Vaccines and Related Biological Products Advisory Committee
Meeting Date: 1/25/07

FDA Briefing Document for Pentacel:
Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine Combined
Manufactured by Sanofi Pasteur Limited

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1. General Information

1.1 Proposed Indication

Sanofi Pasteur Limited has submitted a Biologics License Application (BLA) for Pentacel to be used for the prevention of diphtheria, tetanus, pertussis, poliomyelitis and invasive disease caused by *Haemophilus influenzae* type b (Hib), in infants and children 6 weeks through 6 years of age. The proposed regimen is administration of a single intramuscular injection at ages 2, 4, 6, and 15-18 months.

1.2 Items for VRBPAC Discussion

The discussion and voting items for the Committee will focus on whether the data submitted in the BLA support the safety and efficacy of Pentacel for the proposed indication. With regard to the efficacy of Pentacel, CBER requests that the Committee focus on pertussis (with particular emphasis on the immune responses to pertactin) and Hib. Of note, the response to pertactin was inferior following Pentacel relative to the control DTaP vaccines. With regard to the response to the Hib component two clinical studies show inconsistent results: in one study Pentacel was inferior to the control and in the other it was similar to the control.

1.3 Product Information

The formulation, per dose, of Pentacel and comparator vaccines that were used in pivotal controlled clinical studies of Pentacel is presented in Table 1. In one of the pivotal studies, Pentacel was compared to separately administered HCPDT + ActHIB + POLIOVAX. In a second controlled pivotal study, Pentacel was compared to separately administered DAPTACEL + ActHIB + IPOL. While the design of the pivotal studies will be described in further detail in Section 3, this section is intended to orient the Committee to the composition of the Control products in relation to Pentacel.

Table 1. Antigenic composition of Pentacel and Control vaccines used in pivotal clinical studies

Antigen	Pentacel	HCPDT	DAPTACEL†	ActHIB†	POLIOVAX†	IPOL†
Diphtheria toxoid	15 Lf	15 Lf	15 Lf	-	-	-
Tetanus toxoid	5 Lf	5 Lf	5 Lf	-	-	-
Detoxified pertussis toxin (PT)	20 μg	20 μg	10 μg	-	-	-
Filamentous hemagglutinin (FHA)	20 μg	20 μg	5 μg	-	-	-
Fimbriae 2 & 3 (FIM)	5 μg	5 μg	5 μg	-	-	-
Pertactin (PRN)	3 μg	3 μg	3 μg	-	-	-
Inactivated poliovirus type 1	40 DU	-	-	-	40 DU	40 DU
Inactivated poliovirus type 2	8 DU	-	-	-	8 DU	8 DU
Inactivated poliovirus type 3	32 DU	-	-	-	32 DU	32 DU
PRP	10 μg (bound to 24 μg tetanus toxoid)	-	-	10 μg (bound to 24 μg tetanus toxoid)	-	-

† U.S.-licensed vaccine
DU = D-antigen Units
PRP = purified polyribosyl-ribitol-phosphate capsular polysaccharide of Hib

In 1999, when the initial clinical study of Pentacel intended to support U.S. licensure was planned, two DTaP vaccines were under clinical development by Sanofi Pasteur Limited. One of these vaccines is referred to by the applicant as HCPDT (hybrid component pertussis vaccine combined with diphtheria and tetanus toxoids adsorbed). HCPDT, which is not licensed in the U.S., is a DTaP vaccine with the same formulation as the DTaP component of Pentacel. The applicant's other DTaP vaccine is U.S. licensed DAPTACEL. While DAPTACEL and HCPDT are produced from the same diphtheria, tetanus and pertussis antigens, HCPDT contains twice the amount of detoxified pertussis toxin (PT) and four times the amount of filamentous hemagglutinin (FHA) as contained in DAPTACEL. In 2002, DAPTACEL was licensed in the U.S. as a four dose series for infants and children 6 weeks through 6 years of age. The approved schedule of administration of DAPTACEL is 2, 4, 6 and 15-20 months of age.

ActHIB manufactured by Sanofi Pasteur SA is the Hib conjugate vaccine that is used to formulate Pentacel. In 1993, ActHIB was licensed in the U.S. for use in infants, with an approved schedule of 2, 4, 6, and 15-18 months of age.

