not appropriate to present the proportion of subjects with anti-PT levels below the specified cut-offs.

The post-dose three response of subjects with anti-fimbriae and anti-pertactin levels < LOQ to the other pertussis antigens is shown in Table 100 and Table 101. The limited number of subjects makes it difficult to draw conclusions however, the data suggest that non-responders to pertactin may also have a sub-optimal response to other pertussis antigens in these vaccines.

Table 99: Study P3T06 Stage I Percent of subjects with post dose 3 antibody levels* below specified cut-off levels PPI population.

	Pooled DAPTACEL group			Pentacel.		
Post-Dose 3 Antigen Level	**n/N**	**%**	**(95%CI)**	**n/N**	**%**	**(95%CI)**
FHA						
% <3 EU/mL (LOQ)	0/1016	0.0	(0.0, 0.4)	0/318	0.0	(0.0, 1.2)
% <20 EU/mL	319/1016	31.4	(28.6, 34.4)	8/318	2.5	(1.1, 4.9)
% <50 EU/mL	782/1016	77.0	(74.3, 79.5)	80/318	25.2	(20.5, 30.3)
FIM						
% <17 EU/mL (LOQ)	10/1015	1.0	(0.5, 1.8)	1/318	0.3	(0.0, 1.7)
% <50 EU/mL	41/1015	4.0	(2.9, 5.4)	6/318	1.9	(0.7, 4.1)
% <100 EU/mL	124/1015	12.2	(10.3, 14.4)	28/318	8.8	(5.9, 12.5)
PRN						
% <3 EU/mL (LOQ)	6/1016	0.6	(0.2, 1.3)	2/318	0.6	(0.1, 2.3)
% <20 EU/mL	208/1016	20.5	(18.0, 23.1)	82/318	25.8	(21.1, 31.0)
% <50 EU/mL	517/1016	50.9	(47.8, 54.0)	188/318	59.1	(53.5, 64.6)

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: p3t06si.pdf page 96

Table 100: Study P3T06 Number of subjects vaccinated with DAPTACEL and Pentacel subjects with post-dose three anti-fimbriae levels < 17 EU/mL (LOQ) with response to other pertussis antigens PPI population

Group	Anti-PT			Anti-FHA			Anti-pertactin		
	<5 EU/mL	<30 EU/mL	<60 EU/mL	<3 EU/mL	<20 EU/mL	<50 EU/mL	<3 EU/mL	<20 EU/mL	< 50 EU/mL
DAPTACEL (n/N)	NA	NA	NA	0/10	6/10	9/10	0/10	10/10	10/10
Pentacel (n/N)	NA	NA	NA	0/1	0/1	1/1	0/1	1/1	1/1

'n' is the number of subjects who achieved the specified criteria.
'N' is the number of subjects with available data from the PP Immunogenicity Population who did not respond(<17 EU/mL) to FIM(2&3).
NA = Not available, anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*Source p3t06.pdf page 3348

Table 101: Study P3T06 Seroresponse of subjects with post-dose three anti-pertactin levels < 3 EU/mL (LOQ) to other pertussis antigens. PPI population

Group	Anti-PT			Anti-FHA			Anti-fimbriae		
	<5 EU/mL	<30 EU/mL	<60 EU/mL	<3 EU/mL	<20 EU/mL	<50 EU/mL	<17 EU/mL	<50 EU/mL	< 100 EU/mL
DAPTACEL (n/N)	NA	NA	NA	0/6	4/6	6/6	0/6	0/6	1/6
Pentacel (n/N)	NA	NA	NA	0/2	0/2	0/2	0/2	0/2	1/2

'n' is the number of subjects who achieved the specified criteria.
'N' is the number of subjects with available data from the PP Immunogenicity Population who did not respond(<3 EU/mL) to PRN.
NA = Not available, anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: p3t06si.pdf page 3350

Presentation of response to pertussis antigens based on pre-vaccination antibody levels.

AP present the post dose three response to each pertussis antigen according to arbitrary pre-vaccination antibody cut-off levels. Table 102 presents the post dose 3 seroresponse rate and GMT to each pertussis antigen based on pre-dose 1 cut-off levels to the antigen. Anti-PT ----- values were generated in a non-specific assay thus, anti-PT seroresponse rates are not presented. Fewer subjects with higher pre-vaccination levels had a 4-fold rise in antibody level following the third dose of either DAPTACEL or Pentacel. The levels of pre-existing antibody also appeared to affect the GMT response to vaccination, although fewer subjects had "high" preexisting antibody those with "higher" pre-existing antibody levels had lower GMTs as compared to subjects with "lower" pre-existing antibody levels. Despite the limitations of the data, in particular the small number of Pentacel subjects with "high" pre-existing antibody levels, this may have implications for vaccination of infants of mothers immunized with pertussis containing vaccines.

At CBER's request sanofi provided the post dose four immune response data according to the same arbitrary pre-dose one cut-off levels. These data together with the post-dose 3 data are shown in Table 112.

Table 102: Study P3T06 Stage I Post dose 3 seroresponse rates and GMTs based upon the pre-vaccination antibody levels.

	Anti-PT			**Anti-FHA**			**Anti-Fimbriae**			**Anti-pertactin**		
Pre-vx ------- level cut-offs	**<5**	**≥5-≤30**	**>30**	**<3**	**≥3-⩽20**	**>20**	**<17**	**⩾17-≤50**	**>50**	**<3**	**⩾3-≤20**	**>20**
DAPTACEL												
Post dose 3 (N=780-784, pooled groups)												
n	NA	NA	NA	255	443	93	596	136	50	427	310	47
% ≥4 x-rise	NA	NA	NA	82.7	51.9	0.0	86.4	69.1	14.0	81.0	61.3	8.5
GMT	NA	NA	NA	34.37	29.03	21.14	311.47	183.74	108.83	47.32	35.78	23.81
Pentacel Group												
Post dose 3 (N=244-247)												
n	NA	NA	NA	87	137	23	189	41	14	142	92	13
% 4x rise	NA	NA	NA	90.8	71.5	17.4	88.4	68.3	35.7	82.4	50.0	7.7
GMT	NA	NA	NA	83.58	70.68	58.83	288.32	224.32	217.22	38.88	30.47	27.62

N = number of subjects with a valid serology result pre-dose 1 and/or post dose 3.
n = number of PPI subjects with pre-vaccination antibody levels.
NA = Not available, anti-PT values were generated in the ------ performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: p3t06si.pdf page 3354, September 7, 2006 questions1_133.pdf page 320

Reverse cumulative distribution curves were presented for the post-dose 3 response to PT, FHA, FIM, pertactin, PRP, diphtheria, tetanus, polio serotypes 1, 2 and 3. These are not presented in this review.

Stage II

Pre-dose 4 immune response data:
Pre-dose 4 GMT levels for subjects in Group 1 (DAPTACEL + ActHIB at 15-16m) and Group 4 (Pentacel at 15-16m) are presented in Table 103. Data presented in this table are from subjects included in the PPI population of Stage II. Not unexpectedly, antibody levels to PRP, FHA, fimbriae, pertactin, diphtheria and tetanus antigens have declined during the time since vaccination. Anti-PT ----- values were generated in a non-specific assay thus, PT GMTs are not presented.

Table 103: Study P3T06 Pre-dose 4 GMT levels to PRP, pertussis antigens*, diphtheria and tetanus toxoids for those subjects in the Stage II PPI population

Antigens	Group 1 (DAPTACEL + ActHIB)			Group 4 (Pentacel at 15-16m)		
	N	GMT	(95% CI)	N	GMT	(95% CI)
PRP (ug/mL)	323	0.25	(0.21, 0.29)	335	0.29	(0.24, 0.34)
FHA (EU/mL)	322	5.37	(4.81, 6.00)	346	12.94	(11.76, 14.24)
FIM (EU/mL)	320	29.07	(26.11, 32.38)	346	35.53	(32.15, 39.26)
PRN (EU/mL)	321	7.83	(6.97, 8.79)	344	6.32	(5.67, 7.04)
Diphtheria (IU/mL)	310	0.57	(0.51, 0.64)	328	0.57	(0.51, 0.64)
Tetanus (IU/mL)	314	0.50	(0.45, 0.54)	337	0.48	(0.44, 0.52)

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: p3t06sii.pdf page 922

Pre-dose 4 anti-PRP levels ($\geq$ 0.15 ug/mL) are presented in Table 104. Approximately 60-65% of subjects administered three doses of ActHIB or Pentacel had seroprotective levels at 15-16m of age, prior to administration of a fourth dose of Pentacel or ActHIB. Although non-inferiority acceptance criteria were not pre-specified sanofi pasteur have provided the 2-sided 90% CI on the difference in rates of anti-PRP $\geq$ 0.15 ug/mL.

Table 104: Study P3T06 Pre-dose 4 anti-PRP seroprotective levels for those subjects in the Stage II PPI population

Antigens	Group 1 (DAPTACEL + ActHIB)			Group 4 (Pentacel at 15-16m)			Group 1 minus group 4 (90% CI)
	n/N	%	(95% CI)	n/N	%	(95% CI)	
PRP % ≥ 0.15 ug/mL	196/323	60.7	(55.1, 66.0)	219/335	65.4	(60.0, 70.5)	-4.69 (-10.88, 1.49)

'n' is the number of subjects who met the criteria of the test indicated.
'N' is the total number of subjects with available serology data from the PP Immunogenicity Population.
Group 1: Received 4th Dose of DAPTACEL® and ActHIB® at 15 to 16 months.
Group 4: Received 4th Dose of Pentacel alone at 15 to 16 months.
Source; p3t06sii.pdf page 944-945

Stage II- Non-inferiority of seroconversion/seroprotection rates elicited by Pentacel administered alone at 15-16 months of age compared to DAPTACEL administered with ActHIB at 15-16 months of age – Table 105 presents the results of the primary non-inferiority analyses of the response to a fourth dose of Pentacel (Group 4) relative to a fourth dose of DAPTACEL and ActHIB (group 1). Using 2-sided 90% CI for the difference in seroconversion/seroprotection rates the statistical criteria for non-inferiority between groups (UL 90% CI <10%) was met for all antigens except PT. Anti-PT ----- values were generated in a non-specific assay thus, anti-PT seroconversion rates and the non-inferiority analysis are not presented. Analyses using the 95% CI for the difference in rates were not pre-specified in the protocol, however these analyses were provided (p3t06sii.pdf page 904) and are shown in the table. Non-inferiority criteria were not prespecified in the protocol for anti-diphtheria and anti-tetanus levels ⩾1.0 IU/mL.

Table 105: Study P3T06 Stage II Seroconversion/seroprotection rates* and non-inferiority analyses one month following a fourth dose of Pentacel compared to DAPTACEL + ActHIB administered at 15-16 months

Antigens	Group 1 DAPTACEL + ActHIB at 15-16m			Group 4 Pentacel at 15-16m			Group 1minus Group 4[2]		
	n/N	%	95% CI	n/N	%	95% CI		90% CI	95% CI
FHA (EU/mL) ≥4-fold rise[1]	192/242	79.3	(73.7, 84.3)	205/232	88.4	(83.5, 92.2)	-9.02	(-14.53, -3.52)	(-15.58, -2.46)
FIM (EU/mL) ≥4-fold rise [1]	217/237	91.6	(87.3, 94.8)	215/230	93.5	(89.5, 96.3)	-1.92	(-5.92, 2.08)	(-6.68, 2.85)
PRN (EU/mL) ≥4-fold rise[1]	237/241	98.3	(95.8, 99.5)	215/232	92.7	(88.5, 95.7)	5.67	(2.55, 8.79)	(1.95, 9.39)
Diphtheria									
≥0.1 IU/mL	328/328	100.0	(98.9, 100.0)	341/341	100.0	(98.9, 100.0)	0.00	NA	NA
≥1.0 IU/mL*	314/328	95.7	(92.9, 97.6)	329/341	96.5	(93.9, 98.2)	-0.75	(-3.21, 1.71)	(-3.68, 2.19)
Tetanus									
≥0.1 IU/mL	334/334	100.0	(98.9, 100.0)	352/352	100.0	(99.0, 100.0)	0.00	NA	NA
≥1.0 IU/mL*	332/334	99.4	(97.9, 99.9)	327/352	92.9	(89.7, 95.4)	6.50	(4.15, 8.86)	(3.70, 9.31)
PRP									
≥1.0 ug/mL	326/340	95.9	(93.2, 97.7)	353/361	97.8	(95.7, 99.0)	-1.90	(-4.08, 0.28)	(-4.50, 0.70)

[1] Fold rise is calculated by post-dose 4/pre-dose 1 titer.
[2] Non-inferiority: Upper limit of the two-sided 90% CI of the seroresponse difference (Group 1 – Group 4) is <10%.
*Criteria for non-inferiority were not specified.
Group is defined as per randomization.
Group 1 received the 4th dose of DAPTACEL® concomitantly with the 4th dose of ActHIB® at 15-16 months of age. The 1st dose of M-M-R®II and VARIVAX®, and the 4th dose of Prevnar® were given at 12 months.
Group 4 received the 4th dose of Pentacel at 15-16 months of age. The 1st dose of M-M-R®II and VARIVAX®, and the 4th dose of Prevnar® were given at 12 months. GMTs are based on the number of subjects with available serology data from the PP Immunogenicity Population.
*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
NA = Not Applicable.
Source: p3t06sii.pdf page 92, 93, 95 and 900

Stage II -Non-inferiority of GMTs following Pentacel administered alone at 15-16 months compared to DAPTACEL administered with ActHIB at 15-16 months of age – Table 106 presents the results of the primary non-inferiority analyses of the response to a fourth dose of Pentacel (Group 4) relative to a fourth dose of DAPTACEL and ActHIB (Group 1). Using 2-sided 90% CI for the ratio of GMTs the statistical criteria for non-inferiority between groups (UL 90% CI <1.5) were met for all antigens except pertactin (UL 90% CI = 2.25), tetanus (UL 90% CI =1.71) and PT (the ----- values were generated in a non-specific assay). The clinical significance of failing to demonstrate non-inferiority to pertactin is unknown since there is currently, no well accepted correlate of efficacy for pertussis. However, the response to pertactin is significantly diminished as compared to the response to the same quantity of pertactin contained in DAPTACEL. Although the response to tetanus is decreased as compared to the response to the tetanus toxoid contained in DAPTACEL this is likely not of clinical relevance since 100% of children had anti-tetanus levels $\geqslant$0.1 IU/mL and 93-99% had levels $\geqslant$1.0 IU/mL (see Table 106 above). Non-inferiority criteria were not pre-specified for the analysis of GMT to PRP-T.

Table 106: Study P3T06 Stage II GMTs and non-inferiority analyses for the pertussis antigens† and diphtheria and tetanus toxoids one month following a fourth dose of Pentacel compared to DAPTACEL + ActHIB administered at 15-16 months. PP Immunogenicity.

Antigens	Group 1 (DAPTACEL + ActHIB)			Group 4 (Pentacel at 15-16m)			Group 1/Group 4[1]		
	N	GMT	(95% CI)	N	GMT	(95% CI)		(90% CI)	(95% CI)
FHA (EU/mL)	345	64.02	(58.81, 69.69)	366	107.94	(99.42, 117.20)	0.59	(0.54, 0.66)	(0.53, 0.67)
FIM (EU/mL)	347	513.54	(457.72,576.17)	367	553.39	(496.11, 617.27)	0.93	(0.81, 1.06)	(0.79, 1.09)
PRN (EU/mL)	347	186.07	(168.16, 205.88)	367	93.59	(83.98, 104.31)	1.99	(1.76, 2.25)	(1.72, 2.30)
Diphtheria (IU/mL)	328	5.69	(5.11, 6.34)	341	5.15	(4.66, 5.70)	1.10	(0.98, 1.25)	(0.96, 1.28)
Tetanus (IU/mL)	334	4.98	(4.61, 5.37)	352	3.19	(2.96, 3.44)	1.56	(1.43, 1.71)	(1.40, 1.74)
PRP (ug/mL)*	340	20.49	(17.32, 24.24)	361	17.71	(15.30, 20.50)	1.16	(0.96, 1.39)	(0.93, 1.44)

†anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

* Non-inferiority criteria were not prespecified.

[1] Non-inferiority: Upper limit of the two-sided 90% CI of the GMT ratio is <1.5.

Group is defined as per randomization.

Group 1 received the 4th dose of DAPTACEL® concomitantly with the 4th dose of ActHIB® at 15-16 months of age. The 1st dose of M-M-R®II and VARIVAX, and the 4th dose of Prevnar were given at 12 months.

Group 4 received the 4th dose of Pentacel at 15-16 months of age. The 1st dose of M-M-RII and VARIVAX, and the 4th dose of Prevnar were given at 12 months. Shaded cells: non inferiority criteria not met.

Stage II -Observational Objectives

Presentation of GMTs to polio following a fourth dose of Pentacel – the response of subjects to pertussis antigens, diphtheria, tetanus and PRP following a fourth dose of Pentacel or DAPTACEL administered with ActHIB have been presented above (Table 105 and 106). The response to a fourth dose of polio administered to subjects enrolled in group 4 (Pentacel) is shown in Table 107. The GMT is higher than noted after three doses.

Table 107: Study P3T06 Stage II Polio GMTs following a fourth dose of Pentacel administered at 15-16m of age. PPI population.

Antigen	Group 4 (Pentacel at 15-16m)		
	N	GMT	(95% CI)
Polio 1	298	3341.73	(2804.08, 3982.47)
Polio 2	334	4436.69	(3854.26, 5107.13)
Polio 3	302	10187.91	(8348.29, 12432.91)

Presentation of post-dose 4 anti-tetanus and anti-diphtheria responses according to pre-specified threshold levels pre-dose 4. – Table 108 presents the results of an analysis of the response to diphtheria and tetanus toxoids according to pre-specified cut-off levels. The rates of seroresponse based on pre-dose 4 cut-off levels appear to be similar (overlapping 95% CIs) for both groups. Any difference is unlikely to be clinically significant since 100% of subjects in both groups had post-dose four anti-body levels $\geqslant$ 0.1 IU/mL to both antigens.

Table 108: Study P3T06 Stage II Analysis of post –dose 4 seroresponse[1] to diphtheria and tetanus toxoids based on pre-dose 4 levels. PPI population

Antigen	Criteria		Group 1 (DAPTACEL + ActHIB)			Group 4 (Pentacel)		
	Pre-dose4	Post dose 4	n/N	%	95% CI	n/N	%	95% CI
Diphtheria IU/mL	<0.1	$\geqslant$ 0.4*	17/20	85.0	(62.1, 96.8)	13/19	68.4	(43.4, 87.4)
	≥0.1-<2.0	≥4-fold[2]	229/247	92.7	(88.7, 95.6)	241/254	94.9	(91.4, 97.2)
	≥2.0	≥2-fold[2]	29/32	90.6	(75.0, 98.0)	32/35	91.4	(76.9, 98.2)
Tetanus IU/mL	<0.1	$\geqslant$0.4*	6/6	100.0	(54.1, 100.0)	11/12	91.7	(61.5, 99.8)
	≥0.1-<2.0	≥4-fold[2]	254/286	88.8	(84.6, 92.2)	231/301	76.7	(71.6, 81.4)
	≥2.0	≥2-fold[2]	6/11	54.5	(23.4, 83.3)	6/14	42.9	(17.7, 71.1)

* September 7, 2006 submission clarified this should be $\geqslant$ 0.4 IU/mL.
[1] Defined as those who had both pre-Dose 4 and post-Dose 4 bleeds and satisfied pre-Dose 4 condition.
[2] The fold-rise is calculated by Post-Dose 4/Pre-Dose 4 antibody level.
Note: n is the number of subjects in the treatment group satisfying the post-Dose 4 criteria.
Group 1: Received 4th Dose of DAPTACEL® and ActHIB® at 15 to 16 months.
Group 4: Received 4th Dose of Pentacel alone at 15 to 16 months.
Source: p3t06sii.pdf page 956

Anti-pertussis response post-dose 4 stratified by post dose 3 anti-pertactin levels. The study report contains a presentation of post dose 4 GMTs for Stage II per-protocol population stratified by post-dose 3 anti-pertactin cut-off levels, these data are presented in Table 109. Approximately 25% of subjects had post-dose 3 anti-pertactin levels $\leq$ 20 EU/mL. The data suggest that those subjects in groups 1 and 4 with post dose 3 anti-pertactin levels $\leqslant$ 20 EU/mL do not respond to a

fourth dose of either fimbriae or pertactin as well as those subjects with post dose 3 levels >20 EU/mL. The response of these subjects to FHA may be less affected. Anti-PT values were generated in a non-specific thus it is not appropriate to present these data. The available data suggest that poor responders to pertactin may also be poor responders to fimbriae and to further doses of pertactin. The clinical relevance of this is unclear.