Both POLIOVAX (Sanofi Pasteur Limited) and IPOL (Sanofi Pasteur SA) are U.S.-licensed inactivated poliovirus vaccines. POLIOVAX and IPOL contain the same amounts of inactivated poliovirus types 1, 2, and 3. POLIOVAX is the same as the inactivated poliovirus vaccine component of Pentacel. For manufacture of POLIOVAX, the polioviruses are grown on MRC-5 cells. For manufacture of IPOL, the polioviruses are grown on VERO cells. Currently, POLIOVAX is not distributed in the U.S.

1.4 Previous Human Experience with Pentacel

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.

1.5 Chronology of Regulatory Review

July 2005	BLA submitted
May 2006	Complete Response Letter issued
September 2006	Response to Complete Response Letter submitted

2 Historical Regulatory Background

As mentioned previously, HCPDT and DAPTACEL were the control (comparator) DTaP vaccines used in the controlled pivotal studies of Pentacel. Because of the relevance to the clinical development of Pentacel in the U.S., the following sections will provide an overview of the pivotal pertussis efficacy and immunogenicity data used to support licensure of DAPTACEL in the U.S., as well as an overview of the efficacy and safety of HCPDT.

2.1 DAPTACEL: Efficacy against Pertussis

The Sweden I Efficacy Trial, conducted in Sweden from March 1992 through January 1995, was the pivotal pertussis efficacy study of DAPTACEL. In the Sweden I Efficacy Trial, the efficacy of DAPTACEL was evaluated relative to a control DT vaccine. The efficacy of a two-component (PT and FHA) acellular pertussis vaccine manufactured by GlaxoSmithKline (not licensed in the U.S.) and a whole cell DTP vaccine (Sanofi Pasteur Inc.) that was licensed in the U.S. at the time of the trial, was also evaluated. Approximately 2,500 infants received DAPTACEL at 2, 4, and 6 months of age. The protective efficacy of three doses 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). The protective 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).

To support licensure of DAPTACEL in the U.S. a study was designed to bridge the DAPTACEL efficacy data from the Sweden I Efficacy Trial to the U.S. population, using immunogenicity data (U.S. Bridging Study). The antibody response (GMCs and % of subjects with four-fold rise in concentration) to pertactin following three doses of the same lot of DAPTACEL (Lot 6) administered at 2, 4, and 6 months of age was significantly lower in U.S. infants relative to infants from the Sweden I Efficacy Trial (Tables 2 and 3). The post-dose 3 responses to the other pertussis antigens were similar in U.S. and Swedish infants (Tables 2 and 3).

Table 2. U.S. Bridging Study and Sweden I Efficacy Trial-- comparison of post-dose 3 DAPTACEL pertussis GMCs

	Sweden I Lot 6 GMC (EU/ml) N=83[1]	**US Bridging Lot 6 GMC (EU/ml) N=106-107**	**Ratio of GMCs 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 (0.84, 1.16)
FIM	323.9	376.0	1.16 (0.91, 1.49)
PRN	**121.21**	**65.65**	**0.54 (0.43, 0.69)***

* CI is out of the equivalency boundary of (0.5, 2.0) applied retroactively by the sponsor.
[1]The available sera from the Sweden I Efficacy Trial represented a non-random sample of less than half of the serum samples initially available from subjects who received DAPTACEL in the trial.
Source: DAPTACEL BLA Clinical Review, page 19; FDA Briefing Document for DAPTACEL, 11/3/00 meeting of the Vaccines and Related Biologics Products Advisory Committee

Table 3. 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[1] 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)**

Note: statistical criteria for evaluating differences in rates of 4-fold rise between studies were not specified.
[1] The available sera from the Sweden I Efficacy Trial represented a non-random sample of less than half of the serum samples initially available from subjects who received DAPTACEL in the trial.
Source: DAPTACEL BLA Clinical Review, page 19

Since children in the U.S. Bridging Study did not receive a fourth dose of DAPTACEL, it was not possible to evaluate their response to pertactin following a fourth dose.
In a separate Canadian study, in which children received four doses of DAPTACEL at 2, 4, 6, and 17-18 months of age, post-dose 4 GMCs to each of the pertussis antigens were at least as high as those observed in the Sweden I Efficacy Trial after three doses of DAPTACEL (Table 4).

Table 4. Pertussis GMCs, post-dose 4 DAPTACEL Canadian study and post-dose 3 DAPTACEL Sweden I Efficacy Trial

	Sweden I post-dose 3 DAPTACEL[1] N=83		**Canadian Study post-dose 4 DAPTACEL N=273-275**	
	GMC (EU/ml)	(95% CI)	GMC (EU/ml)	(95% CI)
PT	72.6	(61.1, 86.4)	171	(153, 191.1)
FHA	43.2	(37.7, 49.4)	117.6	(107.5, 128.6)
FIM	323.9	(258.1, 406.5)	518.6	(451.2, 596.1)
PRN	121.1	(102.6, 143.2)	241.7	(214.2, 272.8)

[1] The available sera from the Sweden I Efficacy Trial represented a non-random sample of less than half of the serum samples initially available from subjects who received DAPTACEL in the trial.
Source: DAPTACEL BLA Clinical Review page 40

The Sweden I Efficacy Trial and the U.S. and Canadian immunogenicity bridging data provided the pivotal data used to support the efficacy of DAPTACEL for U.S. licensure. Based on these data, four doses of DAPTACEL constitute a primary immunization course for pertussis in U.S. children. While the fourth dose of DAPTACEL was initially approved for administration at 17-20 months of age, in November 2006, the approved age range for the fourth dose was expanded to 15-20 months of age, based on data submitted in a Supplement to the DAPTACEL BLA. Thus, the current approved schedule for DAPTACEL is 2, 4, 6, and 15-20 months of age.

The Pentacel BLA includes: 1) a comparison of the immune response of U.S. children administered four doses of Pentacel to the response of children administered three doses of DAPTACEL in the Sweden I Efficacy Trial, and 2) a study in which the safety and immunogenicity of Pentacel were compared to that of DAPTACEL in U.S. children.

2.2 HCPDT: Efficacy against Pertussis and Safety

Efficacy and safety data on HCPDT from another pertussis efficacy trial, the Sweden II Efficacy Trial, were considered supportive for licensure of DAPTACEL and also were submitted as supportive data with the Pentacel BLA. Since HCPDT was used as a comparator DTaP vaccine in the clinical development for Pentacel and because HCPDT is not licensed in the U.S., this section will provide a brief overview of efficacy and safety data on HCPDT from the Sweden II Efficacy Trial.

In the Sweden II Efficacy Trial, the safety and efficacy of three DTaP vaccines, 1) HCPDT; 2) a three-component (PT, FHA, and pertactin) DTaP vaccine manufactured by Chiron (not licensed in the U.S.); and 3) the same two-component DTaP vaccine that was evaluated in the Sweden I Efficacy Trial, were compared to that of a British whole-cell DTP vaccine (Medeva). The trial was conducted in Sweden from September 1993 through October 1996.

In the Sweden II Efficacy Trial, approximately 20,000 infants were randomized to each of the four study groups. The majority of infants were vaccinated at 3, 5 and 12 months of age. In the HCPDT group, 18,183 infants were vaccinated at 3, 5, and 12 months of age and 2,551 were vaccinated at 2, 4, and 6 months of age. The primary analyses estimated the efficacy of three doses of the acellular pertussis vaccines relative to three doses of the Medeva whole-cell DTP vaccine. In these analyses, following HCPDT, the relative risk vs. the whole-cell DTP vaccine for culture-confirmed pertussis with at least 21 days of paroxysmal cough was 0.85 (95% CI 0.41, 1.79). Following HCPDT, the relative risk vs. the whole-cell DTP vaccine for culture-confirmed pertussis with cough of any duration or without cough was 1.35 (95% CI 0.75, 2.43).