Table 109: Study P3T06 Stage II Post dose 4 GMT to FHA fimbriae, and pertactin* based on post dose 3 anti-pertactin seroresponse levels. PPI population

	Group 1 (DAPTACEL + ActHIB)		Group 4 (Pentacel)	
Post dose 3 anti-pertactin level	**N**	**GMT (95% CI)**	**N**	**GMT (95% CI)**
	Anti-FHA level post dose 4			
< 5 EU/mL	7	63.94 (21.96, 186.21)	10	69.36 (22.18, 216.93)
≥5-<10 EU/mL	23	60.71 (46.27, 79.65)	17	87.35 (65.13, 117.15)
≥10- ≤20 EU/mL	39	51.63 (40.25, 66.23)	52	96.08 (77.61, 118.94)
≤ 20 EU/mL	69	55.7 (46.4, 66.9)	79	90.3 (74.3, 109.8)
>20 EU/mL	217	69.32 (62.28, 77.16)	207	122.29 (110.12, 135.81)
	Anti-Fim 2 & 3 GMT post dose 4			
<5 EU/mL	7	361.85 (92.70, 412.49)	10	414.18 (225.41, 761.03)
≥5-<10 EU/mL	23	271.94 (191.90, 385.37)	17	316.95 (184.93, 543.21)
≥10-≤20 EU/mL	39	264.61 (181.33, 386.13)	52	486.42 (393.36, 601.49)
≤ 20 EU/mL	69	275.6 (212.6, 357.4)	79	434.7 (359.4, 525.6)
>20 EU/mL	219	633.83 (554.31, 724.75)	207	707.23 (620.01, 806.71)
	Anti-pertactin GMT post dose 4			
< 5 EU/mL	7	53.73 (19.74, 146.28)	10	20.58 (11.42, 37.09)
≥5-<10 EU/mL	23	97.89 (63.93, 149.88)	17	33.21 (19.49, 56.61)
≥10-≤20 EU/mL	39	98.78 (75.91, 128.55)	52	49.83 (41.09, 60.42)
≤ 20 EU/mL	69	92.6 (74.5, 115.1)	79	40.8 (33.8, 49.3)
>20 EU/mL	219	226.87 (201.95, 254.85)	207	125.72 (109.89, 143.83)

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: p3t06sii.pdf page 958-960, September 7, 2006 Questions1_133.pdf page 321

Anti-pertussis response post-dose 4 stratified by post-dose 4 anti-pertactin levels: In response to a query from CBER sanofi provided an analysis of post-dose 4 response to PT, FHA and fimbriae in subjects with post dose 4 anti-pertactin levels ⩽ 20EU/mL and ≥ 20 EU/mL. These data are presented in Table 110. Of Pentacel subjects 26 (~10%) had post-dose 4 levels ⩽ 20 EU/mL, fewer (3, ~1%)) of those who had received DAPTACEL had post-dose 4 levels ⩽ 20 EU/mL. This analysis suggests that those subjects who are poor responders to pertactin have lower antibody levels to FHA and fimbriae as compared to those subjects with anti-pertactin levels >20 EU/mL post-dose4. Sanofi states that the GMTs to FHA and fimbriae tended to be higher among subjects in the Pentacel group for both stratified anti-pertactin levels. Anti-PT values were generated in a non-specific ------- thus, these values are not acceptable and it is not appropriate to present the response to PT among subjects with anti-pertactin levels ⩽20 EU/mL and > 20 EU/mL.

Table 110: P3T06 Stage II Anti- FHA and Fim GMTs post-dose 4 among subjects with post-dose 4 anti-pertactin levels ⩽ 20 EU/mL and > 20EU/mL.

		Pentacel N= 366-367			DAPTACEL N = 346-347		
Post-dose4 anti-pertactin level		**n**	**GMT**	**95% CI**	**n**	**GMT**	**95% CI**
≤ 20 EU/mL	FHA	26	54.9	(33.8,89.2)	3	25.9	(2.9,231.9)
	FIM	26	229.7	(126.1,418.4)	3	146.6	(18.1, 1186.2)
>20 EU/mL	FHA	340	113.7	(105.1,123.0)	342	64.5	(59.3,70.2)
	FIM	341	591.8	(532.1,658.0)	344	519.2	(462.7,582.6)

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: September 7, 2006 questions1_133.pdf page 322

Reverse cumulative distribution curves –are not presented in this review.

Analysis of seroresponders based on a revised definition of seroresponders: Using this revised definition seroconversion post dose 4 was defined as ⩾ LOQ for subjects with pre-dose 1 antibody levels < LOQ (anti-FHA <5 EU/mL, anti-fimbriae <17 EU/mL and anti-pertactin <5 EU/mL) or ⩾ pre-dose 1 for subjects with pre-dose 1 ≥ LOQ. These analyses are presented in Table 111. Because anti-PT values were generated in a non-specific ----- these values are not acceptable to CBER and are not presented. Sanofi pasteur note in their study report that this definition is compatible with that used for evaluation of the acellular pertussis based combination most recently licensed in the US (Pediarix). However, it should be noted that the definition of seroresponder used in evaluation of Pediarix was based on pre-dose 1 antibody levels compared to those following a third dose administered at 6 months of age using the assay developed and run by GSK. CBER has not concurred with this revised definition of seroresponder for assessment of Pentacel due to concerns about assay precision. Although sanofi pasteur state that non-inferiority was met since the UL of the 90% CI of the difference in rate (DAPTACEL minus Pentacel) was <10% it should be noted this was not a prespecified analysis with pre-defined acceptance criteria.

Table 111: Study P3T06 Seroconversion rates† and non-inferiority following a fourth dose of DAPTACEL or Pentacel using a revised definition of seroconversion. PPI population.

Antigens	**Criteria**	**Group 1 DAPTACEL n/N % (95% CI)**	**Group 4 Pentacel n/N % (95% CI)**	**Non-inferiority Comparison Group 1 minus Group 4* (90% CI)**
FHA (EU/mL)	**≥5**	229/242 94.6 (91.0, 97.1)	228/232 98.3 (95.6, 99.5)	-3.65 (-6.41, -0.88)
FIM (EU/mL)	**≥17**	234/237 98.7 (96.3, 99.7)	228/230 99.1 (96.9, 99.9)	-0.40 (-1.96, 1.17)
PRN (EU/mL)	**≥5**	240/241 99.6 (97.7, 100.0)	229/232 98.7 (96.3, 99.7)	0.88 (-0.52, 2.28)

Seroconversion is ≥ 5 EU/mL for subjects with pre-Dose 1 antibody level < 5 EU/mL or post-Dose 4 antibody level ≥ pre-Dose 1 antibody level for subjects with pre-Dose 1 antibody level ≥5 EU/mL (≥17 EU/mL (LOQ) is used for FIM).

†anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
*Non-inferiority criteria not pre-specified
Source: p3t06sii.pdf page 104

6.3.3 Comments and Conclusions:

Non-inferiority of Pentacel relative to separately administered US-licensed vaccines DAPTACEL, ActHIB and IPOL:
In Study P3T06 subjects were administered DAPTACEL or Pentacel concomitantly with other US-licensed vaccines at 2, 4 and 6 months of age. During Stage II the response of subjects administered a fourth dose of Pentacel was compared to those of subjects administered a fourth dose of DAPTACEL concomitantly with ActHIB at 15-16 months of age.

Because the PT ----- performed in the sanofi pasteur, Canada, laboratory was determined to be non-specific the values are unacceptable to CBER. Therefore, a comparison of anti-PT levels following Pentacel or separately administered vaccines is not available for the randomized immunogenicity population from this Study. The data to support non-inferiority of response to PT antigen of Pentacel compared to separately administered vaccines is based on a subset of sera from Study P3T06 (see Section 6.3.4).

Following the third dose non-inferiority of the response to FHA, fimbriae, pertactin, diphtheria, tetanus, and to PRP-T was demonstrated when Pentacel was administered as compared to separately administered vaccines.

Following the fourth dose non-inferiority was demonstrated for rate of four fold rise relative to pre-dose 1 antibody levels for FHA, fimbriae and pertactin, for the rate of anti-tetanus and anti-diphtheria seroprotective levels $\geqslant$0.1 IU/mL and anti-PRP seroprotective levels $\geqslant$ 1.0 ug/mL. Non –inferiority was also demonstrated for GMT response to FHA, fimbriae and diphtheria toxoid. Non-inferiority was not demonstrated for the GMT response to pertactin (UL 90% CI ratio =2.25) and tetanus toxoid (UL 90% CI ratio = 1.71). The diminished GMT response to tetanus toxoid is not clinically relevant since 100% of subjects in both groups had anti-tetanus seroprotective levels $\geqslant$ 0.1 IU/mL and 93-99% had levels $\geqslant$ 1.0IU/mL. With regard to the diminished response to pertactin the manufacturer notes (p3t06sii.pdf page 146-147) that since the rate of 4-fold rise met the criteria for non-inferiority the lower GMT "does not seem to be of clinical significance in this study." An analysis of seroresponse using a revised definition was presented (Table 111) to support non-inferiority of response to pertactin and the use of antibody levels >5 EU/mL as indicative of protection. However, there is no well accepted clinical or laboratory correlate of immunity to pertussis thus, it is unclear whether the diminished GMT response affects effectiveness.

The DAPTACEL immunogenicity data has been submitted to support co-administration of DAPTACEL with other US-licensed vaccines (STN 103666/5071). This supplement and a revised DAPTACEL package insert were approved November 9, 2006.

An analysis of post dose 3 and 4 response to the pertussis antigens based on arbitrary pre-dose 1 vaccination levels is shown in the following table (Table 112). Sanofi state that higher pre-immunization antibody levels had a trend toward lower post-dose 3 GMTs, this trend was also observed following the fourth dose for FHA and fimbriae but not pertactin (Table 51 which presents pertussis GMTs and seroresponse rates based on pre-vaccination antibody levels of

children enrolled in Sweden I and Study 494-01 presented a similar finding for pertactin). These post-immunization data stratified by pre-existing antibody levels should be interpreted with caution however, due to the small number of subjects in particular those with high pre-existing antibody levels. These data also show that among subjects with pre-vaccination anti-pertactin levels ≤20 EU/mL administered Pentacel the post-dose 4 anti-pertactin levels (~90 EU/mL) were lower than the post-dose 4 level achieved by such subjects administered four doses of DAPTACEL (~174 EI/mL).

Table 112: Study P3T06 post dose 3 and 4 seroresponse rates and GMTs* stratified by pre-vaccination antibody levels.

	Anti-PT*			**Anti-FHA**			**Anti-Fimbriae**			**Anti-pertactin**		
Pre-vx ------- level cut-offs	**<5**	**≥5-≤30**	**>30**	**<3**	**≥3-⩽20**	**>20**	**<17**	**⩾17-<50**	**>50**	**<3**	**⩾3-≤20**	**>20**
DAPTACEL												
Post dose 3 (N=780-784, pooled groups)												
n	NA	NA	NA	255	443	93	596	136	50	427	310	47
% ≥4 x-rise	NA	NA	NA	82.7	51.9	0.0	86.4	69.1	14.0	81.0	61.3	8.5
GMT	NA	NA	NA	34.37	29.03	21.14	311.47	183.74	108.83	47.32	35.78	23.81
Post dose 4[1] (N=237-242)												
n	NA	NA	NA	81	131	30	175	41	21	129	96	16
% ⩾ 4x rise	NA	NA	NA	100.0	82.4	13.3	98.9	90.2	57.1	100.0	100.0	75.0
GMT	NA	NA	NA	67.5	66.4	49.2	579.4	396.8	339.3	175.6	173.3	221.8
Pentacel Group												
Post dose 3 (N=244-247)												
n	NA	NA	NA	87	137	23	189	41	14	142	92	13
% 4x rise	NA	NA	NA	90.8	71.5	17.4	88.4	68.3	35.7	82.4	50.0	7.7
GMT	NA	NA	NA	83.58	70.68	58.83	288.32	224.32	217.22	38.88	30.47	27.62
Post dose 4 (N= 230-232)												
n	NA	NA	NA	80	132	20	180	35	15	134	86	12
% 4x rise	NA	NA	NA	100.0	90.2	30.0	98.3	88.6	60.0	99.3	88.4	75.0
GMT	NA	NA	NA	127.9	107.8	80.4	640.8	399.7	421.5	90.0	90.2	201.6

N = number of subjects with a valid serology result pre-dose 1 and/or post dose 3 or post-dose4.
n = number of PPI subjects with pre-vaccination antibody levels.
*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
[1] For DAPTACEL at dose 4 only Group 1 is presented (DAPTACEL + ActHIB at 15 months of age)
Source: p3t06si.pdf page 3354, September 7, 2006 questions1_133.pdf page 320.

Response to PRP-T administered as ActHIB or Pentacel: In study P3T06 the criteria for demonstration of non-inferiority of response to ActHIB following the third or fourth dose were met. However, the proportion of subjects with an anti-PRP levels of $\geqslant$ 1 ug/mL following the third dose of ActHIB or Pentacel in P3T06 appears lower than observed with previous experience with ActHIB.

Table 113 presents data from previous studies on responses to ActHIB or OmniHIB (PRP-T manufactured by Aventis Pasteur, Inc. and distributed by GlaxoSmithKline) administered to U.S. infants at 2, 4, and 6 months of age. The studies are listed by study period, in approximate chronological order. For comparative purposes the responses to ActHIB observed in control subjects enrolled in Study 494-01 and P3T06 are also included. The serology assays for non-BLA studies were conducted in various laboratories using ----------. Except for the first study listed in the table, the proportion of infants who achieved an anti-PRP level $\geq$1.0 µg/mL following the third dose of PRP-T ranged from approximately 89% to 97%, with post-dose 3 GMTs ranging from approximately 5.5 µg/mL to 7.8 µg/mL. Several factors (e.g., race/ethnicity, concomitantly administered vaccines, degree of natural exposure and boosting, assay) may affect the observed immune responses following Hib vaccines, and it is difficult to interpret comparisons across studies. The anti-PRP assay and the data supporting the transfer of the anti-PRP assay to a different laboratory (see Section 5.5) have been reviewed by a member of the BLA committee and found to be acceptable. The clinical relevance of the apparently lower anti-PRP responses following ActHIB that were observed in Study P3T06 relative to previous experience with PRP-T also is not known. In a separate study, M5A07, the effect of concomitantly administered Prevnar on the immune responses to the first three doses of Pentacel were assessed. Summary tables of the per protocol immunogenicity analyses from Study M5A07 were submitted to the Pentacel BLA, and suggest that co-administration of Prevnar did not interfere with the immune response to PRP-T following three doses of Pentacel. The final study report for Study M5A07, has not been submitted to this BLA.

Table 113. Summary of available data on clinical experience with ActHIB or OmniHIB administered at 2, 4, and 6 months of age in U.S. infants (Studies included in the Pentacel BLA shaded).

Study period	Concomitantly administered vaccines	Race/ Ethnicity of enrolled subjects	N	pre-dose 1 GMT (95% CI)	post-dose 3 GMT (µg/ml) (95% CI)	post-dose 3 % ≥0.15 µg/ml (95% CI)	post-dose 3 % ≥1.0 µg/ml (95% CI)	Assay Laboratory	Source
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12/99-4/02	HCPDT, POLIOVAX, RECOMBIVAX HB (2 and 6 mo), Prevnar (3 doses 63%, 2 doses 30%, 0 or 1 dose 7% of subjects)	60% Caucasian 11% African Am. 13% Hispanic 7% Asian 9% Other (safety pop., N=1032)	401	n/a	6.2 (5.4, 7.2)	98.3 (96.4, 99.3)	88.8 (85.3, 91.7)	sanofi pasteur-US	494-01si.pdf
5/01-1/04	DAPTACEL, IPOL, RECOMBIVAX HB (at 2 and 6 mo), Prevnar	77% Caucasian 6% African Am. 7% Hispanic 1% Asian 9% Other	1128	n/a	2.3 (2.1, 2.5)	93.3 (91.6, 94.7)	70.8 (68.1, 73.5)	sanofi pasteur-US	p3t06 si.pdf

[1] Decker MD, Edwards KM, et al. Comparative trial in infants of four conjugate *Haemophilus influenzae* type b vaccines J Pediatr 1992;120:184-189

[2] Granoff DM, Anderson EL, et al. Differences in the immunogenicity of three *Haemophilus influenzae* type b conjugate vaccines in infants J Pediatr 1992;121:187-194

DTwP = Diphtheria and tetanus toxoids and whole-cell pertussis vaccine

OPV = live oral poliovirus vaccine

Tripedia = DTaP manufactured by Aventis Pasteur, Inc.

Pediarix = Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine Combined manufactured by GlaxoSmithKline

Infanrix = DTaP manufactured by GlaxoSmithKline

Engerix B = Hepatitis B Vaccine (Recombinant) manufactured by GlaxoSmithKline

Orimune = live oral poliovirus vaccine manufactured by Lederle Laboratories

HCPDT = unlicensed DTaP vaccine manufactured by Aventis Pasteur Ltd.; HCPDT is the DTaP component of Pentacel

n/a indicates not available

Source: Clinical review of DAPTACEL supplement 103666/5071 by Dr. Karen Farizo

Because of concerns about the apparently relatively low immune responses (specifically GMTs and proportion ≥1.0 μg/ml) following three doses of ActHIB in Study P3T06, CBER requested an analysis of pre-dose 4 seroprotection rates. At 15-16 months of age, approximately two-thirds (60.7%) of subjects who had received three doses of ActHIB or three doses of Pentacel (65.4%) at 2, 4, and 6 months of age had a pre-dose 4 anti-PRP level ⩾0.15 μg/ml, the level of antibody that historically has been accepted as correlating with at least short-term protection against invasive Hib disease. Following the fourth dose of ActHIB or Pentacel 95.9 and 97.8% of subjects in the DAPTACEL and Pentacel groups respectively, had anti-PRP levels ⩾1.0 ug/mL, the level historically accepted as correlating with long-term protection.

The Integrated Summary of Immunogenicity (isi.pdf page 134) states that the most relevant study for evaluation of the immunogenicity of Pentacel is Study P3T06 in which the control vaccines represent standard of care. Sanofi pasteur note that the post-dose 3 anti-PRP data from Study P3T06 "are in concordance with other non-pivotal published studies in which either Pentacel or a HCPDT//PRP-T combination vaccine elicited very similar anti-PRP response as its separately administered ActHIB controls." In one referenced study following three doses of Pentacel approximately 85% of Canadian subjects achieved anti-PRP levels ⩾ 1.0 ug/mL and GMT 4.4 ug/mL (the control group received a Canadian licensed whole cell DTP-IPV-PRP-T vaccine; Mills *et al.* 1998 Vaccine 16: 576-585). In the other study Taiwanese infants who received HCPDT//PRP-T vaccine containing the same DTaP and PRP-T components as contained in Pentacel achieved a GMT 11.8 ug/mL, 94% had seroprotective levels ⩾1.0 ug/mL (the control group administered DTaP and ActHIB separately achieved GMT 13.0 ug/mL, 99% had seroprotective levels ⩾1.0 ug/mL; Lee *et al.* Pediatrics 1999 103: 25-30). All assays were performed at sanofi pasteur-Canada. No data comparing the sanofi pasteur-Canada serological assay to that performed by sanofi-pasteur-US and used to assess P3T06 sera has been provided in this BLA. In comparison with these data the response of infants enrolled in P3T06 to three doses of Pentacel or ActHIB is lower than expected. Sanofi pasteur note race/ethnicity as a factor affecting the response to PRP-T and at CBER's request provided a summary of response to PRP-T by race/ethnicity across studies (see Section 7.0).

Immune response to Polio: In Study P3T06 subjects administered DAPTACEL also received IPOL at 2, 4 and 6 months of age, these subjects did not receive a fourth dose of IPOL in the study. Those subjects randomized to receive Pentacel received a fourth dose of polio antigens at 15-16m of age. Following three doses of either vaccine 100% of subjects had had protective titers to each of the poliovirus serotypes.

Immune response to Prevnar: In Study P3T06 all subjects received the first three doses of Prevnar coadministered with Pentacel or DAPTACEL at 2, 4 and 6 months of age. Although there is no generally accepted protective level of antibody to the pneumococcal serotypes contained in Prevnar, antibody levels of ≥ 0.15 μg/mL and ≥ 0.50 μg/mL and GMTs were examined. Although no formal non-inferiority analyses compared the response of Prevnar co-administered with Pentacel to that of Prevnar co-administered with Pentacel the Seroresponse rates and GMTs were comparable (overlapping 95% CIs).

Immune response to hepatitis B vaccine: In study P3T06, subjects were to have received the first dose of hepatitis B vaccine (manufacturer not specified) from birth to 28 days before the first dose of study vaccine. At 2 and 6 months of age, the second and third doses of hepatitis B vaccine were with RECOMBIVAX HB, administered concomitantly with DAPTACEL, IPOL, ActHIB, and Prevnar or with Pentacel and Prevnar. Following the third dose of hepatitis B vaccine, among subjects in the pooled DAPTACEL groups, the anti-HBsAg GMT was 127

mIU/mL and 92.4% had a protective titer ≥10.0 mIU/mL. Among subjects in the Pentacel group the anti-HBsAg GMT was 121 mIU/mL and 89.8% had a protective titer ⩾10mUI/mL.

This response to three doses of hepatitis B vaccine appears diminished in comparison to the data presented in Study 494-01 in which infants administered Pentacel achieved anti-HBsAg GMT 365 mIU/mL and 98% had a protective titer ⩾10mIU/mL.

In Study 494-03, among 169 subjects who received hepatitis B vaccine on a 0, 2, 6 months schedule, with the first dose administered outside of the study and the second and third doses with RECOMBIVAX HB administered concomitantly with Pentacel and Prevnar, 98.2% had an anti-HBs ≥10 mIU/ml, with a GMT of 292.0 mIU/ml at 7 months of age. Among 83 subjects who received all three doses of hepatitis B vaccine with RECOMBIVAX HB concomitantly with Pentacel and Prevnar at 2, 4, and 6 months of age, 100% had an anti-HBs ≥10 mIU/ml, with a GMT of 424.2 mIU/ml at 7 months of age.

6.3.4 Study P3T06 Sera Re-test Plan and Results

Re-assay of sera from Study P3T06 and reanalysis of non-inferiority of response to pertussis toxoid antigen of Pentacel relative to DAPTACEL.

6.3.4.1 Background and Rationale/Objective

In the initial BAL submission evaluation of the effectiveness of the pertussis antigens of Pentacel were evaluated by comparison of the immune responses of US-children administered four doses in Study 494-01 to those of infants administered three doses of DAPTACEL in the Sweden I efficacy study. Immunogenicity of the pertussis antigens of Pentacel compared to DAPTACEL were also evaluated in Study P3T06 following three and four doses of each vaccine. In March 2007, CBER became aware of data which suggested that the PT ----- conducted in the Canadian laboratory generated higher ----- values compared to the values obtained in the sanofi pasteur-US, laboratory. Preliminary information submitted to the Adacel license file (STN 125111/108) suggested that the ---------- ---------- ----------. In an April 23, 2007, CR letter CBER requested sanofi pasteur submit the results of their on-going investigation to the Pentacel BLA and address the implications of this finding for the assessment of immunogenicity of the PT antigen of Pentacel. Following review of the information submitted and discussions between sanofi pasteur and CBER representatives during a May 18, 2007, meeting CBER requested that sanofi pasteur provide a plan for reassessment of immunogenicity of the PT component of Pentacel to support a claim of non-inferiority relative to DAPTACEL. Because the PT ----- assay had been moved to the US laboratory and was no longer performed in the Canadian laboratory the immunogenicity data would be generated in the US laboratory. Thus, the applicant was asked to demonstrate that the PT ----- performed in the US laboratory was adequate to assess the response to this antigen in sera from infants and children (see June 8, 2007 CR letter, August 20, 2007 IR letter from CBER and CBER review by S. Menzies and D. Burns). Sanofi provided a plan to reassay available sera from Study P3T06 and evaluate non-inferiority of response to the pertussis toxoid component of Pentacel relative to DAPTACEL (July 4, 2007 and August 13, 2007 BLA submissions). Following further discussions with CBER this was revised and a proposal submitted to the BLA October 18, 2007. CBER concurred with the proposal and the immunogenicity data to support non-inferiority of the PT antigen of Pentacel relative to that of DAPTACEL were submitted December 21, 2007. The following is a review of this submission.

6.3.4.2 Study P3T06 Design Overview

See Section 6.3 (Trial #4, Study P3T06 review).

Primary immunogenicity objectives

Stage I

1. To compare the 4-fold rise rates and the GMCs elicited by the PT antigen in Pentacel (group 4) with that of DAPTACEL (pooled groups 1, 2 and 3) when these vaccines are co-administered with other recommended vaccines, after the infant series.

Stage II

1. To compare the 4-fold rise rates and the GMCs elicited by the PT antigen in Pentacel (Group 4) with that in DAPTACEL (Group 1), after the toddler dose.

6.3.4.3 Immunogenicity Endpoints and Evaluation Criteria

Primary Endpoints and Evaluation criteria

Table 114: Study P3T06 Sera reassay: Endpoints and Evaluation criteria

Antigen	Endpoint	Non-inferiority Criteria
Stage I		
PT	≥4-fold rise (post dose 3 vs. pre-dose1)* GMT**	UL 95% CI difference DAPTACEL (Groups 1-3) minus Pentacel (Group 4) <10%. UL 95% CI ratio DAPTACEL (Groups 1-3)/ Pentacel (Group 4) <1.5.
Stage II		
PT	≥4-fold rise (post dose 4 vs. pre-dose1)** GMT**	UL 95% CI difference DAPTACEL (Groups 1**) minus Pentacel (Group 4) <10%. UL 95% CI ratio DAPTACEL (Groups 1-3)/ Pentacel (Group 4) <1.5.

*Fold-rise calculation:
Post-vx <LLOQ and pre-dose 1 <LLOQ, then fold-rise was calculated as 0.5LLOQ/0.5LLOQ,
Post-vx <LLOQ and pre-dose 1 ≥LLOQ, then fold-rise was calculated as 0.5LLOQ/pre-vx antibody level,
Post-vx ≥LLOQ and pre-dose 1 <LLOQ, then fold-rise was calculated as post-vx antibody level/LLOQ,
Post-vx ≥LLOQ and pre-dose 1 ≥LLOQ, then fold-rise was calculated
as post-vx antibody level/pre-vaccination antibody level
**At the subject level, if a serology value was <LLOQ, then for the analysis of GMC, the value was imputed as 0.5LLOQ prior to the log-transformation.
*** Group is defined as per randomization. Group 1 received the 4th Dose of DAPTACEL concomitantly with the 4th Dose of ActHIB at 15-16 months of age. The 1st dose of MMR and varicella vaccines, and the 4th Dose of Prevnar were given at 12 months. Group 4 received the 4th Dose of Pentacel at 15-16 months of age. The 1st dose of MMR and varicella vaccines, and the 4th Dose of Prevnar were given at 12 months.
Source: p3t06_retest_rep.pdf page 11-12

Comparison of available sera with all Per Protocol sera:
To evaluate how representative the available retest sera were to sera evaluated in Study P3T06 an analysis of GMC response of available sera relative to all PP sera for each pertussis antigen was provided. "Representativeness" would be concluded if the LL and UL 2-sided 95% CI ratio (P3T06 PP population [Canadian assay] / re-test sample [Canadian assay]) for each pertussis antigen were >2/3 and <1.5 at pre-Dose 1, post-Dose 3 and post-Dose 4. Reverse cumulative distribution curves for each pertussis antigen were also provided (not shown).

Retest Plan
Sera were retested at sanofi pasteur US laboratory ----- using ----------.
All sera were retested in December 2007.

Available Sera

Table 115 presents the number of available sera.

Table 115: P3T06 sera reassay. Sample Availability

Selection Criteria	Pentacel	DAPTACEL
Post-Dose 3		
Per-Protocol for Stage I	374	1167
All Pertussis serological results post-Dose 3	318	1015
PT serological result pre-Dose 1	219	712
≥25 µL of sera remaining Post-Dose 3 and Pre-Dose 1	144	486
Post-Dose 4		
Per-Protocol for Stage II	371	349*
All Pertussis serological results post-Dose 4	366	345*
PT serological result pre-Dose 1	207	222*
≥25 µL of sera remaining Post-Dose 4 and Pre-Dose 1	113	128*

*DAPTACEL Stage II Group 1 subjects (received 4th dose of DAPTACEL and ActHIB at 15 months of age)
Source: p3t06_retest_rep.pdf page 14

6.3.4.4 Statistical Considerations

Sample size and statistical power
The sample size was the number of available samples. Based on 144 Pentacel and 486 DAPTACEL paired samples the overall power to evaluate non-inferiority after the infant series is 95.6%. After the toddler series based on 113 available Pentacel and 128 DAPTACEL paired samples the power to evaluate non-inferiority is 90.6%.

Analysis populations

Analysis population Sera for analysis met the following criteria:
• Subjects were part of the PP population [met all inclusion/exclusion criteria, received all 3 (Stage I) or 4 doses (Stage II) of study vaccines as per randomization and within protocol intervals, blood sampling was performed within specified windows, and had a valid serology results post-dose 3 or 4 for at least one DAPTACEL or Pentacel antigen].
• Serological results for each pertussis antigen, post-Dose 3 (Stage I) or post-Dose 4 (Stage II).
• PT serological result, pre-Dose 1.
• ≥25 µL of sera remaining pre-Dose 1, and post-Dose 3 (Stage I) or post-Dose 4 (Stage II).

Statistical criteria for non-inferiority analyses
The protocol-specified statistical criteria for non-inferiority of 4-fold response rates and GMTs between study groups were based on the 95% CIs for difference in rates between groups and the ratios of GMTs, respectively.

6.3.4.5 Results

Immunogenicity analyses and data presentation

Comparison of available P3T06 sera with all Per Protocol P3T06 sera

As shown in Table 116, the available sera from Pentacel subjects met the criteria for "representativeness" since the LL and UL 95% CI of the GMC ratio for FHA, FIM and pertactin

antigens were >2/3 and <1.5, respectively. Similarly, as shown in Table 117 the available DAPTACEL sera meet the criteria for demonstration of "representativeness."

Of note, the DAPTACEL sera were available from children randomized to receive one of three lots of DAPTACEL as part of the DAPTACEL lot consistency evaluation. No evaluation of equivalence of response to PT among these sera was provided.

Table 116: P3T06 sera reassay.Comparison of GMTs* of available Pentacel Study P3T06 sera with PP sera.

Pentacel Subjects		Re-Test Sample		PP Population		PP Population / Re-Test Sample	
Bleed	**Antigen**	**N**	**GMT[1] (95% CI)**	**N**	**GMT[1] (95% CI)**	**Ratio**	**(95% CI)[2]**
Pre-dose1	FHA	163	4.49 (3.82; 5.27)	272	4.64 (4.10; 5.25)	1.03	(0.85; 1.26)
	FIM	163	11.40 (10.34; 12.57)	269	11.75 (10.85; 12.72)	1.03	(0.91; 1.17)
	PRN	163	3.00 (2.59; 3.48)	272	3.06 (2.72; 3.43)	1.02	(0.84; 1.23)
Post-dose 3	FHA	144	74.62 (66.59; 83.62)	318	73.68 (68.52; 79.23)	0.99	(0.87; 1.13)
	FIM	144	270.11 (239.00; 305.27)	318	268.15 (247.21; 290.87)	0.99	(0.86; 1.15)
	PRN	144	37.63 (32.43; 43.67)	318	36.05 (32.27; 40.27)	0.96	(0.79; 1.16)
Post-dose 4	FHA	113	112.61 (95.96; 132.15)	366	107.94 (99.42; 117.20)	0.96	(0.81; 1.14)
	FIM	113	636.22 (539.70; 750.00)	367	553.39 (496.11; 617.27)	0.87	(0.70; 1.08)
	PRN	113	89.70 (75.01; 107.27)	367	93.59 (83.98; 104.31)	1.04	(0.84; 1.30)

N. is the total number of subjects with available serology data from the Immunogenicity Per Protocol Population.

[1]Geometric means for the Re-Test Sample and PP Population are calculated using results from the ------ Assay.

[2] Equivalence is achieved when both the lower and upper limit of each 95% CI are >2/3 and <1.5.

* Anti-PT ----- values were generated in a non-specific assay thus the values are unacceptable to CBER.

Source: p3t06_retest_rep.pdf page 15

Table 117: P3T06 sera reassay.Comparison of GMTs* of available DAPTACEL Study P3T06 sera with PP sera.

DAPTACEL Subjects		Re-Test Sample		PP Population		PP Population / Re-Test Sample	
Bleed	Antigen	N	GMT (95% CI)	M	GMT (95% CI)	Ratio	(95% CI)
Pre-dose 1	FHA	514	5.15 (4.69; 5.65)	806	4.87 (4.52; 5.25)	0.95	(0.84; 1.07)
	FIM	513	12.19 (11.47; 12.95)	797	12.20 (11.61; 12.82)	1.00	(0.93; 1.08)
	PRN	514	3.18 (2.93; 3.44)	799	3.15 (2.94; 3.37)	0.99	(0.89; 1.10)
Post-dose 3	FHA	486	29.83 (27.91; 31.89)	1016	29.22 (27.91; 30.60)	0.98	(0.90; 1.06)
	FIM	486	260.87 (240.75; 282.67)	1015	267.18 (253.15; 282.00)	1.02	(0.93; 1.13)
	PRN	486	41.78 (38.21; 45.69)	1016	43.25 (40.68; 45.99)	1.04	(0.93; 1.15)
Post-dose 4	FHA	128	62.68 (54.94; 71.51)	345	64.02 (58.81; 69.69)	1.02	(0.87; 1.20)
	FIM	128	618.90 (515.01; 743.74)	347	513.54 (457.72; 576.17)	0.83	(0.67; 1.03)
	PRN	128	182.67 (154.53; 215.94)	347	186.07 (168.16; 205.88)	1.02	(0.84; 1.24)

N. is the total number of subjects with available serology data from the Immunogenicity Per Protocol Population.
[1]Geometric means for the Re-Test Sample and PP Population are calculated using results from the ------ Assay.
[2] Equivalence is achieved when both the lower and upper limit of each 95% CI are >2/3 and <1.5.
*Anti-PT ----- values were generated in a non-specific assay thus the values are unacceptable to CBER.
Source: p3t06_retest_rep.pdf page 16

Stage 1 Non-inferiority of Pentacel relative to DAPTACEL. Using 95% CI for the difference in 4-fold response rates the statistical criterion for the response to the PT following three doses of Pentacle or DAPTACEL (pooled) were met. These data are presented in Table 118.

Table 118: P3T06 sera reassay: Anti-PT seroconversion rates and non-inferiority analysis following three doses of Pentacel or DAPTACEL (available PP sera retested in sanofi pasteur US)

Antigen and criteria	Pentacel n/N % (95% CI)	DAPTACEL n/N % (95% CI)	Non-Inferiority Comparison DAPTACEL minus Pentacel [3]	
			%	95% CI difference
PT (EU/mL) ≥4-fold rise[1]	137/143[2] 95.8 (91.1; 98.4)	420/481[2] 87.3 (84.0; 90.2)	-8.49	(-12.92; -4.05)

[1]The fold-rise for the Representative Sample is calculated by (post-Dose 3 [--- (US) Assay] / pre-Dose 1 [GCI (US) Assay])
[2]For 1 of the selected 144 Pentacel Stage I subjects and 5 of the 486 DAPTACEL subjects, blood sample quantities were insufficient to perform the paired test.
[3]Non-inferiority is achieved when the UL 95% CI is <10%.
Notes: N is the total number of subjects with available serology data from the Immunogenicity Population.
n: is the number of subjects who met the criteria of the test indicated.
Source: p3t06_retest_rep.pdf page 18

Stage 1 Non-inferiority of Pentacel relative to DAPTACEL. Using 95% CI for the ratio of GMTs the statistical criterion for non-inferiority of the response to PT was met. These data are presented in Table 119.

Table 119: P3T06 sera reassay: Anti-PT GMT and non-inferiority analysis following three doses of Pentacel or DAPTACEL (available PP sera retested in sanofi pasteur US laboratory)

Antigen	Pentacel N GMT (95% CI)	DAPTACEL N GMT (95% CI)	Non-Inferiority Comparison DAPTACEL/ Pentacel [3]	
			ratio	95% CI ratio
PT (EU/mL) [1]	143[2] 102.62 (93.91; 112.15)	485[2] 61.88 (58.29; 65.70)	0.60	(0.53; 0.68)

[1]Geometric means for the Re-test Sample are calculated using results from the ---- (US) Assay.
[2]For 1 of the selected 144 Pentacel Stage I subjects and 1 of the 486 DAPTACEL subjects, blood sample quantities were insufficient to perform the test.
[3]Non-inferiority is achieved when the UL 95% CI is <1.5.
Note: .N is the total number of subjects with available serology data from the Immunogenicity Population.
Source: p3t06_retest_rep.pdf page 19

Stage II Non-inferiority of Pentacel relative to DAPTACEL Using 95% CI for the difference in 4-fold response rates the statistical criterion for the response to PT following four doses of Pentacle or DAPTACEL were met. These data are presented in Table 120.

Table 120: Study P3T06: Anti-PT seroconversion rates and non-inferiority analysis following four doses of Pentacel or DAPTACEL (available PP sera retested in sanofi pasteur US laboratory)

Antigen and criteria	Pentacel n/N % (95% CI)	DAPTACEL n/N % (95% CI)	Non-Inferiority Comparison DAPTACEL - Pentacel [3]	
			%	95% CI difference
PT (EU/mL) ≥4-fold rise[1]	106/113 93.8 (87.7;97.5)	116/127[2] 91.3 (85.0;95.6)	-2.47	(-9.08; 4.14)

[1]The fold-rise for the Representative Sample is calculated by (post-Dose 4 [--- (US) Assay] / pre-Dose 1 [--- (US) Assay])
[2] For 1 of the selected 128 DAPTACEL Stage II subjects, blood sample quantity was insufficient to perform the paired test.
[3]Non-inferiority is achieved when the UL 95% CI is <10%.
Notes: .N is the total number of subjects with available serology data from the Immunogenicity Population.
n is the number of subjects who met the criteria of the test indicated.
Source: p3t06_retest_rep.pdf page 20

Stage II Non-inferiority of Pentacel relative to DAPTACEL Using 95% CI for the ratio of GMTs the statistical criterion for non-inferiority of the response to PT following four doses of Pentacle or DAPTACEL was met. These data are presented in Table 121.