In the Sweden II Efficacy Trial, commonly occurring local and systemic adverse events were not actively monitored following vaccination. Safety monitoring was directed at detecting selected serious adverse events through six months after the third dose. Fever $\geq$40.5°C within 24 hours following vaccination occurred significantly less frequently following HCPDT relative to whole cell DTP [Relative Risk = 0.19; 95% confidence interval (0.08, 0.42)]. Convulsions and suspected convulsions within three days

following vaccination occurred significantly less frequently following HCPDT relative to whole cell DTP [Relative Risk = 0.31; 95% confidence interval (0.10, 0.94)]. There were no statistically significant differences between the four vaccine groups with respect to SIDS, other deaths, acute neurological events lasting more than 30 minutes within 72 hours post-vaccination, infantile spasms, hypotonic-hyporesponsive episodes (HHE) within 48 hours post-vaccination, invasive bacterial infections or other life threatening events.

In the Sweden II Efficacy Trial, HHE was defined as loss of muscle tone and a diminished or absent response to stimulation. The rate of HHE following HCPDT (14 per 10,000 subjects or 0.47 per 1000 doses) and the other DTaP study vaccines was noted to be relatively high compared with historical data for DTaP vaccines. It was postulated that differences in HHE definitions, safety monitoring procedures, vaccination schedules, and use of concomitant vaccines in the Sweden II Efficacy Trial and earlier studies may have contributed to this observation.

In the Sweden II Efficacy Trial, there were no cases of encephalopathy or encephalitis within 7 days post-vaccination. Of two cases of suspected encephalitis reported, one occurred 190 days following the third dose of HCPDT and one occurred 98 days following the three-component DTaP vaccine.

Active surveillance for hospitalized cases of encephalitis among the Sweden II Efficacy Trial participants and eligible non-participants was conducted separately from the main safety follow-up in the trial. During an approximately 2-year period, one case of suspected encephalitis among study participants (N=82,892; group not specified) and three cases among 17,607 eligible non-participants were identified, corresponding to rates of 1/100,000 for study participants and 17/100,000 for non-participants. The three non-participants with suspected encephalitis had culture-confirmed pertussis.

Although not submitted with the Pentacel BLA, the DAPTACEL BLA included data from comparative studies that evaluated more commonly occurring local and systemic adverse events following HCPDT or DAPTACEL. Overall, rates of such events following HCPDT were comparable to those observed following DAPTACEL.

The Pentacel BLA includes a study which compared the safety and immunogenicity of Pentacel to that of HCPDT. Insufficient sera from children administered HCPDT in the Sweden II Efficacy Trial were available to perform a serologic bridge between U.S. children administered Pentacel and children administered HCPDT in the Sweden II Efficacy Trial.

3 Clinical Development of Pentacel in the U.S.

3.1 Evaluation of Efficacy

Evaluation of the efficacy of the diphtheria, tetanus, polio and PRP-T components of Pentacel was based on a comparison of immune responses, using established serologic correlates of protection or GMCs, relative to separately administered vaccine components (HCPDT + POLIOVAX + ActHIB) or all U.S licensed vaccines (DAPTACEL + IPOL +

ActHIB) in U.S. children. The evaluation of the efficacy of the pertussis component, which does not have a generally accepted correlate of protection, was based upon: 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 U.S. children.

3.2 Overview of Pivotal Studies

The immunogenicity and safety of Pentacel were evaluated in four pivotal studies, in which 5,980 subjects received at least one dose of Pentacel. In three of the studies, a total of 4,198 subjects were enrolled to receive four doses of Pentacel. In the other study, a fourth dose of Pentacel was evaluated in 1,782 subjects who previously received three doses of Pentacel. All four pivotal studies were multicenter studies. In two of the pivotal studies, the immunogenicity and safety of Pentacel were evaluated relative to control vaccines: HCPDT + POLIOVAX + ActHIB in one study, and DAPTACEL + IPOL + ActHIB in the other. In the two controlled studies, subjects were randomized to receive either Pentacel or separately administered Control vaccines. The other two pivotal studies did not include a control vaccine. Table 5 provides an overview of the four pivotal studies, including the vaccination schedule for Pentacel and Control vaccines, as well as for the other concomitantly administered vaccines. In subsequent tables in this document, the study groups generally will be identified by Pentacel or Control vaccines, without listing the other concomitantly administered vaccines.