Table 121: Study P3T06: Anti-PT GMT and non-inferiority analyses following four doses of Pentacel or DAPTACEL (available PP sera retested in sanofi pasteur US laboratory)

Antigen	Pentacel N GMT (95% CI)	DAPTACEL N GMT (95% CI)	Non-Inferiority Comparison DAPTACEL/ Pentacel [2]	
			ratio	95% CI ratio
PT (EU/mL) [1]	113 107.89 (93.68;124.26)	128 100.29 (86.02;116.94)	0.93	(0.75;1.15)

[1]Geometric means for the Re-test Sample are calculated using results from the --- (US) Assay.
[2]Non-inferiority is achieved when the UL 95% CI is <1.5.
Note: .N is the total number of subjects with available serology data from the Immunogenicity Population.
Source: p3t06_retest_rep.pdf page 21

6.3.4.6 Comments and Conclusions

Non-inferiority of response to the PT component of Pentacel relative to PT component of separately administered DAPTACEL:
A subset of sera from Study P3T06 were reassayed in the sanofi pasteur US facility ----------. PT ---------- was used to coat the plates. Following the third and fourth dose non-inferiority of the response to PT (anti-PT seroconversion rate [≥4-fold rise] and GMT) was demonstrated when Pentacel was administered as compared to separately administered DAPTACEL. These data constitute the only data demonstrating non-inferiority of response to the PT component of Pentacel relative to separately administered DAPTACEL.

With regard to the GMT, the data suggest that following the fourth dose of Pentacel the PT GMT (108 EU/mL) does not increase relative to the post-dose 3 level (103 EU/mL). A fourth dose of

DAPTACEL however, induces a GMT of 100 EU/mL compared to 62 EU/mL following the third dose.

6.4 Trial #4

6.4.1 Applicants Protocol # and Protocol Title

Study 5A9908, Safety and Immunogenicity Study of PENTACEL When Administered as a Fourth Dose at 15 to 18 Months of Age

6.4.1.1 Rationale/Objectives

Study 5A9908 was designed to assess the safety and immunogenicity of Pentacel when administered at 15-18 months of age.

Specific objectives relevant to the immunological evaluation of Pentacel are listed below.

Primary immunogenicity objective

To demonstrate that the seroconversion and seroprotection rates to the antigens in Pentacel are similar when the 4th dose is administered at a range of 15 to 18 months of age.

Secondary immunogenicity objective

To demonstrate that the immune responses to the antigens in Pentacel, as assessed by geometric mean titers (GMTs), are similar when the 4th dose is administered at a range of 15 to 18 months of age.

Observational immunogenicity objective

1. To assess the immune response associated with age at the time of vaccination when Pentacel is administered as a 4th dose at 15 to 18 months of age.

2. To assess the immune response to Diphtheria and Tetanus for all groups combined based on seroresponse thresholds.

6.4.1.2 Design overview

Study 5A9908 was an open label, randomized, multi center study to assess the safety and immunogenicity of Pentacel given to subjects 15-18 months of age. The trial involved seven centers in Canada. Three centers participated in assessment of immunogenicity, all seven centers participated in assessment of safety. All subjects were recruited at 12 months of age. The study was divided into two parts – Part 1 a safety and immunogenicity study and Part 2 a safety study. Subjects received MMR and varicella at 12 months of age (unless already received). Subjects were randomized to receive Pentacel at 15, 16, 17 or 18 months of age. A second dose of MMR was offered to those subjects who resided in an area where this dose was routinely given at 18 months of age; when administered MMR was given at least 60 days after Pentacel.

6.4.1.3 Population

The study period was 15 August 2000, through 21 October 2001. Subjects were enrolled at seven Canadian centers. All subjects had received a three doses series of Pentacel by 8 months of age. The study period was 15 August 2000, to 21 October 2001.

6.4.1.4 Products mandated by the protocol

Study vaccines – schedule of administration

Table 122: Study 5A9908: Schedule of vaccine administration

Group	MMR_{II},[1] VARIVAX[2]	Pentacel
Group 1	12m	15m (≥15m < 16m)
Group 2	12m	16m (≥16m <17m)
Group 3	12m	17m (≥17m <18m)
Group 4	12m	18m (≥18m <19m)

[1]The first dose of MMR was offered at 12m if not already administered.
[2]Varicella was offered at 12 months of age.

Prevnar was not administered to subjects during this study, subjects had not received previous doses of Prevnar.

Study vaccines – formulation and lot numbers. All study vaccines except Pentacel are licensed in the US.

- Pentacel (DTaP-IPV used to reconstitute ActHIB):

Formulation as described in **Section 1.2.3**

Lot numbers: DTaP-IPV Lot C0154B and ActHIB Lot P1332.

For the following vaccines lot numbers were identified and recorded at time of use.

- MMR_{II} (Measles, Mumps, and Rubella Virus Vaccine Live, Merck & Co., Inc.): Each 0.5 ml dose contains not less than 1,000 TCID50 (tissue culture infectious doses) of measles virus; ----- TCID50 of mumps virus; and 1,000 TCID50 of rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients and approximately 25 mcg of neomycin. The product contains no preservative. Product was purchased in Canada.

- VARIVAX [Varicella Virus Vaccine Live (Oka/Merck); Merck & Co., Inc.]: Each 0.5 ml dose contains a minimum of 1350 plaque forming units of Oka/Merck varicella virus, approximately 25 mg of sucrose, 12.5 mg hydrolyzed gelatin, 3.2 mg sodium chloride, 0.5 mg monosodium L-glutamate, 0.45 mg of sodium phosphate dibasic, 0.08 mg of potassium phosphate monobasic, 0.08 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of sodium phosphate monobasic, EDTA, neomycin, and fetal bovine serum. The product contains no preservative. Product was purchased in Canada.

Study vaccines: route of administration
Pentacel was injected intramuscularly. MMR_{II} and VARIVAX were injected subcutaneously.

6.4.1.5 Immunogenicity Endpoints and Evaluation Criteria

Antibody assays
See Section 5.5 for an overview of serological assays.

If the volume of serum obtained was limited, assays were to be prioritized as follows: PRP, pertussis antigens, diphtheria, tetanus and polioviruses.

Primary endpoints and evaluation criteria

Equivalence of the immune response following a dose of Pentacel at 15 -16 months relative to Pentacel administered at 17-18 months of age

Table 123 presents the criteria for evaluation of seroprotection/seroconversion following a dose of Pentacel administered at 15-16 months of age relative to Pentacel administered at 17-18 months of age.

Table 123: Primary Immunogenicity Endpoints and Equivalence criteria for evaluation of seroprotection/seroconversion following Pentacel administered at 15-16 months or 17-18 months

Antigen	Endpoint	Equivalence criteria
PRP	≥ 1.0 µg/mL	90% CI difference rates (15-16m minus 17-18m) -10%-10%
Diphtheria	≥ 0.10 IU/mL	
Tetanus	≥ 0.10 IU/mL	
Poliovirus type 1	≥ 1:8	
Poliovirus type 2		
Poliovirus type 3		
PT	4-fold rise (post-dose 4 vs. per-dose 4)	
FHA		
FIM		
PRN		

Source: 5a9908.pdf page 1143

Secondary Endpoints and Evaluation criteria

Equivalence of the immune response following a dose of Pentacel at 15-16m relative to Pentacel administered at 17-18 months of age.

Table 124 presents the criteria for evaluation of the GMT response to each antigen following a dose of Pentacel administered at 15-16 months of age relative to Pentacel administered at 17-18 months of age.

Table 124: Study 5A9908 Secondary Immunogenicity criteria for evaluation of equivalence of GMT response following Pentacel administered at 15-16 months or 17-18 months

Antigen	Endpoint and Equivalence criteria
PRP	GMT 2-sided 90% CI ratio GMTs (15-16months/17-18months) between 2/3-1.5
Diphtheria	
Tetanus	
Polio virus type 1	
Polio virus type 2	
Polio virus type 3	
PT	
FHA	
FIM	
Pertactin	

Observational Endpoints

Immune response associated with age when Pentacel is administered at 15-18 months.

Table 125 presents the observational evaluations of immune response to diphtheria and tetanus toxoid for all groups combined based on pre-immunization titers.

Table 125: Study 5A9908 Observational anti-diphtheria and anti-tetanus endpoints

Pre-dose 4 anti-diphtheria and anti-tetanus level	Post dose 4 endpoint
Any	≥0.1 IU/mL ≥1.0 IU/mL
≤0.1 IU/mL	≥0.4 IU/mL
≥0.1 – 2 IU/mL	≥4-fold rise
≥2.0 IU/mL	≥2-fold rise

6.4.1.6 Surveillance/Monitoring

Immunogenicity
Serum samples were collected from subjects recruited into Part 1 (safety and immunogenicity study) prior to vaccination at Visit 2 (at least 30 days from visit 1 at approximately 12 months of age) and 21-48 days after Pentacel administered at 15- 18 months of age. Immune responses were not assessed to vaccines administered at 12 months of age (i.e. MMR_{II} and VARIVAX).

6.4.1.7 Statistical Considerations

Sample size and statistical power
The planned total immunogenicity sample size was 760 "Part 1" subjects randomized at 12 months of age to receive Pentacel at 15, 16, 17 or 18 months of age. For the purposes of analysis subjects were evaluated by groups: Pentacel administered at 15-16 months relative to 17-18 months. Power calculations presented for each of the primary and secondary endpoints were based on 300 subjects per group, with no adjustment for multiple comparisons, these calculations indicated at least 91% power for each endpoint.

Analysis populations

Intent to treat population The ITT immunogenicity population includes all participants who received Pentacel vaccine, regardless of whether Pentacel was administered within vaccination windows, whether the post-vaccination visits were within prescribed windows, and whether the blood sample was obtained within the blood sampling schedules. This population includes all participants whose data was captured in the safety and immunogenicity databases.

Per-protocol immunogenicity population The per-protocol for immunogenicity (PPI) population includes participants who met all eligibility criteria, were vaccinated with Pentacel and were bled within the appropriate window.

Statistical criteria for non-inferiority analyses

The protocol-specified statistical criteria for demonstration of non-inferiority of GMTs between study groups were based on the 90% CIs for the ratios of GMTs. Likewise, the protocol-specified statistical criteria for demonstration of non-inferiority of seroprotection or seroconversion rates between study groups were based on the 90% CIs for differences in rates between groups. However, CBER currently recommends use of 2-sided 95% CIs for ratios of GMTs for both lot consistency and non-inferiority analyses, as well as 2-sided 95% CIs for rate differences for non-inferiority analyses.

6.4.2 Results

6.4.2.1 Populations enrolled/analyzed

Table 126 presents a summary of the immunogenicity populations for Study 5A9908.

Table 126: Study 5A9908 Summary of Subject Disposition- number of subjects randomized, immunized, bled and included in the immunogenicity populations

Immunogenicity disposition	**Pentacel vaccination group**				
	15 months N (%)	**16 months N (%)**	**17 months N (%)**	**18 months N (%)**	**Total N (%)**
All randomized for immunogenicity	**205 (100)**	**204 (100)**	**203 (100)**	**205 (100)**	**817 (100)**
Received 4th dose Pentacel[1]	**196 (95.6)**	**193 (94.6)**	**194 (95.5)**	**188 (91.7)**	**771 (94.3)**
Missed, unable or refused to bleed post-dose 4	4	2	2	7	15
ITT immunogenicity	**192 (93.6)**	**191 (93.6)**	**192 (94.5)**	**181 (88.2)**	**756 (92.5)**
Protocol violations[2]					
Did not satisfy eligibility criteria	2	4	2	6	14
Treatment assignment error	1	0	2	1	4
Visit out of time interval or age window	0	2	1	0	3
PP Immunogenicity population[3]	**189 (92.1)**	**185 (90.6)**	**187 (92.1)**	**174 (84.8)**	**735 (89.9)**

[1]As per study design, 760 subjects (190 from each of the 15, 16, 17, and 18 month age groups) were intended to be bled for the immunogenicity analyses. Subjects in this category are those that had Dose 4 of Pentacel, the post-Dose 4 blood draw, and a valid serology test result for at least 1 antigen at post-Dose 4. Subjects with only a pre-Dose 4 bleed are excluded.

[2]Only 1 primary reason for exclusion/violation per subject was selected in the order listed

[3]Defined as all subjects who were enrolled in the trial, received a dose of Pentacel, satisfied the eligibility criteria, were assigned to the correct age group, had both the pre- and post-immunization blood draws within window, and had a valid postdose serology test result for at least 1 antigen. The PP population was

used only in the immunogenicity analyses; therefore, a subject may not have completed the 60-day safety follow-up but still have been included in the PP Immunogenicity Population.
Source: 5a9908.pdf page 63, 118

6.4.2.2 Immunogenicity Analyses and Data Presentation

In this review results of primary, secondary and observational analyses are presented. Results are presented for the PPI population, results for the ITT immunogenicity population were similar. PT antibody levels were generated in the ----- performed in the sanofi pasteur, Canada, laboratory. Because this assay has been determined to be non-specific these data are not acceptable to CBER and are not presented in this review.

Prevaccination antibody levels

Prevaccination antibody levels were determined for all Pentacel antigens. The pre-vaccination GMTs of groups randomized to receive Pentacel at 15, 16, 17 and 18 months of age to each of the Pentacel antigens is shown in Table 127. Of note, although the 95% CIs are generally overlapping there is a trend toward lower GMTs to FHA, fimbriae, pertactin and polio antigens with increasing age before receipt of the fourth dose of Pentacel. Anti-PT ----- values were generated in a non-specific assay thus, are not presented.

Table 127: Study 5A9908 pre-dose 4 GMTs* to Pentacel antigens in subjects aged 15, 16, 17 and 18 months of age. PPI population

Antigen	15 months		16 months		17 months		18 months		Pooled groups	
	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)	N	GMT (95% CI)
PRP (ug/mL)	187	0.41 (0.33, 0.51)	185	0.32 (0.25, 0.41)	187	0.42 (0.34, 0.53)	174	0.37 (0.29, 0.47)	733	0.38 (0.34, 0.43)
Diphtheria (IU/mL)	182	0.14 (0.12, 0.17)	184	0.11 (0.09, 0.14)	187	0.09 (0.08, 0.11)	173	0.08 (0.07, 0.10)	726	0.11 (0.10, 0.12)
Tetanus (IU/mL0	184	0.51 (0.45, 0.57)	182	0.43 (0.37, 0.50)	186	0.45 (0.39, 0.51)	170	0.42 (0.36, 0.49)	722	0.45 (0.42, 0.48)
FHA (EU/mL)	188	18.48 (16.13, 21.18)	183	16.24 (14.28, 18.47)	187	15.50 (13.40, 17.94)	173	12.89 (10.96, 15.16)	731	15.71 (14.62, 16.88)
FIM (EU/mL)	185	44.15 (37.45, 52.04)	182	36.95 (31.45, 43.42)	186	35.46 (30.49, 41.24)	174	34.92 (29.67, 41.09)	727	37.74 (34.85, 40.88)
PRN (EU/mL)	187	11.31 (9.66, 13.24)	183	10.01 (8.48, 11.82)	187	9.89 (8.40, 11.64)	173	9.44 (7.90, 11.29)	730	10.16 (9.35, 11.03)
Polio 1 (1/dil)	187	161.37 (128.34, 202.91)	185	96.33 (76.18, 121.80)	187	84.67 (67.78, 105.77)	173	79.32 (62.55, 100.59)	732	101.57 (90.40, 114.10)
Polio 2 (1/dil)	182	362.73 (293.33, 448.55)	185	244.30 (197.44, 302.27)	187	234.20 (190.20, 288.38)	173	223.40 (181.09, 275.59)	727	261.18 (234.99, 290.28)
Polio 3 (1/dil)	180	263.03 (206.54, 334.98)	184	164.15 (129.35, 208.31)	187	124.52 (99.25, 156.21)	173	99.45 (77.01, 128.43)	724	152.46 (134.92, 172.27)

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: 5a9908.pdf page 68-69

Equivalence of seroprotection/seroconversion rates when the fourth dose of Pentacel is administered at 15-16 months or 17-18 months of age. Using 90% CI for the difference in seroconversion/seroprotection rates the statistical criteria for equivalence between the response to the Pentacel antigens following a fourth dose of Pentacel at 15-16 months or 17-18 months were met. Anti-PT ----- values were generated in a non-specific assay thus, anti-PT seroconversion rates and the analysis of equivalence of response to PT are not presented. These data are presented in Table 128 (95% CI on the rate of seroconversion/seroprotection are not provided).

Table 128: Study 5A9908 Seroconversion/seroprotection rates* and equivalence analyses following the fourth dose of Pentacel administered at 15-16 months of age or 17-18 months of age.

Antigen and criteria	Pentacel at 15-16 months	Pentacel at 17-18 months	Equivalence comparison	
	n/N %	n/N %		90% CI difference
PRP **≥1.0 ug/mL**	368/374 98.4	358/361 99.2	-0.77	(-2.10, 0.55)
Diphtheria **≥1.0 IU/mL**	353/373 94.6	346/361 95.8	-1.21	(-3.79, 1.37)
Tetanus **≥1.0 IU/mL**	359/374 96.0	347/356 97.5	-1.48	(-3.64, 0.68)
FHA **≥4-fold rise[2]**	322/371 86.8	333/360 92.5	-5.71	(-9.39, -2.02)
FIM **≥4-fold rise[2]**	343/367 93.5	344/360 95.6	-2.10	(-4.87, 0.68)
PRN **≥4-fold rise[2]**	349/370 94.3	334/360 92.8	1.55	(-1.45, 4.54)
Polio 1 **≥1:8**	373/374 99.7	361/361 100.0	-0.27	(-0.71, 0.17)
Polio 2 **≥1:8**	373/373 100.0	361/361 100.0	0.00	(NA)
Polio 3 **≥1:8**	373/373 100.0	360/360 100.0	0.00	(NA)

[1]Equivalence is achieved when the 90% CI on the difference in rates (15-16m minus 17-18m) -10%-10%
[2]The fold-rise is calculated by post-4th Dose / pre-4th Dose antibody level.
*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*Source: 5a9908.pdf page 65

Equivalence of GMT response when the fourth dose of Pentacel is administered at 15-16 months or 17-18 months of age. Using 90% CI for the ratio of GMTs the statistical criteria for equivalence of the response to the antigens in Pentacel were met. Anti-PT ----- values were generated in a non-specific assay thus, PT GMTs and the analysis of equivalence of response to PT are not presented. These data are presented in Table 129 (95% CI on the GMTs for each antigen in the groups was not provided).

Table 129: GMTs and equivalence analyses following the fourth dose of Pentacel administered at 15-16 months of age or 17-18 months of age. PPI population.

Antigen	Pentacel at 15-16 months		Pentacel at 17-18 months		Equivalence Analysis Group 15-16m/Group 17-18m[1]	
	N	GMT	N	GMT		90% CI ratio
PRP (ug/mL)	374	29.17	361	36.45	0.80	(0.68, 0.94)
Diphtheria (IU/mL)	373	4.42	361	5.04	0.88	(0.78, 0.99)
Tetanus (IU/mL)	374	4.22	356	4.95	0.85	(0.78, 0.93)
FHA (EU/mL)	374	177.25	361	211.08	0.84	(0.78, 0.91)
FIM (EU/mL)	374	780.83	361	862.67	0.91	(0.80, 1.03)
PRN (EU/mL)	374	176.81	361	191.84	0.92	(0.82, 1.04)
Polio 1 (1/dil)	374	4065.82	361	4068.56	1.00	(0.86, 1.16)
Polio 2 (1/dil)	373	7458.23	361	7335.73	1.02	(0.89, 1.16)
Polio 3 (1/dil)	373	8314.69	360	6622.00	1.26	(1.08, 1.46)

1 Equivalence is achieved when the 90% CI on the ratio of the GMTs (15-16 months/17-18 months) is between 2/3-1.5

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

Source: 5a9908.pdf page 66-67.

Observational Analyses

Immune response associated with age at the time of vaccination. GMTs and seroresponse/seroprotection rates to each of the Pentacel antigens is presented in Table 130 and 131. The GMTs were similar in each group. Anti- PT values were generated in a non-specific ----- thus the response to PT by age of vaccination is not presented. The 95% CI on the rates of seroresponse/seroprotection were not provided however, the rates appear similar between groups.

Table 130: Study 5A9908 GMTs* one month following a fourth dose of Pentacel administered at 15, 16, 17 or 18 months of age. PPI population

Antigen		Pentacel at 15 months		Pentacel at 16 months		Pentacel at 17 months		Pentacel at 18 months
	N	GMT	N	GMT	N	GMT	N	GMT
PRP (ug/mL)	189	29.92 (24.58, 36.43)	185	28.42 (23.86, 33.86)	187	37.15 (31.14, 44.33)	174	35.71 (28.90, 44.13)
Diphtheria (IU/mL)	189	4.47 (3.86, 5.18)	184	4.37 (3.82, 5.00)	187	4.65 (3.98, 5.43)	174	5.50 (4.75, 6.37)
Tetanus (IU/mL)	189	4.42 (3.98, 4.91)	185	4.02 (3.58, 4.51)	185	4.80 (4.30, 5.37)	171	5.11 (4.60, 5.68)
FHA (EU/mL)	189	172.67 (156.57, 190.42)	185	182.05 (167.94, 197.34)	187	205.45 (185.92, 227.02)	174	217.32 (196.61, 240.20)
FIM (EU/mL)	189	837.67 (726.21, 966.23)	185	726.75 (627.57, 841.60)	187	887.05 (767.89, 1024.70)	174	837.22 (710.67, 986.31)
PRN (EU/mL)	189	187.71 (163.39, 215.63)	185	166.33 (144.52, 191.43)	187	197.60 (169.98, 229.72)	174	185.83 (158.83, 217.41)
Polio 1 (1/dil)	189	4717.36 (3897.23, 5710.08)	185	3493.03 (2904.12, 4201.35)	187	4111.20 (3423.14, 4937.57)	174	4023.23 (3397.15, 4764.69)
Polio 2 (1/dil)	189	8466.90 (7243.23, 9897.29)	184	6547.12 (5493.76, 7802.46)	187	7329.91 (6280.39, 8554.82)	174	7341.98 (6328.46, 8517.83)
Polio 3 (1/dil)	188	9372.05 (7960.98, 11033.23)	185	7362.32 (6169.32, 8786.01)	187	7023.94 (5784.12, 8529.51)	173	6213.36 (5113.37, 7549.97)

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: 5a9908.pdf page 68

Table 131: Study 5A9908 Seroconversion/seroprotection rates* one month following a fourth dose of Pentacel administered at 15, 16, 17 or 18 months of age. PPI population

Antigen	Criteria	Pentacel at 15m	Pentacel at 16m	Pentacel at 17m	Pentacel at 18m
		n/N %	n/N %	n/N %	n/N %
PRP	≥1.0 ug/mL	185/189 97.9	183/185 98.9	186/187 99.5	172/174 98.9
Diphtheria	≥0.1 IU/mL	189/189 100.0	184/184 100.0	187/187 100.0	174/174 100.0
	≥1.0 IU/mL	178/189 94.2	175/184 95.1	176/187 94.1	170/174 97.7
Tetanus	≥0.1 IU/mL	189/189 100.0	185/185 100.0	185/185 100.0	171/171 100.0
	≥1.0 IU/mL	184/189 97.4	175/185 94.6	178/185 96.2	169/171 98.8
FHA	≥4-fold rise [1]	162/188 86.2	160/183 87.4	173/187 92.5	160/173 92.5
FIM	≥4-fold rise [1]	170/185 91.9	173/182 95.1	178/186 95.7	166/174 95.4
Pertactin	≥4-fold rise [1]	174/187 93.0	175/183 95.6	173/187 92.5	161/173 93.1
Polio 1	≥1:8 dilution	188/189 99.5	185/185 100.0	187/187 100.0	174/174 100.0
Polio 2	≥1:8 dilution	189/189 100.0	184/184 100.0	187/187 100.0	174/174 100.0
Polio 3	≥1:8 dilution	188/188 100.0	185/185 100.0	187/187 100.0	173/173 100.0

[1]The fold-rise is calculated by post-4th Dose / pre-4th Dose antibody levels.
*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: 5a9908.pdf page 71

Immune response to diphtheria and tetanus toxoids. Table 132 presents the immune response to diphtheria and tetanus toxoids based on pre-defined pre-vaccination antibody levels. The 95% CI on these rates were not provided in the study report.

Table 132: Study 5A9908. Seroresponse to diphtheria and tetanus toxoids following a fourth dose of Pentacel administered at 15, 16, 17 or 18 months of age based on pre-vaccination antibody levels.

Pre-dose 4 level	Post dose 4 response	Pentacel at 15m		Pentacel at 16m		Pentacel at 17m		Pentacel at 18m		Groups pooled	
Diphtheria		**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
≤0.1 IU/mL	≥0.4 IU/mL	76	98.7	79	94.9	88	94.3	108	98.1)	351	96.6
>0.1-<2.0 IU/mL	≥4-fold rise[1]	106	100.0	104	100.0	99	100.0	65	100.0)	374	100.0
≥2.0 IU/mL	≥2-fold rise [1]	0	0	0	0	0	0	0	0	0	0
Tetanus											
≤0.1 IU/mL	≥0.4 IU/mL	12	100.0	22	100.0	10	90.0	14	100.0	58	98.3
>0.1-<2.0 IU/mL	≥4-fold rise [1]	170	84.7	152	86.8	169	92.3	150	92.7	641	89.1
≥2.0 IU/mL	≥2-fold rise [1]	2	100.0	8	75.0	6	83.3	6	66.7	22	77.3

The fold-rise is calculated by post-4th dose / pre-4th dose antibody levels.
Source: 5a9908.pdf page 73

6.4.3 Comments and Conclusions

Equivalence of administration of the fourth dose of Pentacle at 15-16 months of age and 17-18 months of age was demonstrated for PRP, FHA, fimbriae, pertactin, diphtheria, tetanus and poliovirus GMTs and seroconversion/seroprotection rates. The response to PT cannot be evaluated.

6.5 Study M5A07
Study M5A07 was not designed to support the licensure of Pentacel. However, the sponsor has submitted the results of immunogenicity analyses following the third dose of Pentacle to the file.

Protocol Title:
Immunogenicity assessment of Pentacel when given at different times from or concurrently with a pnuemococcal vaccine

Rationale/Objectives
The results of Study 494-01 raised the possibility of decreased serological response to the pertussis and PRP antigens when Pentacel was co-administered with Prevnar. Following discussion of these data during the pre-BLA meeting of April 2003 CBER requested that sanofi initiate a study to evaluate whether administration of Prevnar concurrently with Pentacel affected the response to the pertussis and PRP antigens following the third and fourth dose of Pentacel. A summary of the third dose data are presented.

Study Design Overview
Table 134 presents an overview of Study M5A07 Stage I. Post dose 4 data were not submitted in the application.

Table 134: Study M5A07 overview and summary of analysis populations

Study Design/ Characteristics	**M5A07 Stage I**
Study Design	Phase 3, randomized, controlled, multi-center study designed to assess the safety and immunogenicity of Pentacel when given at different times from or concurrently with Pneumococcal conjugate vaccine.
Study Vaccine	Group 1: Pentacel + Prevnar® at 2, 4, and 6 months Group 2: Pentacel at 2, 4, and 6 months with Prevnar 1 month later
Other Vaccines	Hepatitis B: 2 and 7 months
Number of Subjects who Received Pentacel.	ITT Immunogenicity Population: 480 subjects for Pentacel+Prevnar 485 subjects for Pentacel PP Immunogenicity Population: 447 subjects for Pentacel+Prevnar 439 subjects for Pentacel
Primary Immunogenicity Endpoints	Non-inferiority of Pentacel when given at different times from or concurrently with Prevnar
Trial Period	30 October 2003, to 15 October 2004

Source: isi.pdf page 33

Results:

Seroconversion/seroprotection rates and GMTs following three doses of Pentacel administered concomitantly with and without Prevnar are presented in Tables 134 and 135. Based on the summary data provided all prespecified non-inferiority criteria were met for seroprotection/seroconversion rates and GMTs following the third dose of Pentacel. PT antibody levels were generated in the ----- performed in the sanofi pasteur, Canada, laboratory. Because

this assay has been determined to be non-specific these data are not acceptable to CBER and are not presented. Immunogenicity data following four doses of Pentacel are not provided in the BLA.

Table 134: Study M5A07 Stage I Seroconversion/seroresponse rates* following three doses of Pentacel co-administered with Prevnar (Group 1) or separately (Group 2).

Antigen	Criteria	Group 1 n/N % (95% CI)	Group 2 n/N % (95% CI)	Non-inferiority Comparison [1] Group 2 minus Group 1 (95% CI)
PRP (ug/mL)	≥0.15	415/433 95.8 (93.5, 97.5)	407/427 95.3 (92.9, 97.1)	-0.53 (-3.27, 2.22)
	≥1.0	334/433 77.1 (72.9, 81.0)	340/427 79.6 (75.5, 83.3)	2.49 (-3.01, 7.99)
FHA (EU/mL)	≥4-fold rise	360/441 81.6 (77.7, 85.1)	357/436 81.9 (77.9, 85.4)	0.25 (-4.86, 5.36)
FIM (EU/mL)	≥4-fold rise	387/422 87.6 (84.1, 90.5)	384/438 87.7 (84.2, 90.6)	0.11 (-4.24, 4.47)
PRN (EU/mL)	≥4-fold rise	327/444 73.6 (69.3, 77.7)	314/438 71.7 (67.2, 75.9)	-1.96 (-7.84, 3.92)
Diphtheria (IU/mL)	≥0.01 IU/mL	432/432 (100.0) (99.1, 100.0)	422/422 100.0 (99.1, 100.0)	0.00 NA
	≥0.1 IU/mL	413/432 95.6 (93.2, 97.3)	419/422 99.3 (97.9, 99.9)	3.69 (1.59, 5.78)
Tetanus (IU/mL)	≥0.01 IU/mL	424/424 100.0 (99.1, 100.0)	416/416 100.0 (99.1, 100.0)	0.00 NA
	≥0.1 IU/mL	424/424 100.0 (99.1, 100.0)	416/416 100.0 (99.1, 100.0)	0.00 NA
Polio 1 (1/dil)	≥1:8	406/406 100.0 (99.1, 100.0)	395/396 99.7 (98.6, 100.0)	-0.25 (-0.75, 0.24)
Polio 2 (1/dil)	≥1:8	422/422 100.0 (99.1, 100.0)	415/415 100.0 (99.1, 100.0)	0.00 NA
Polio 3 (1/dil)	≥1:8	410/410 100.0 (99.1, 100.0)	396/396 100.0 (99.1, 100.0)	0.00 NA

*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*

Non-inferiority is achieved when the UL 95% CI <10%

Source: isi.pdf page 113

Table 135: Study M5A07 Stage I GMT for PRP and pertussis antigens* following three doses of Pentacel co-administered with Prevnar (Group 1) or separately (Group 2)

Antigen	Group 1 N GMT (95% CI)	Group 2 N GMT (95% CI)	Non-Inferiority Comparison [1] Group 2/Group 1 (90% CI)
PRP (µg/mL)	433 3.32 (2.85, 3.87)	427 3.60 (3.09, 4.20)	1.09 (0.91, 1.30)
FHA (EU/mL)	447 82.41 (77.40, 87.75)	439 77.80 (72.62, 83.35)	0.94 (0.87, 1.02)
FIM (EU/mL)	447 272.47 (251.39, 295.32)	439 280.97 (258.02, 305.97)	1.03 (0.93, 1.14)
PRN (EU/mL)	447 45.70 (41.59, 50.23)	439 44.28 (40.11, 48.89)	0.97 (0.86, 1.09)

[1] Non-inferiority is achieved when the upper limit of the 90% CI of the GMT ration (Group 2/Group 1) is <1.5.
Group 1 received Pentacel concurrently with Prevnar. Group 2 received Pentacel staggered with Prevnar.
*anti-PT values were generated in the ----- performed at sanofi pasteur, Canada. During review of this BLA this assay was determined to be non-specific thus, the anti-PT values generated are not acceptable to CBER. See *Section 5.5*
Source: isi.pdf page 115

Comments and Conclusions

An observational evaluation of the response to Pentacel when administered concomitantly with Prevnar in Study 494-01 suggested that the post-dose 3 GMT to PRP and the pertussis antigens may be affected by the number of doses of Prevnar co-administered at 2, 4 and 6 months of age. Because Prevnar is standard of care it is not feasible to evaluate the response to Pentacel when administered with Prevnar compared to a group of subjects who do not receive Prevnar at any time. In Study M5A07 control subjects were administered Prevnar one month following Pentacel. The summary data from Study M5A07 show that the response to all Pentacel antigens evaluated, including PRP-T and pertactin, are similar whether Pentacel is coadministered with Prevnar or separately (Prevnar one month later). Because PT ------ values were generated in a non-specific assay it is not appropriate to present or comment on the response to PT.

6.6 Study M5A10

Background

The two pivotal studies, 494-01 and P3T06, showed inconsistent results with regard to anti-PRP levels ≥1.0 ug/mL and GMTs. In study 494-01 the response of subjects administered three doses of Pentacel did not meet the criteria for non-inferiority compared to three doses of separately administered ActHIB. In Study P3T06 the criteria for non-inferiority were met although the anti-PRP responses following Pentacel and ActHIB appeared lower than observed in Study 494-01 with the most notable difference in the ActHIB arms of the two studies (see Table 2 of this review). CBER's August 20, 2007 IR letter requested sanofi address the potential for an increase in cases of invasive Hib disease over time if the immune response to the Hib component of Pentacel is diminished relative to separately administered ActHIB as observed in Study 494-01. In response to this letter sanofi provided a revised concept document for their Hib surveillance project (Study M5A15, August 31, 2007 submission). In a telephone meeting between CBER and sanofi representatives on September 11, 2007 CBER requested sanofi consider a pre-licensure study to evaluate the anti-PRP immune response following three doses of Pentacel relative to separately administered ActHIB. CBER proposed that this study evaluate several lots of consecutively manufactured ActHIB (see minutes of September 11, 2007 teleconference for details). In lieu of performing a pre-licensure study sanofi offered to provide post-dose 3 Hib data from Study M5A10. These data were submitted to the BLA on October 26, 2007, the protocol was submitted December 4, 2007. CBER agreed that, pending review of these data, if non-inferiority was demonstrated to separately administered ActHIB an additional study would not be required.

6.6.1 Applicants Protocol # and Protocol Title

Study M5A10 A multi-center, randomized, open-label clinical trial designed to compare the immunogenicity and safety of 3 doses of DAPTACEL®, ActHIB®, and IPOL® and a 4th dose of DAPTACEL and ActHIB (US-licensed schedule) with either: 4 doses of Pentacel®; a 4th dose of DAPTACEL and ActHIB administered after 3 doses of Pentacel; or 4 Doses of DTaP-IPV and ActHIB in infants (Infant Series) and toddlers (4th dose).

6.6.1.1 Objective/Rationale

Subjects who have received four doses of Pentacel during the first two years of life may be considered to have received the recommended 4 doses of IPV if the 4th dose was administered at least 4 weeks following the previous dose and the child was at least 18 weeks of age (MMWR Dec. 2006). Consequently such children do not need to receive a 5th dose of IPV at 4-6 years of age. Study M5A10 was designed to "corroborate that a schedule consisting of 3 doses of Pentacel and a 4th dose of DAPTACEL and ActHIB or 4 doses of Pentacel or 4 doses of DTaP-IPV (licensed in Canada under the name Quadracel®) and ActHIB is as safe and immunogenic as a schedule based on 3 doses of the licensed equivalent vaccines DAPTACEL, IPOL, and ActHIB and a 4th dose of DAPTACEL and ActHIB."

Specific objectives relevant to the immunological evaluation of the Hib component of PENTACEL relative to separately administered DAPTACEL, IPOL and ActHIB are listed below for Stage I of Study M5A10. The October 28, 2007 BLA submission contains only the results of the assessment of response to the PRP-T component following three doses of Pentacel compared to ActHIB. A final study report has not been submitted to the BLA. Study M5A10 is a two-staged study, with Stage I vaccines administered at 2, 4, and 6 months of age, and Stage II study vaccines administered at 12 months and between 15 and 17 months of age.

Primary immunogenicity objectives (only those relevant to the evaluation of the PRP-T component of Pentacel relative to separately administered DAPTACEL + IPOL + ActHIB are provided)
Stage I

1. To compare the immune responses to all antigens elicited by 3 doses of Pentacel to those elicited by 3 doses of separately administered ActHIB (+DAPTACEL + IPOL) as measured by anti-PRP seroprotection rates

Secondary immunogenicity objectives

Stage I –

1. To compare the anti-PRP responses elicited by 3 doses of Pentacel to those elicited by 3 doses of separately administered ActHIB (+DAPTACEL + IPOL) as measured by geometric mean concentrations.

Observational immunogenicity Objectives

Stage I
1. To present for all groups anti-PRP seroprotection rates and GMCs with their corresponding 95% CI and reverse cumulative distribution curves (RCDC) for each antigen.

6.6.1.2 Design Overview
Study M5A10 is a two-staged, randomized, multicenter, controlled, open-label study, with Stage I vaccines administered at 2, 4, and 6 months of age, and Stage II vaccines administered between 12 and 17 months of age.

Subjects were randomized at 2 months of age if 1mL blood sample had been obtained. Subjects were randomized into one of four groups using a centralized, non-stratified computer generated randomization code.

The planned duration of the study (first visit to last contact), per subject, was 19 months.

6.6.1.3 Population
The study period from the beginning of Stage I to completion of Stage I (last subject's 30-day follow-up post dose 3) was November 10, 2005 through March 29, 2007. Subjects were enrolled from 38 U.S. centers.

6.6.1.4 Products mandated by the protocol

Study vaccines—schedule of administration

Tables 136 and 137 present the schedule of administration of study vaccines.

Table 136: Study M5A10: Schedule of vaccine administration during Stage I

Group	2, 4, and 6 months	0, 2 and 6 months*
1	DAPTACEL, IPOL, ActHIB, and Prevnar	Hepatitis B vaccine
2	Pentacel and Prevnar	Hepatitis B vaccine
3	HCPDT-IPV, ActHIB, and Prevnar	Hepatitis B vaccine
4	Pentacel and Prevnar	Hepatitis B vaccine

* All subjects received hepatitis B vaccine at 0, 2, and 6 months; the first dose (manufacturer not specified) was administered outside of the study; the second and third doses were with RECOMBIVAX HB or EngerixB, administered as part of the study.

Table 137. Study M5A10: Schedule of vaccine administration during Stage II

Study Group	Months of Age	Vaccines
1	12	MMR_{II}, VARIVAX/ ProQuad + Prevnar
	15	DAPTACEL + ActHIB
2	12	MMR_{II}, VARIVAX/ ProQuad + Prevnar
	15	DAPTACEL + ActHIB
3	12	MMR_{II}, VARIVAX/ ProQuad + Prevnar
	15	HCPDT + ActHIB
4	12	MMR_{II}, VARIVAX/ ProQuad + Prevnar
	15	Pentacel

Per the protocol Version 4.0 dated March 29, 2006 (December 4, 2007 submission to BLA) "Rotateq and/or Hepatitis A (12-18 months of age) vaccines may be administered according to their respective package insert recommendations."