Since the results of one of the pivotal studies suggested the possibility that co-administration of Prevnar with Pentacel may interfere with the immune responses to PRP and some of the acellular pertussis antigens CBER requested that the applicant initiate a study to evaluate the immunogenicity and safety of four doses of Pentacel administered at different times from or concurrently with Prevnar. This study, M5A07, initially was not considered pivotal in the clinical development of Pentacel. However, CBER requested that a summary of the post-dose 3 immunogenicity data from Study M5A07 be included in the BLA. The applicant anticipates that the final study report for Study M5A07, including the post-dose 4 data, will be completed by the end of 2006. However, the Committee should note that at the time of writing this document, the post-dose 4 data from Study M5A07 have not been submitted to the Pentacel BLA.

Table 5. Pentacel pivotal clinical studies

Study/ Country/ Dates	Objectives	Schedule of Pentacel and Control Vaccines	Concomitant Vaccines	Safety Population[1] (N)	Per Protocol[2] Immunogenicity (PPI) Population (N)
494-01/ U.S./ 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)	Pentacel: 2, 4, 6, 15 mo. HCPDT + POLIOVAX + ActHIB: 2, 4, 6, 15 mo.	Prevnar at 2, 4, 6 mo. (in ~80% of subjects)[3] RECOMBIVAX HB at 2 and 6 mo. (4th dose of Prevnar at 12 mo. non-concomitantly with Pentacel)	Pentacel: 2506 HCPDT + POLIOVAX + ActHIB: 1032	Post dose 3: Pentacel :1136 HCPDT+POLIOVAX +ActHIB: 403 Post dose 4: Pentacel: 883, HCPDT+POLIOVAX+ActHIB: 291
494-03/ U.S./ 7/10/00-12/26/02	Pentacel safety and immunogenicity Concomitant vs. staggered administration of 4th dose of Pentacel with Prevnar, MMR_{II} and VARIVAX	Pentacel: 2, 4, 6, 15-16 mo.	Prevnar at 2, 4, 6 mo. RECOMBIVAX HB at 2, 4, and 6 mo. or at 2 and 6 mo. Prevnar, MMR_{II}, and VARIVAX concomitantly with 4th dose of Pentacel or staggered schedule	Pentacel: 1207	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 Pentacel 4th dose at different ages	Pentacel: 15, 16, 17 or 18 mo.	none	Pentacel: 1782	Post-dose 4: Pentacel: 735
P3T06/ U.S/ 5/4/01-1/21/04	DAPTACEL lot consistency Co-administration of 4th dose of DAPTACEL with ActHIB, Prevnar, MMR_{II} and VARIVAX Safety and immunogenicity of Pentacel relative to DAPTACEL + IPOL + ActHIB	Pentacel: 2, 4, 6, 15-16 mo. DAPTACEL + ActHIB: 2, 4, 6, 15-16 mo.; IPOL: 2, 4, 6 mo.	Prevnar at 2, 4, 6 mo. RECOMBIVAX HB at 2 and 6 mo. ActHIB, Prevnar, MMR_{II}, VARIVAX concomitantly with 4th dose of DAPTACEL or staggered schedule	Pentacel: 485 DAPTACEL + IPOL + ActHIB (doses 1-3): 1454 DAPTACEL + ActHIB (dose 4): 418[4]	Post dose 3: Pentacel: 374 DAPTACEL + IPOL+ActHIB: 371 Post-dose 4: Pentacel: 371 DAPTACEL + ActHIB: 349

[1]The safety population included all subjects who received at least one dose of Pentacel or Control vaccine.
[2]The PPI population included subjects who received Pentacel or Control vaccines, had blood draws within specified windows and had a serology result post dose 3 or 4.
[3]Prevnar was introduced after initiation of the study.
[4]In Study P3T06, control subjects were randomized to one of three study groups for the fourth dose: Group 1 received MMR_{II} + VARIVAX + Prevnar at 12 months of age; and DAPTACEL + ActHIB at 15-16 months of age. Group 2 received DAPTACEL + ActHIB + MMR_{II} + VARIVAX + Prevnar at 15-16 months of age. Group 3 received ActHIB + MMR_{II} + VARIVAX + Prevnar at 15-16 months of age; and DAPTACEL alone at 16-17 months of age. Group 1 (N=418) served as the control for the fourth dose of Pentacel.