This review will present the Stage I anti-PRP data from Group 1, 2 and 4.

The protocol-specified interval between Visit 1 (dose 1 study vaccines) and Visit 2 was 45-75 days. The protocol-specified interval between Visit 2 and 3 vaccine administration was 45-75 days. The protocol specified interval for the post-dose 3 blood sample was 30-48 days post Visit 3.

Study vaccines—formulation and lot numbers (only Stage I vaccines administered to subjects in Groups 1, 2 and 4 are described):

- Pentacel (DTaP-IPV used to reconstitute ActHIB).

The formulation of Pentacel per 0.5mL dose is described in **Section 1.2.3**

DTaP-IPV Lot number: C2440A

ActHIB Lot number: UE709AA (bulk Y0890)

- DAPTACEL

DAPTACEL, composition per 0.5 ml dose:
Active Ingredients:
10 µg Pertussis Toxoid (PT)
5 µg Filamentous hemagglutinin (FHA)
5 µg Fimbriae (FIM) 2 & 3
3 µg Pertactin (PRN)
15 LF Diphtheria toxoid

5 LF Tetanus toxoid
Adjuvant: 0.33 mg aluminum
Excipient: 0.6% 2-phenoxyethanol

Lot number C2377A ----------

- ActHIB, Haemophilus b Conjugate Vaccine produced by Aventis Pasteur SA, is a lyophilized powder reconstituted with saline diluent. Each 0.5 ml dose is formulated to contain 10 μg of purified capsular polysaccharide conjugated to 24 μg of inactivated tetanus toxoid.
  Lot UE709AA.

- IPOL is poliovirus vaccine, inactivated, and produced by Aventis Pasteur SA. Each 0.5 ml dose is formulated to contain 40 D antigen units of Type 1 (Mahoney), 8 D antigen units of Type 2 (MEF-1), and 32 D antigen units of Type 3 (Saukett) poliovirus. Also present are 0.5% 2-phenoxyethanol and a maximum of 0.02% formaldehyde per dose as preservatives. Neomycin (< 5 ng), streptomycin (< 200 ng) and polymyxin B (< 25 ng) may be present. Residual calf serum protein is less than 1 ppm in the final vaccine.
  IPOL lot Y0575 was used.

For the following vaccines, lots available at individual study sites were used:

- Prevnar, [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), Wyeth]: Each 0.5 ml dose of Prevnar contains 2 μg of each polysaccharide for *Streptococcus pneumoniae* serotypes 4, 9V, 14, 18C, 19F, and 23F and 4 μg of serotype 6B (16 μg total polysaccharide); approximately 20 μg of CRM_{197} protein; and 0.125 mg of aluminum as aluminum phosphate adjuvant.

- RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant), Merck & Co., Inc]: Each 0.5 ml dose contains 5 μg of purified HBsAg without preservative.

- ENGERIX-B [Hepatitis B Vaccine (Recombinant), GlaxoSmithKline Biologicals]: Each 0.5mL pediatric dose contains 10 μg of purified HBsAg without preservative

The following vaccines were supplied and administered by the study sites outside the study protocol:
Rotateq (Rotavirus Vaccine, Live, Oral, Pentavalent; Merck & Co., Inc.)
HAVRIX (Hepatitis A Vaccine, Inactivated; GlaxoSmithKline Biologicals)
VAQTA (Hepatitis A Vaccine, Inactivated; Merck & Co., Inc.)

Stage I Study vaccines: route of administration

Pentacel, DAPTACEL, ActHIB, Prevnar, and RECOMBIVAX HB and ENGERIX-B were injected intramuscularly. IPOL was injected subcutaneously.

6.6.1.5 Immunogenicity Endpoints and Criteria for Evaluation of the Response to PRP-T

Antibody Assays
See **Section 5.5** for an overview of the anti-PRP serology assay.

Primary endpoints and evaluation criteria

Stage I—

Table 138. Study M5A10: Primary Immunogenicity Endpoints and Non-inferiority criteria for evaluation of anti-PRP seroprotection rates following 3 doses of Pentacel (groups 2 and 4) or DAPTACEL + IPOL + ActHIB (group 1), post-dose 3

Antigen	Endpoint	Non-inferiority Criteria
PRP	⩾0.15 ug/mL ⩾1.0 ug/mL	UL 95% CI difference DAPTACEL (Group 1) minus Pentacel (Groups 2 and 4) < 10%

Source: Oct 26, 2007 m5a10_prot_v4.pdf (December 4, 2007 submission)

Secondary endpoints and evaluation criteria

Stage I – secondary endpoints
Table 139 Study M5A10: Secondary Endpoints and Non-inferiority criteria for evaluation of anti-PRP GMCs following 3 doses of Pentacel (groups 2 and 4) or DAPTACEL + IPOL + ActHIB (group 1)

Antigen	Endpoint	Non-inferiority Criteria
PRP	GMC	UL 90% CI ratio DAPTACEL (Group 1)/Pentacel (Group 2 and 4) < 1.5

6.6.1.6 Surveillance/Monitoring

Immunogenicity
In Stage I, serum samples were collected prior to vaccination at Visit 1 (42-89 days of age) and 30-48 days after the third dose of DAPTACEL or Pentacel at 7 months of age.

6.6.1.7 Statistical Considerations

Sample size and statistical power
The planned total sample size was 2,160 subjects randomized equally to one of the Stage I vaccine groups (540 per group). An attrition rate of 15% to the end of Stage I was considered for statistical power calculations (459 subjects per group). An additional 8% attrition was considered for per-protocol population calculations (422 subjects per group). Power calculations presented for each of the primary and secondary immunogenicity endpoints for Stage I were based on 422 subjects per group, and indicated at least 90% power for each endpoint. The overall power of the study considering all endpoints for Stage I was 80.1%.

Analysis populations

Intent to treat immunogenicity population The ITT population for immunogenicity included any subject who received all three doses of DAPTACEL or Pentacel (for Stage I) or who received the fourth dose of DAPTACEL or Pentacel (for Stage II) regardless of whether they adhered to the study eligibility criteria or their immunization and bleeding visits were within the protocol-specified windows, and had a valid serology test post-dose 3 (for Stage I) or post-dose 4 (for Stage II) for at least one DAPTACEL or Pentacel antigen. Analyses were based on the original randomization.

Per-protocol immunogenicity population The per-protocol population for immunogenicity included all eligible subjects who met all inclusion/exclusion criteria at study entry, received the correct vaccines (according to the randomized schedule) for all doses (three doses for Stage I analyses), had all doses and blood draws within windows as specified in the protocol, and had a valid serology test result post-dose 3 (for Stage I) for at least antigen.

Statistical criteria for non-inferiority analyses

The protocol-specified statistical criteria for non-inferiority of GMCs between study groups were based on the 90% CIs for the ratios of GMCs. The protocol-specified statistical criteria for non-inferiority of seroprotection rates between study groups were based on the 95% CIs for differences in rates between groups. However, CBER currently recommends use of 2-sided 95% CIs for ratios of GMCs for non-inferiority analyses, as well as 2-sided 95% CIs for rate differences for non-inferiority analyses. To be consistent with current policy, the manufacturer provided analyses of non-inferiority using 95% CIs for GMC, in addition to the protocol-specified analyses using 90% CIs.

6.6.2 Results

Only results that are relevant to the evaluation of the PRP-T component of Pentacel are included in this review. RCDCs are not presented.

6.6.2.1 Populations enrolled/analyzed

Table140 presents a summary of the immunogenicity populations in Stage I of M5A10. The Stage I DAPTACEL groups have been pooled.

Table 140: Summary of Subject Disposition – number of subjects randomized, immunized, bled and included in the immunogenicity populations

Immunogenicity disposition		
Stage I	**Pooled Pentacel (Groups 2 and 4 (%)**	**ActHIB (%)**
Randomized	1084	543
Subject participation by randomized treatment	1083	538
Received three doses by randomized treatment	999	496
Bled pre dose 1	NA	NA
Received three doses of ActHIB or Pentacel[1]	**999 (100.0)**	**496 (100.0)**
Received three doses of ActHIB or Pentacel and bled post-dose 3	**918**	**455**
serum sample not available in laboratory	2	0
ITT immunogenicity[3]	**916 (91.7%)**	**455 (91.7%)**
Protocol violations[4]		
Did not satisfy eligibility criteria	2	1
Treatment error	5	1
Visit out of time interval or age window	62	28
Other	13	2
PP Immunogenicity Population[5]	**834 (83.5%)**	**423 (85.2%)**

Source: Oct 26, 2007 m5a10prp_si_hib_report.pdf page 17
NA not available
[1] subjects classified according to randomized treatment
[2] table 5.1 in P3T06 Stage I (p3t06si.pdf page 80) study report and table 5.2 P3T06 Stage II study report (p3t06sii.pdf page 86) do not indicate whether subjects are classified by treatment or randomization
[3] ITT Immunogenicity Population: Defined as those subjects who had 3 doses of study vaccine and a valid serology test result for at least 1 Pentacel antigen at post-Dose 3
[4] Only one primary reason for termination per subject is selected in the order listed.
[5] Stage I PP Immunogenicity Population: Defined as eligible subjects who received all 3 doses as randomized, had all doses and post-Dose 3 blood drawn within windows, and had a valid serology test result for at least 1 antigen at post-Dose 3; The PP Immunogenicity Population was used only in the Immunogenicity analyses

6.6.2.2. Immunogenicity Analyses and Data Presentation

In this review results of analyses of response to the PRP component of Pentacel are presented. Results are presented for the PPI population. Results for the ITT immunogenicity population were similar. A summary report was submitted to the BLA no information is provided on the use of Rotateq and hepatitis A vaccine among study subjects.

Demographics

Table 141: Study M5A10 Summary of subject demographics (PP Immunogenicity Population).

	Pentacel (Groups 2&4)	DAPTACEL (Group 1)
N	**834**	**423**
Sex: Male, n (%) Female, n (%)	 433 (51.9) 401 (48.1)	 233 (55.1) 190 (44.9)
Mean Age (Months*) Std Median Range	2.1 0.27 2.1 [1.4; 2.9]	2.1 0.26 2.1 [1.4; 2.9]
Caucasian, n (%) Black, n (%) Hispanic, n (%) Asian, n (%) Other, n (%)	622 (74.6) 42 (5.0) 105 (12.6) 5 (0.6) 60 (7.2)	306 (72.3) 26 (6.1) 56 (13.2) 4 (0.9) 31 (7.3)

* Age (months) = (Date of 1st Vaccination . Date of Birth + 1) / (365.25) * 12.
Source: Oct 26, 2007 m5a10prp_si_hib_report.pdf page 18

Prevaccination antibody levels:
Prevaccination anti-PRP levels were not provided.

Stage I

Stage I Non-inferiority of PRP component of Pentacel relative to ActHIB (+ DAPTACEL + IPOL). Using 95% CI for difference in seroprotection rates the statistical criteria for non-inferiority between the response to PRP-T following three doses of Pentacel (Groups 2 and 4 combined) or DAPTACEL were met. These data are presented in Table 142.

Table 142: Study M5A10 Seroprotection rates and non-inferiority analyses following three doses of Pentacel or ActHIB. PPI population.

PRP	Pentacel (Groups 2 and4 combined) n/N % (95%CI)	ActHIB (Group 1) n/N % (95%CI)	Non-inferiority ActHIB minus Pentacel[1]	
			%	95% CI
≥ 0.15 ug/mL	775/826 93.8 (92.0, 95.4)	380/421 90.3 (87.0, 92.9)	-3.56	(-6.84; -0.29)
≥ 1.0 ug/mL	620/826 75.1 (72.0, 78.0)	315/421 74.8 (70.4, 78.9)	-0.24	(-5.33; 4.85)

[1]Non-Inferiority is achieved when the upper limit of the 95% CI of 2-sided 95% CI is <10%.
Note: 'n' is the number of subjects who achieved the criteria specified.
'N' is the number of subjects with a valid serology result Post-Dose 3
Source: Oct 26, 2007 m5a10_si_hib_report.pdf page 19 and 22

Stage I Non-inferiority of PRP component of Pentacel relative to ActHIB. Using 90% CI for the ratio of GMCs the statistical criteria for non-inferiority between the response to PRP-T following three doses of Pentacel (Groups 2 and 4 combined) or DAPTACEL were met. These data are

presented in Table 143. Although not specified in the protocol the manufacturer provided the 95% CI on the ratio.

Table 143: Study M5A10 PRP GMCs and non-inferiority analyses following three doses of Pentacel or ActHIB. PPI.

	Pentacel (Groups 2 and4 combined)		ActHIB (Group 1)		Non-inferiority ActHIB/Pentacel		
	N	Geometric Mean	N	Geometric Mean	Ratio	(90% CI)	(95% CI)
PRP (µg/mL)	826	2.52 (2.25, 2.81)	421	2.38 (2.01, 2.81)	0.94	(0.80; 1.11)[1]	(0.78; 1.15)

[1]Non-inferiority is achieved when the upper limit of each 90% CI is <1.5.
N is the total number of subjects with available serology data.
Source: Oct 26, 2007 m5a10_si_hib_report.pdf page 20 and 22

Other Analyses:

Race/ethnicity and response to PRP-T
The response to PRP following three doses of Pentacel or ActHIB by race/ethnicity is presented in Table 144 and 145 respectively.

Table 144: Immune response to PRP-T by race/ethnicity in subjects administered three doses of Pentacel in Study M5A10, PPI

	Caucasian	Black	Hispanic	Asian	Other
Study M5A10					
N = 826	617	42	103	5	59
% ⩾0.15 ug/mL	93.2 (90.9; 95.1)	95.2 (83.8; 99.4)	99.0 (94.7; 100.0)	100.0 (47.8; 100.0)	89.8 (79.2; 96.2)
% ⩾1.0 ug/mL	72.9 (69.2; 76.4)	73.8 (58.0; 86.1)	82.5 (73.8; 89.3)	100.0 (47.8; 100.0)	83.1 (71.0; 91.6)
GMT	2.38 (2.08; 2.71)	2.41 (1.46; 3.96)	3.61 (2.82; 4.62)	6.35 (1.21; 33.46)	2.33 (1.52; 3.57)

Source: Oct 26, 2007 m5a10prp_si_hib_report.pdf

Table 145: Immune response to PRP-T by race/ethnicity in subjects administered three doses of ActHIB in Study M5A10, PPI

	Caucasian	Black	Hispanic	Asian	Other
Study M5A10					
N = 421	304	26	56	4	31
% ⩾0.15 ug/mL	89.5 (85.5; 92.7)	80.8 (60.6; 93.4)	96.4 (87.7; 99.6)	100.0 (39.8; 100.0)	93.5 (78.6; 99.2)
% ⩾1.0 ug/mL	71.7 (66.3; 76.7)	65.4 (44.3; 82.8)	92.9 (82.7; 98.0)	100.0 (39.8; 100.0)	77.4 (58.9; 90.4)
GMT	2.08 (1.70; 2.54)	1.49 (0.64; 3.51)	5.13 (3.50; 7.54)	5.71 (3.75; 8.69)	2.85 (1.55; 5.25)

Source: Oct 26, 2007 m5a10prp_si_hib_report.pdf

6.6.3 Comments and Conclusions

Because of concerns regarding the potential for an increase in cases of invasive Hib disease over time if the immune response to the Hib component of Pentacel is diminished relative to separately administered ActHIB sanofi provided the immunogenicity data from Study M5A10. These data

show that following three doses of Pentacel non-inferiority of the response to PRP-T was demonstrated compared to separately administered ActHIB. The failure of Study 494-01 to demonstrate non-inferiority of the PRP-T component of Pentacel relative to separately administered ActHIB has not been explained. However, the data from two randomized studies, M5A10 and Study P3T06, show non-inferiority of response to the PRP-T component of Pentacel relative to separately administered ActHIB. Based upon these data CBER concluded that an additional pre-licensure study would not be required.

7. Overview of Effectiveness

Effectiveness of Pentacel

Evaluation of the effectiveness of the tetanus, diphtheria, polio and PRP-T components of Pentacel was based on a comparison of immune responses, using established correlates of protection and, for some antigens, GMTs, relative to separately administered vaccines in US children. There is no established serological correlate of protection against pertussis. The evaluation of the effectiveness of the pertussis component was based on a comparison of immune responses in US children administered four doses of Pentacel to those in Swedish infants following three doses of DAPTACEL in a clinical endpoint efficacy study. The evaluation of the effectiveness of the pertussis component was also based on a comparison of immune responses relative to separately administered vaccines in US children.

The Pentacel BLA contains two studies comparing the immune response of Pentacel to that of separately administered vaccines: Study 494-01 evaluated non-inferiority of Pentacel antigens relative to separately administered HCPDT, ActHIB and POLIOVAX. In Study P3T06 control subjects were administered DAPTACEL, ActHIB and IPOL. In this study, non-inferiority was evaluated for the response to diphtheria, tetanus, pertussis and PRP-T components.

Data on the epidemiology of invasive Hib disease and pertussis were provided in the BLA. These data and US-epidemiological data are summarized in this section.

Polio

Response to polio virus serotypes 1, 2 and 3 administered as Pentacel or Inactivated Polio Virus Vaccine (POLIOVAX or IPOL)

Following three doses of Pentacel in Study 494-01 non-inferiority was demonstrated for polio virus seroprotective levels ($\geq$1:8) of neutralizing antibodies to each serotype as compared to POLIOVAX, and >99% of subjects in both groups had protective neutralizing antibody against each poliovirus serotype. Although non-inferiority of polio seroprotective levels was not evaluated in Study P3T06, >99% of subjects administered Pentacel or control vaccine (IPOL) had seroprotective levels $\geq$ 1:8 to each of the serotypes.

Diphtheria and tetanus toxoids

Response to diphtheria and tetanus toxoids administered as Pentacel or DTaP (HCPDT or DAPTACEL)

Tetanus: Anti-tetanus toxin neutralization levels $\geq$0.01 IU/mL measured in the ---------- ---------- ---------- are considered protective. Based on review of post-immunization anti-tetanus toxoid levels measured using the sanofi-pasteur-US ELISA and the ---------- ----------, CBER considers ELISA levels $\geq$ 0.1 IU/mL measured using the AP- US ELISA the minimum protective level.

Following three doses of Pentacel in Study 494-01, over 99% of subjects had an anti-tetanus toxoid level $\geq$0.1 IU/mL. Although non-inferiority criteria were not prespecified for antibody levels $\geq$ 0.1 IU/mL the UL of the 90% CI on the difference in seroresponse levels is <10%. Following three doses of Pentacel or DAPTACEL in Study P3T06, >99% of subjects had an anti-tetanus toxoid level $\geq$0.1 IU/mL.

Diphtheria: Available data indicate that an anti-diphtheria toxin level ≥0.01 IU/mL is the lowest level giving some degree of protection, while a level ≥0.1 IU/mL may be needed for full protection.

Following three doses of Pentacel in Study 494-01, >99% of subjects had an anti-diphtheria toxin level ≥0.01 IU/mL, and 92.1% had an anti-diphtheria toxin level ≥0.1 IU/mL. Non-inferiority relative to HCPDT was demonstrated for anti-diphtheria toxin levels ≥ 0.01 IU/mL. Although non-inferiority criteria were not prespecified for antibody levels ≥ 0.1 IU/mL the UL of the 90% CI on the difference (DAPTACEL minus Pentacel) in seroresponse levels is <10%. Following three doses of Pentacel in Study P3T06, 100% of subjects achieved an anti-diphtheria toxin level ≥0.01 IU/mL, and >98% had an anti-diphtheria toxin level ≥ 0.1 IU/mL. Non-inferiority of Pentacel relative to DAPTACEL was demonstrated for anti-diphtheria toxin levels ≥ 0.01 IU/mL and GMT.

PRP-T

Response to PRP-T administered as Pentacel or ActHIB

Anti-PRP has been shown to correlate with protection against Hib disease. Based on efficacy studies with Hib polysaccharide (not Hib-conjugate) vaccines and data from passive antibody studies, a post-vaccination anti-PRP level of 0.15μg/mL has been accepted as correlating with protection[4] and 1.0 μg/mL with long-term (1 year) protection[5,6]. Although the relevance of these levels to Hib conjugate vaccines is not entirely clear, they have been used to evaluate the effectiveness of Hib conjugate vaccines and combination vaccines containing Hib components.

In the two comparative pivotal studies, Pentacel was non-inferior to separately administered ActHIB with regard to post-dose 3 anti-PRP levels ≥0.15 μg/mL. However, these two studies showed contradictory results with regard to anti-PRP levels ≥1.0 μg/mL and GMTs. In study 494-01 the proportion of subjects with anti-PRP levels ≥1.0 ug/mL and the GMT were lower following three doses of Pentacel compared to three doses of separately administered ActHIB (Table 20 and 21). In Study P3T06 the proportion of subjects with anti-PRP levels ≥1.0 ug/mL and the GMT were similar following three doses of Pentacel or separately administered ActHIB (96 and 98). However, the anti-PRP responses following both Pentacel and ActHIB in Study P3T06 appeared to be lower than observed in Study 494-01, with the most notable differences in the ActHIB arms of the two studies (e.g., post-dose 3 GMT 2.29ug/mL for Study P3T06 and 6.23 ug/mL for Study 494-01) (Table 2).

In studies which did not include an ActHIB comparator, following the third dose of Pentacel, the anti-PRP GMT ranged from 2.8-3.6 ug/mL and the proportion of subjects with PRP antibody levels ≥1.0 ug/mL ranged from 75.6-79.6%, consistent with the Pentacel arms of the comparative studies (Table 2).

In Studies 494-01 and P3T06, the post-dose 3 anti-PRP responses appeared to predict the proportion of subjects with seroprotective levels at 15 months of age prior to receipt of a fourth

[4] Robbins JB, Parke JC, Schneerson R. Quantitative measurement of "natural" and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. Pediatr Res 1973;7:103

[5] Kayhty H, et al. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis 1983;147:1100

[6] Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. J Infect Dis 1984;149:1034

dose of PRP-T: In Study 494-01, 67% of subjects administered Pentacel had anti-PRP levels ≥0.15 ug/mL compared with 81% of subjects administered ActHIB separately. At 15-16 months of age prior to administration of the fourth dose of PRP-T, 61-65% of P3T06 subjects had anti-PRP levels <0.15 ug/mL (Table 2).

Sanofi pasteur and CBER have considered whether the anti-PRP immune response seen in Pentacel studies is consistent with previous ActHIB experience. CBER has also considered whether the observed variability in anti-PRP responses may be due to differences in assays, lot-to-lot variability, co-administered vaccines and/or the race/ethnicity of subjects.

Comparison to historical data Table 146 presents historical data provided by sanofi pasteur on the responses to ActHIB administered with Tripedia or DAPTACEL and other recommended vaccines, for studies conducted between 1995 and 1997 for which all sera were assayed by sanofi pasteur-US. Since the PRP assay used for the Pentacel pivotal studies was performed by sanofi pasteur-US and was validated in 1995, comparisons to the data in Table 2 should eliminate assay differences as a factor that may contribute to differences in anti-PRP responses across studies. The anti-PRP assay used by sanofi pasteur has been reviewed by a member of the Pentacel review committee and found to be acceptable.

Table 146: Historical anti-PRP response data generated using the sanofi pasteur-US ----: Post dose 3 response to ActHIB administered with DAPTACEL and Tripedia vaccines– non-BLA studies conducted 1995 -2000

With the notable exception of the control group in Study 494-01, the post-dose 3 anti-PRP GMTs observed in the pivotal studies of Pentacel generally appear to be somewhat lower than those observed in historical studies of ActHIB (compare Tables 2 and 146).

Response to ActHIB lots used in Pentacel studies Several PRP-T bulk lots have been used in Pentacel studies (Table 147). All lots used in these studies met the lot –release specifications and were released by CBER.

In Study 494-01 subjects administered ActHIB separately received the same bulk lot of PRP-T and other vaccine antigens as subjects administered Pentacel Lot #3. The GMT was lower (non-overlapping 95% CI) when this bulk PRP-T lot was administered as Pentacel compared to separately administered as ActHIB (6.23 vs. 3.64). The proportion of subjects with anti-PRP seroprotective levels $\geqslant$ 1.0 ug/mL was lower following Pentacel (81.7%) compared to ActHIB (88.8%). In contrast, in Study P3T06 in which the same bulk lot of PRP-T was administered as Pentacel or ActHIB, the anti-PRP responses did not differ between the groups. In response to a query from CBER, sanofi provided a summary of manufacturing information for each of the lots of ActHIB used in Studies 5A9908, 494-01, 494-03 and P3T06 (date of manufacture of final bulk, concentrate bulk, PRP lot number, *H. influenzae* and *C. tetani* MS and WS #) and significant manufacturing changes incorporated into each lot used in pivotal clinical studies. All changes to the ActHIB license had been reviewed by CBER and found to be acceptable.

Table 147: ActHIB lot administered to subjects in each study group as Pentacel or separately as ActHIB

Study	**Vaccine administered***	**ActHIB lot # administered**	
		Stage I	**Stage II**
5A9908	Pentacel	NA	P1332 (bulk P1332)
494-01	Pentacel Group 1 Group 2 Group 3	 P1394 (bulk P1394) P1332 (bulk P1332) UA480A (R0181 bulk)	 UA480A (R1081 bulk)
	ActHIB	UA480A (R0181 bulk)	UA480A (R1081 bulk)
494-03	Pentacel	UA480AE (R1081 bulk)	UA480AE (R1081 bulk)
P3T06	Pentacel	UA596AB (T0222)	UA685AA (U0487 bulk)
	ActHIB	UA596AB (T0222)	UA685AA (U0487 bulk)
M5A07	Pentacel + Prevnar	UA854AA (W0981 bulk)	NA
	Pentacel staggered Prevnar	UA854AA (W0981 bulk)	NA
M5A10	Pentacel	UE709AA (Y0890 bulk)	NA
	ActHIB	UE709AA (Y0890 bulk)	NA

*For co-administered vaccines see study reports
Source: study reports and September 7, 2006 questions141_156.pdf page 9-10, Oct 26, 2007 m5a10prp_si_hib_report.pdf.

Co-administered vaccines and the response to ActHIB
Polio A diminished response to PRP-T among children administered three doses of IPV (IPOL) or two doses of IPV plus a dose of OPV concurrently with Tripedia/ActHIB (TriHIBit) at 2, 4 and 6 months of age compared to those infants administered Tripedia or TriHIBit co-administered with OPV (Orimune) was described in a study by Rennels *et al* (Ped Inf Dis J. 2000, 19: 417-423). No study group received Tripedia + ActHIB + IPV. These data are summarized in Table 148.

Table 148: Response to PRP-T when administered as ActHIB or TriHIBit concomitantly with OPV IPV/OPV or IPV at 2, 4 and 6 months of age

	Tripedia + ActHIB OPV, OPV, OPV	TriHIBit + OPV, OPV, OPV	TriHIBit + IPV, IPV, OPV	TriHIBit + IPV, IPV, IPV
	N =	N =		
GMT	4.43 (3.3, 5.9)	3.17 (2.3, 4.3)	1.33 (0.9, 1.9)	1.21 (0.9, 1.7)
% ⩾0.15 ug/mL*	98	94	86	84
% ⩾1.0 ug/mL*	81	78	58	53

Source: Rennels et al. 2000,
Serology assays were performed by sanofi pasteur-US.
95% CI on seroprotective levels not provided.

A study by Daum *et al* (Ped Inf Dis J 2000 19: 710-717) evaluated the response to PRP-T administered as TriHIBit at 2, 4, and 6 months of age with either IPV (IPOL) or OPV (Orimune) at 2 and 4 months of age (Table 149). The authors concluded that there was no significant interference in the response to PRP-T when TriHIBit was administered with IPV as compared to OPV. At 7 months of age 74-77% of subjects in both groups had anti-PRP levels ⩾1.0 ug/mL. The GMT at 7 months of subjects who had received IPV was 2.44 ug/mL (95% CI 1.73, 3.42), the GMT of subjects who had received OPV was 3.12 ug/mL (95% CI 2.39, 4.07). The anti-PRP levels seen following three doses of Pentacel are similar to those following three doses of TriHIBit administered to infants in this study.

Of note, TriHIBit is licensed for use as a booster dose in children 15-18 months of age, it is not licensed for use in infants.

Table 149: Anti-PRP response at 7 months of age following three doses of TriHIBit at 2, 4 and 6 months of age co-administered with IPV (IPOL) or OPV at 2, and 4 months of age.

	TriHIBit at 2, 4, 6m+ HepB + IPV at 2, 4m	**TriHIBit at 2, 4, 6m HepB + OPV at 2, 4m**
	N = 103	**N =125**
Post dose 3		
% ≥0.15 ug/mL	90.3 (84.6, 96.0)	95.2 (91.5, 99.0)
% ≥1.0 ug/mL	73.8 (65.3, 82.3)	76.8 (69.4, 84.2)
GMT	2.44 (1.73, 3.42)	3.12 (2.39, 4.07)

Source: Daum et al 2000
Serology assays were performed by sanofi pasteur-US

Pnuemococcal conjugate vaccine An exploratory analysis of anti-PRP response according to the number of Prevnar doses co-administered with Pentacel or ActHIB during the infant series suggested that the post-dose 3 response may be affected by the number of co-administered Prevnar doses (Table 23 and 24). Study M5A07 was designed to address whether co administration of Prevnar interfered with the response to Pentacel. The summary data provided in the BLA indicate that co-administration of Prevnar does not diminish the post-dose three response to the PRP-T component of Pentacel as compared to the response when Pentacel is administered at 2, 4 and 6 months and Prevnar at 3, 5 and 7 months of age (Table 134 and 135).

Race/ethnicity and response to ActHIB
In response to a query from CBER sanofi pasteur provided an analysis of post-dose 3 response to PRP based on race/ethnicity for each pivotal study (494-01, 494-03 and P3T06) as well for Study M5A10. These data are summarized below. Sanofi pasteur state that "in general higher rates of

seroprotection and GMTs were observed in the Asian population, followed by the Hispanic, Black and Caucasian populations." In each pivotal study seroprotection rates and GMTs appear lower in Caucasian subjects as compared to other subjects. However, the general conclusions of each of the comparative studies (494-01 and P3T06) are supported when seroprotective rates and GMTs are compared within each racial/ethnic group.

Table 150: Immune response to PRP-T based on race/ethnicity in subjects administered three doses of Pentacel in pivotal studies and M5A10, PPI

	Caucasian	**Black**	**Hispanic**	**Asian**	**Other**
Study 494-01	n (%)	n (%)	n (%)	n (%)	n (%)
N = 1127	701 (62.2%)	112 (9.9%)	126 (11.1%)	68 (6.0%)	120 (10.6%)
%≥ 0.15ug/mL	93.4 (91.3, 95.2)	100.0 (96.8, 100.0)	98.4 (94.4, 99.8)	98.5 (92.1, 100.0)	97.5 (92.9, 99.5)
% ≥ 1.0ug/mL	74.9 (71.5, 78.1)	86.6 (78.9, 92.3)	88.9 (82.1, 93.8)	88.2 (78.1, 94.8)	81.7 (73.6, 88.1)
GMT	2.58 (2.28, 2.92)	3.98 (3.11, 5.09)	5.67 (4.48, 7.16)	4.87 (3.44, 6.90)	3.92 (3.02, 5.09)
Study 494-03					
N = 270	168 (62.2%)	16 (5.9%)	58 (21.4%)	6 (2.2%)	22 (8.1%)
% ≥ 0.15 ug/mL	91.7 (86.4, 95.4)	100.0 (79.4, 100.0)	100.0 (93.8, 100.0)	100.0 (54.1, 100.0)	95.5 (77.2, 99.9)
% ≥ 1.0 ug/mL	71.4 (64.0, 78.1)	75.0 (47.6, 92.7)	84.5 (72.6, 92.7)	100.0 (54.1, 100.0)	77.3 (54.6, 92.2)
GMT	2.14 (1.64, 2.79)	3.06 (1.41, 6.64)	5.49 (3.85, 7.83)	6.11 (2.49, 14.99)	2.84 (1.56, 5.20)
Study P3T06					
N = 365	284 (77.8%)	24 (6.5%)	26 (7.1%)	3 (0.8%)	28 (7.6%)
% ≥ 0.15 ug/mL	90.8 (86.9, 93.9)	91.7 73.0, 99.0)	100.0 (86.8, 100.0)	100.0 (29.2, 100.0)	100.0 (87.7, 100.0)
% ≥ 1.0 ug/mL	70.4 (64.7, 75.7)	83.3 (62.6, 95.3)	80.8 (60.6, 93.4)	66.7 (9.4, 99.2)	71.4 (51.3, 86.8)
GMT	2.18 (1.78, 2.66)	2.79 (1.44, 5.42)	3.09 (1.61, 5.93)	4.76 (0.03, 704.9)	2.57 (1.47, 4.50)
Study 494-03					
N = 270	168 (62.2%)	16 (5.9%)	58 (21.5%)	6 (2.2)	22 (8.1%)
% ⩾0.15 ug/mL	91.7	100	100	100	95.5
%⩾1.0 ug/mL	71.4	75	84.5	100	77.3
GMT	2.1 (1.64, 2.79)	3.1 (1.41, 6.64)	5.5 (3.85, 7.83)	6.1 (2.49, 14.99)	2.8 (1.56, 5.20)
Study M5A10					
N = 826	617 (74.6%)	42 (5.0%)	103 (12.4%)	5 (0.6%)	59 (7.1%)
% ≥0.15 ug/mL	93.2 (90.9; 95.1)	95.2 (83.8; 99.4)	99.0 (94.7; 100.0)	100.0 (47.8; 100.0)	89.8 (79.2; 96.2)
% ≥1.0 ug/mL	72.9 (69.2; 76.4)	73.8 (58.0; 86.1)	82.5 (73.8; 89.3)	100.0 (47.8; 100.0)	83.1 (71.0; 91.6)
GMT	2.38 (2.08; 2.71)	2.41 (1.46; 3.96)	3.61 (2.82; 4.62)	6.35 (1.21; 33.46)	2.33 (1.52; 3.57)

Source: Sept 7, 2006 Questions1_33.pdf page 409-413, Oct 26, 2007 m5a10prp_si_hib_report.pdf, 49403si.pdf page 488 and 490

Table 151: Immune response to PRP-T in subjects administered three doses of ActHIB in pivotal studies and M5A10, PPI

	Caucasian	Black	Hispanic	Asian	Other
Study 494-01					
N = 401	262 (65.3%)	36 (8.9%)	47 (11.7%)	21 (5.2%)	35 (8.7%)
%≥ 0.15ug/mL	97.3 (94.6, 98.9)	100.0 (90.3, 100.0)	100.0 (92.5, 100.0)	100.0 (83.9, 100.0)	100.0 (90.0, 100.0)
% ≥ 1.0ug/mL	87.4 (82.8, 91.2)	91.7 (77.5, 98.2)	87.2 (74.3, 95.2)	100.0 (83.9, 100.0)	91.4 (76.9, 98.2)
GMT	5.29 (4.41, 6.35)	8.78 (5.73, 13.46)	6.35 (4.17, 9.68)	11.03 (7.35, 16.54)	10.17 (6.33, 16.35)
Study P3T06					
N = 1128	892 (79.0%)	63 (5.5%)	68 (6.0%)	6 (0.5%)	99 (8.7%)
%≥ 0.15ug/mL	92.3 (90.3, 93.9)	100.0 (94.3, 100.0)	94.1 (85.6, 98.4)	100.0 (54.1, 100.0)	97.0 (91.4, 99.4)
% ≥ 1.0ug/mL	69.5 (66.4, 72.5)	76.2 (63.8, 86.0)	79.4 (67.9, 88.3)	83.3 (35.9, 99.6)	72.7 (62.9, 81.2)
GMT	2.04 (1.82, 2.28)	3.19 (2.21, 4.61)	5.32 (3.45, 8.20)	5.11 (0.94, 27.68)	2.89 (2.13, 3.91)
Study M5A10					
N = 421	304 (72.2%)	26 (6.1%)	56 (13.3%)	4 (1.3%)	31 (7.5%)
% ≥0.15 ug/mL	89.5 (85.5; 92.7)	80.8 (60.6; 93.4)	96.4 (87.7; 99.6)	100.0 (39.8; 100.0)	93.5 (78.6; 99.2)
% ≥1.0 ug/mL	71.7 (66.3; 76.7)	65.4 (44.3; 82.8)	92.9 (82.7; 98.0)	100.0 (39.8; 100.0)	77.4 (58.9; 90.4)
GMT	2.08 (1.70; 2.54)	1.49 (0.64; 3.51)	5.13 (3.50; 7.54)	5.71 (3.75; 8.69)	2.85 (1.55; 5.25)

Source: Sept. 7, 2006 Questions1_133.pdf page 409-413, Oct 26, 2007 m5a10prp_si_hib_report.pdf

Effectiveness of the pertussis components of Pentacel

DAPTACEL is approved in the US as a four dose primary series for pertussis. The efficacy of three doses of DAPTACEL (2, 4, and 6 months) against pertussis was demonstrated in a clinical study in Swedish infants (Sweden I). Following three doses of DAPTACEL in US infants, antibody responses to all pertussis antigens except for pertactin were similar to those observed in the Swedish infants. The immune response to pertactin following three doses in US infants was significantly lower than in Swedish infants. The antibody responses to all pertussis antigens in US and Canadian infants after four doses of DAPTACEL (2, 4, 6, 15-20 months) were comparable to those achieved after three doses in Swedish infants.

Because the pertactin content of Pentacel is the same as that of DAPTACEL, effectiveness of the pertussis component of Pentacel was evaluated by comparison of the immune response of US-children administered four doses in Study 494-01 to that of infants administered three doses of DAPTACEL in the Sweden I efficacy study. Immunogenicity of the pertussis component of Pentacel compared to DAPTACEL was also evaluated in Study P3T06 following three and four doses of each vaccine.

Serology bridge to Sweden I: Following four doses of Pentacel (Study 494-01) compared to three doses of DAPTACEL in Sweden I, non-inferiority was demonstrated for FHA and FIM seroconversion rates and GMTs for FHA, FIM and pertactin (Table 52 and 53). Non-inferiority was not demonstrated for pertactin seroconversion rates (89.2% vs. 98.8%; UL of 95% CI for difference DAPTACEL minus Pentacel = 13.2) (Table 52). Although not pre-specified as non-

inferiority analyses, the seroconversion rates and GMTs for FHA following three doses of Pentacel in Study 494-01 were at least as high as those observed following three doses of DAPTACEL in Sweden I. Pertactin seroconversion rates and GMTs and fimbriae GMTs were diminished following three doses of Pentacel as compared to DAPTACEL in Sweden I (Table 46 and 47). CBER has determined the PT ----- to be non-specific and the values are not acceptable thus, a comparison of anti-PT seroconversion rates and GMTs is not available for this serology bridge.

A serology bridge between four doses of Pentacel administered in Study P3T06 to three doses of DAPTACEL in Sweden I was not provided in the BLA.

Study P3T06: Following three doses of each vaccine, non-inferiority of Pentacel relative to DAPTACEL was demonstrated for seroconversion rates and GMT for FHA, FIM and pertactin (Table 94 and 95). Following four doses of each vaccine, non-inferiority of Pentacel relative to DAPTACEL was demonstrated for seroconversion rates for FHA, FIM and pertactin and GMT for FHA and FIM (Table 104 and 105). Although the quantity of pertactin in both vaccines is the same the GMT response to pertactin was diminished in Pentacel recipients as compared to DAPTACEL recipients (93.6 EU/mL vs. 186.1 EU/mL; UL of 90% CI for GMT ratio DAPTACEL/Pentacel = 2.25) (Table 105). A comparison of anti-PT levels was only available for a non-random subset of sera from Study P3T06. In this subset non-inferiority was demonstrated for PT seroconversion rates and GMTs following three and four doses of Pentacel relative to three and four doses of DAPTACEL (Table 118, 119, 120 and 121).

Reduced response to Pertactin In the absence of a correlate for pertussis protection the clinical significance of a diminished response to pertactin is unclear. However, the BLA contains a number of analyses to investigate potential explanations and implications for the reduced response to pertactin following Pentacel:

Effect of co-administered Prevnar
Historically, some inconsistent differences in responses to acellular pertussis antigens have been observed when Prevnar was administered concomitantly with a DTaP manufactured by Wyeth Inc. (Prevnar PI). Prospectively specified exploratory analyses examined pertussis responses following three and four doses of Pentacel or HCPDT in Study 494-01 stratified by the number of doses of Prevnar administered concomitantly with Pentacel. Although the analyses were inconclusive they suggested the possibility of interference in the post-dose 3 and post-dose 4 pertussis responses with increasing number of doses of Prevnar administered concomitantly (Table 23). Post hoc analyses suggested that the post dose 4 response to pertactin may be lower with increasing number of doses of Prevnar co-administered with Pentacel at 2, 4 and 6 months of age (Table 34).

The post-dose 4 response to the pertactin component of Pentacel observed in Studies P3T06 and 494-01 (GMT 94 EU/mL and 95 EU/mL respectively) were similar. However, for subjects who participated in Study 5A9908, Prevnar was not administered concomitantly with any dose of Pentacel. Following a fourth dose of Pentacel administered at 15 months of age, the anti-pertactin GMT was 187.71 (95% CI 163.39, 215.63), notably higher than in the other pivotal studies (70-95 EU/mL).

Summary data from supportive Study M5A07 demonstrate that coadministration of Prevnar with Pentacel did not diminish the post-dose 3 response to pertactin compared to the response following Pentacel administered one month apart from Prevnar.

Antigen redundancy:
The sponsor provided analyses from Study P3T06 suggesting that subjects who are low responders to pertactin following the third dose of Pentacel (or DAPTACEL) also respond less well to FIM and pertactin following the fourth dose of either vaccine (Table 109). A similar finding was seen in Study 494-01 (Table 38).

Response to pertussis antigens based on pre-vaccination antibody levels:
Serology bridge to Sweden I: Subjects in 494-01 had higher anti-pertactin pre-immunization antibody levels (GMT 3.12 EU/mL, 95% CI 2.87-3.40) compared to subjects with available sera from Sweden I (GMT 2.17 EU/mL, 95% CI 1.87-2.51). The sponsor notes that these differences could affect rates of seroconversion measured as four fold rise in antibody levels.

The sponsor has also concluded that the lower pertactin seroconversion rate in Study 494-01 is "likely not clinically relevant" because the post-dose 4 anti-pertactin GMT of Study 494-01 Pentacel subjects with pre-vaccination levels $\geqslant$20 EU/mL exceeds that of the one subject from Sweden I with pre-vaccination antibody level $\geqslant$20 EU/mL (144.43 EU/mL vs. 100 EU/mL, 95% CI not provided) (isi.pdf page 48). It should be noted, however, that the post-dose 3 anti-pertactin GMT of Sweden I subjects with pre-vaccination antibody levels < 20 EU/mL exceeds that of such 494-01 subjects post dose 4 (111.41 EU/mL vs. 88.03 EU/mL, Table 51).

Study P3T06: An analysis of post-dose 3 and 4 responses to the pertussis antigens (except PT) according to arbitrarily defined pre-vaccination levels for subjects enrolled in Study P3T06 was provided in the BLA. Fewer subjects with "high" pre-vaccination antibody levels had a 4-fold rise to the pertussis antigens following three or four doses of either Pentacel or DAPTACEL (Table 112). Although 95% CIs were not provided, it appears that, in general, subjects with higher pre-existing antibodies to FHA, and FIM had lower GMTs to these antigens following the third and fourth dose as compared to subjects with lower pre-existing antibodies. Subjects with "high" pre-existing antibodies to pertactin had lower GMTs following the third dose of DAPTACEL or Pentacel. Following the fourth dose this trend was reversed and those with high pre-existing antibodies had a higher GMT than those with lower levels of pre-existing antibodies. This was most noticeable for Pentacel recipients; the post-dose 4 GMT of those with low pre-existing antibody levels (90 EU/mL) was approximately half of those with high pre-existing antibodies (202 EU/mL) (Table 112).

Response to co-administered vaccines
Prevnar
In Study P3T06 Prevnar was administered with control, standard of care, vaccines or Pentacel at 2, 4 and 6 months of age. Following three doses of Prevnar the proportion of subjects with antibody levels $\geqslant$0.15 ug/mL and $\geqslant$0.5 ug/mL to each of the pneumococcal serotypes appeared similar in both groups. Similarly, the GMT to each of the serotypes appeared similar between groups (Table 97 and 98).

In Study 494-03 a comparison of antibody levels $\geqslant$ 0.15 ug/mL and $\geq$ 0.5 ug/mL, and GMT to each of the pneumococcal serotypes following a fourth dose of Prevnar administered with Pentacel or administered with MMR and varicella at 15 months of age demonstrated non-inferiority for each comparison (Table 78 and 79). All subjects in this study had received three pervious doses of Prevnar concomitantly administered with Pentacel.

No data are available on responses to the first three doses of Prevnar administered concomitantly with or at different times from Pentacel.

Hepatitis B

In Studies 494-01 and P3T06 RECOMBIVAX HB was administered concomitantly with Pentacel at 2 and 6 months of age. In Study 494-03 receipt of a birth dose of hepatitis B vaccine was not an inclusion criterion, thus subjects who had received a birth dose of hepatitis B vaccine were administered RECOMBIVAX HB concomitantly with Pentacel at 2 and 6 months of age while subjects who had not received a birth dose were administered RECOMBIVAX HB concomitantly with Pentacel at 2, 4 and 6 months of age. The hepatitis B vaccines administered at birth were not recorded. Across these three pivotal studies, 89.8%-100% of subjects achieved a protective level of anti-HBsAg following the third dose of hepatitis B vaccine. Within each comparative study the response to hepatitis B when coadministered with Pentacel appeared similar to that observed when administered with control vaccines

MMR and varicella

A secondary endpoint of Study 494-03 was an evaluation of the response to MMR and varicella when administered with Pentacel compared to the response when these vaccines were administered with Prevnar at 15 months of age. Co-administration of MMR and VARIVAX with Pentacel did not adversely affect the seroresponse rates for measles, mumps, rubella or varicella (Table 76).

Rotavirus vaccine and hepatitis A vaccine

Rotavirus Vaccine, live oral, pentavalent (Rotateq) was approved February 3, 2006. Although, the protocol for Study M5A10 was amended to permit administration of rotavirus vaccine and hepatitis A vaccine, a complete study report has not been submitted thus, there are no available data to address response to these vaccines when administered with Pentacel.

Incidence of invasive *Haemophilus influenzae* type b disease and pertussis in Canada and the US

Pentacel was introduced into Canada between July 1997 and April 1998. Since 1998 all provinces have used Pentacel exclusively. Pentacel is administered at 2, 4, 6 and 18 months of age and Quadracel (DTaP-IPV) is administered at 4-6 years of age. Prior to use of Pentacel, DTwP, DTwP-IPV and DTwP-IPV/Hib had been in use. Hib conjugate vaccines were introduced in Canada in 1988 (PRP-D). PRP-T conjugated Hib vaccine was introduced in 1992.

To support effectiveness of the PRP-T and pertussis components of Pentacel the applicant has provided epidemiological data from Canada. These data indicate control of Hib disease relative to the pre-vaccine era and a decrease in the incidence of pertussis relative to the incidence during use of whole cell vaccine(s) with low estimates of effectiveness (Bentsi-Enchill et al. 1997 Vaccine 15: 301-306). A comparison of disease incidence rates in Canada with those in the US was not provided.

Invasive Hib disease:

Canadian epidemiological surveillance data:

Hib epidemiology data provided in the BLA show that cases of Hib disease in Canadian children <5 years have decreased from 321 cases in 1990 (rate: 16.62 per 100,000) to 16 cases in 2002 (rate: 0.92 per 100,000). Table 152 shows the cases of invasive Hib disease in Canada among children less than 5 years of age during 1996-2004 (data for 2003 and 2004 are provisional).

Table 152: Canadian surveillance data Invasive *Haemophilus influenzae* type b disease rate/100,000 among children 0-1, 1-4 and <5 years of age

Year	Rate 0-1 years of age (cases)	Rate 1-4 years of age (cases)	Rate <5 years of age (cases)*
2004	0.95 (3)	0.38 (5)	NA
2003	2.21 (7)	0.15 (2)	NA
2002	2.14 (7)	0.64 (9)	0.92 (16)
2001	2.71 (9)	0.49 (7)	0.97 (17)
2000	1.77 (6)	0.21 (3)	0.50 (9)
1999	1.17 (4)	0.27 (4)	0.77 (14)
1998	1.73 (6)	0.72 (11)	0.80 (15)
1997	5.02 (18)	0.83 (13)	1.56 (30)
1996	3.68 (14)	0.88 (14)	1.22 (24)

Source: http://dsol-smed.phac-aspc.gc.ca/dsol-smed/cgi-bin/ndischart2?DATA_TYPE=R&YEAR_FROM=97&YEAR_TO=04&CAUSE=142&AREA=00&AGE=A&AGE=B&AGE=C&SEX=3&CTIME1=View+Chart

*data in this column from: http://secure.cihi.ca/cihiweb/en/pub_login_PRTWG_2004_Reports_HIB_1990-2002.html, discrepancies in the number of cases are noted between these data and those in the other columns

Among the 12 pediatric tertiary care "IMPACT" hospitals, 29 cases of invasive Hib disease were identified during 2001-2003 (24 of these cases occurred among children ≤ 5 years of age, Scheifele et al. CMJA 2005; 172: 53-56). In 2001 there were 16 cases, 10 in 2002 and 3 in 2003. Among these 29 children, 20 had received no or incomplete primary immunization (11 were < 6 months of age). Nine cases occurred among children who had received three or more doses of Hib vaccine, two of these cases were in previously healthy children. These data are shown in Table 153.

Table 153: Cases of invasive *Haemophilus influenzae* type b disease in IMPACT pediatric centers in Canada (rates not provided)

Year	Cases (pediatric)
2005	NA
2004	NA
2003	3
2002	10
2001	16
2000	4

Source: Scheifele et al. CMAJ 2005; 172:53-56

NA – not available

US epidemiological surveillance data

In 1991, all infants were recommended to receive Hib conjugate vaccines. The incidence of invasive Hib disease among children <5 years of age has declined since 1990 (23/100,000). During 1998-2000 the average annual incidence was 0.34/100,000 among children <5 years of age (MMWR Weekly 2002, 51(11)). These data are presented in Table 154. During this time the highest rate of invasive Hib disease reported among children <5 years was seen in Alaska (9.4/100,000).

Table 154: US National Surveillance Data Invasive *Haemophilus influenzae* type b disease rate/100,000

Year	Rate <1 (cases)‡	Rate 1-4 (cases)‡	Rate <5 years
2005	0.1 (4)	0.0 (5)	NA
2004	0.3 (11)	0.1 (8)	NA
2003	0.47 (19)	0.08 (13)	NA
2002	0.37 (14)	0.13 (20)	0.18 (34)†
2001*	NA	NA	NA
2000	NA	NA	0.3*
1999	NA	NA	0.4*
1998	NA	NA	0.4*

NA not available
‡Source: http://www.cdc.gov/mmwr/summary.html
†Source: MMWR Summary Notif, Dis U.S. 2002
*Source: MMWR Weekly 2002 51(11).

The US Active Bacterial Core Surveillance (ABCs) program is an active laboratory – and population-based surveillance system for invasive bacterial pathogens including Haemophilus influenzae. Initially established in 4 states in 1995 it now operates in 10 states, currently representing a population of over 38 million persons. Cases of invasive Hib disease in patients resident in one of the defined surveillance areas 1997-2005 are shown in Table 155 Among children <5 years of age reported rates of invasive Hib since 2000 are 0.1-0.2/100,000.

Table 155. US ABC Surveillance Data Invasive Haemophilus type b disease rate/100,000 (Surveillance area population ~25-35 million persons).

Year	Rate <5 (cases)	Rate <1	Rate 1	Rate 2-4
2005	0.14 (4)	0.42	0.0	0.14
2004	0.15 (4)	0.63	0	0.07
2003	0.20 (5)	0.80	0.0	0.07
2002	0.1 (3)	0.6	0.0	0.0
2001	0.1 (3)	0.4	0.0	0.1
2000	0.2 (5)	0.9	0.2	0.0
1999	0.6 (10)	1.6	0.0	0.4
1998	0.2 (4)	0.8	0.0	0.1
1997	0.6 (10)	1.7	0.9	0.1

Source: http://www.cdc.gov/ncidod/dbmd/abcs/survreports.htm

Among Canadian children less than 5 years of age rates of Hib disease (Table 152) appear approximately 10 fold higher than rates reported in the US–ABC surveillance data (Table 155). It is difficult to know whether this represents a real difference or is due to different surveillance methods, case definitions and case ascertainment. Factors such as: population density, socioeconomic conditions, race/ethnicity, day-care usage and access to health care can influence disease rates and have not been considered or compared between populations.

Pertussis:
To support effectiveness of the pertussis component of Pentacel the applicant has provided epidemiologic data from Canada (to 2002). Tabulations of these data, and provisional data from 2003 and 2004, obtained from the Public Health Agency of Canada (http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/index_e.html) are presented in Table 156.

In Canada rates of pertussis reported among children 0-1, 1-4 and 5-9 years of age have decreased since 1995. Among children 0-1 year of age 78-91 cases/100,000 were reported during 2001-2004.

Table 156: Canadian surveillance data. Pertussis rate/100,000

Year	Rate 0-1 years	Rate 1-4 years
2004*	91.36	20.15
2003*	72.29	19.07
2002	80.31	27.01
2001	78.23	22.71
2000	118.58	38.08
1999	157.08	44.60
1998	199.81	120.41
1997	123.00	67.93
1996	145.76	97.02
1995	237.09	198.46

Source: http://dsol-smed.phac-aspc.gc.ca/dsol-smed/ndis/index_e.html
*2003 and 2004 data are provisional

The incidence of reported pertussis cases in the US are shown in Table 157. Within the U.S., rates of pertussis among children <1 appear to have been relatively stable during 1996 – 2003, increasing to 97 reported cases/100,000 in 2005. During 1996-2005 the rate of reported pertussis among children 1-4 years was 5-15 cases/100,000.

Table 157: US surveillance data Pertussis rate/100,000

Year	Rate <1 year	Rate 1-4 years
2005	97.1	15.6
2004	80.8	16.3
2003	54.96	7.31
2002	61.80	8.77
2001	49.56	6.32
2000	54.85	5.21
1999	56.87	5.52
1998	56.51	6.27
1997	52.47	5.07
1996	61.53	6.96

Source: http://www.cdc.gov/mmwr/summary.html

Rates of reported pertussis since 2002 among children 0-1 year of age appear comparable between the US and Canada (Canada 80-90/100,000, US 60-97/100,000). However, among Canadian children 1-4 years of age during 2001-2004 the rate of reported pertussis is 19-27/100,000. This rate appears higher than observed among US children 1-4 years of age during 2001-2005 (6-16/100,000, Table 157).

While these data suggest that the rate of reported pertussis may be 2-3 fold higher among Canadian children 1-4 years of age, the case definition and ascertainment may be different. It is difficult to know whether this represents a real difference or is due to different surveillance methods, case definitions and case ascertainment. Factors such as: population density, socioeconomic conditions, race/ethnicity, day-care usage and access to health care can influence disease rates and have not been considered or compared between populations.

8. Recommendations

8.1 Approvability Recommendation

Effectiveness of Pentacel is inferred from immunogenicity. The data provided in the application provide evidence for effectiveness of Pentacel to prevent diphtheria, tetanus, pertussis, poliomyelitis and invasive disease due to *Haemophilus influenzae* type b when administered in a four dose series to children 6 weeks to 18 months of age. Extrapolation of immunogenicity data from these children to older children 19 months through 4 years (59 months) of age is supported by historical experience with use of DAPTACEL and other manufacturers DTaP vaccines and IPV in U.S. children through 6 years of age as well as the use of Hib conjugate vaccines as "catch-up" through 4 years of age.

With regard to the PRP-T component for which there were contradictory results across studies: The results of two studies provide evidence that the effectiveness of the PRP-T component of Pentacel against invasive Hib disease is expected to be similar to the effectiveness of currently administered ActHIB in the US. Reasons for the apparently lower responses to ActHIB in these two studies relative to another previously conducted study are not known.

With regard to the pertussis component: The response to pertactin following Pentacel was diminished as compared to separately administered DAPTACEL. In the absence of a well accepted correlate of pertussis protection, the clinical relevance of this diminished response is unclear.

8.2 Post-marketing Actions

In January 2007, VRBPAC members voted that the data presented supported the safety and efficacy of Pentacel. The committee noted the importance of post-licensure surveillance for invasive Hib disease and pertussis following introduction of Pentacel. In March 2007 the sponsor submitted two concept protocols for surveillance of invasive Hib disease and pertussis among persons administered Pentacel. These protocols, as well as that for the safety study proposed by sanofi pasteur, have been reviewed in the Office of Biostatistics and Epidemiology.

- In coordination with the Centers for Disease Control and Prevention (CDC) sanofi pasteur will report CDC surveillance data on cases of invasive *Haemophilus influenzae* type b (Hib) disease among children 0-4 years of age identified by the Active Bacterial Core Surveillance program for at least 6 years. In conjunction with this surveillance program, sanofi pasteur will conduct sample surveys to provide brand-specific vaccine exposure data and calculate product-specific rates of invasive Hib disease within the monitored population.

- In coordination with the ---------- and the Wisconsin Department of Health and Family Services sanofi pasteur will report surveillance data on cases of pertussis among children less than 5 years of age in the State of Wisconsin, over at least 5 years. In conjunction with this surveillance program sanofi pasteur will provide brand-specific vaccine exposure data and calculate product-specific rates of pertussis within the monitored population.

- Sanofi pasteur has proposed a safety study to further characterize the safety profile of Pentacel vaccine among ~10,000 children.

Sanofi pasteur has also agreed to provide the following:

- A final report for Study M5A07 entitled: Immunogenicity Assessment of Pentacel when given at different times from or concurrently with a pnuemococcal vaccine.

- A final report for Study M5A10 entitled: A multi-center, randomized, open-label clinical trial designed to compare the immunogenicity and safety of 3 doses of DAPTACEL, ActHIB, and IPOL and a 4th dose of DAPTACEL and ActHIB (US-licensed schedule) with either: 4 doses of Pentacel; a 4th dose of DAPTACEL and ActHIB administered after 3 doses of Pentacel; or 4 Doses of DTaP-IPV and ActHIB in infants (Infant Series) and toddlers (4th dose).

- Data from Study P3T10 to support use of DAPTACEL as a fifth dose to complete the DTaP series following four previous doses of Pentacel.

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9. Labeling

Review and revision of the package insert was ongoing at the time this review was finalized. No major issues have been identified. Comments on the draft package insert have been conveyed to the applicant.