4 Subjects Enrolled in Pivotal Studies

4.1 Number of Subjects and Extent of Exposure

Table 6 provides a summary of the number of doses of Pentacel or Control vaccines administered in each of the four pivotal studies. A total of 5,980 subjects received at least one dose of Pentacel and 2,486 subjects received at least one dose of Control vaccines (HCPDT + POLIOVAX + ActHIB in Study 494-01, and DAPTACEL + IPOL + ActHIB in Study P3T06). Overall, 17,021 doses of Pentacel were administered.

Table 6. Pivotal studies: Summary of vaccine exposure, safety population[1]

Received Pentacel or Control[2]	494-01		494-03	P3T06		5A9908
	Pentacel	Control	Pentacel	Pentacel	Control	Pentacel
	N	N	N	N	N	N
Dose 1	2506	1032	1207	485	1454	NA
Doses 1 and 2	2374	945	1115	469	1400	NA
Doses 1, 2 and 3	2294	900	1077	461	1376	NA
Doses 1, 2, 3 and 4	1862	739	958	431	418[3]	NA
Dose 4 only	NA	NA	NA	NA	NA	1782

[1]The safety population included all subjects who received at least one dose of Pentacel or Control vaccine.
[2]The Control vaccines were HCPDT + POLIOVAX + ActHIB in Study 494-01 and DAPTACEL + IPOL + ActHIB (doses 1-3) and DAPTACEL + ActHIB (dose 4) in Study P3T06.
[3]In Study P3T06, control subjects were randomized to one of three study groups for the fourth dose: Group 1 received MMR_{II} + VARIVAX + Prevnar at 12 months of age; and DAPTACEL + ActHIB at 15-16 months of age. Group 2 received DAPTACEL + ActHIB + MMR_{II} + VARIVAX + Prevnar at 15-16 months of age. Group 3 received ActHIB + MMR_{II} + VARIVAX + Prevnar at 15-16 months of age; and DAPTACEL alone at 16-17 months of age. Group 1 (N=418) served as the control for the fourth dose of Pentacel.
NA indicates not applicable
Source: iss.pdf, page 191

4.2 Demographics

Table 7 provides an overall summary of demographics for subjects who were enrolled to receive four consecutive doses of Pentacel in the pivotal studies. Within the two controlled pivotal studies, demographic characteristics (age, sex, race/ethnicity) were similar for Pentacel and Control subjects (data not shown).

Table 7. Studies 494-01, 494-03, and P3T06: Baseline demographics of subjects who received Pentacel, safety population[1]

	Pentacel Subjects from Studies 494-01, 494-03, and P3T06 Combined
	N = 4198
Mean age at first dose (months)	2.1
Sex n (%)	
Male	2090 (49.8)
Female	2108 (50.2)
Race/Ethnicity n (%)	
Caucasian	2567 (61.1)
Black	410 (9.8)
Hispanic	631 (15.0)
Asian	181 (4.3)
Other	409 (9.7)

[1]The safety population included all subjects who received at least one dose of Pentacel.
Source: Iss.pdf, page 60

Across the four pivotal studies, the mean age at receipt of the fourth dose of Pentacel among 5,033 subjects was 16 months. Of subjects who received a fourth dose of Pentacel, 73.4% were Caucasian, 5.9% were Black, 8.4% were Hispanic, 3.9% were Asian, and 8.4% were of other racial/ethnic groups.

5 Immunogenicity

5.1 Immunogenicity Population and Statistical Considerations

The immune responses to Pentacel or Control vaccines were evaluated in sera obtained approximately one month after administration of three or four doses. The primary cohort for immunogenicity analyses was the Per Protocol for Immunogenicity (PPI) population. The PPI population included all eligible subjects who had received all doses of Pentacel or Control vaccines and who had all blood draws within specified windows and had a serology result for at least post-dose 3 or -dose 4. In Study 494-01 the PPI population included subjects who had received 0-3 doses of Prevnar concomitantly with Pentacel at 2, 4 and 6 months of age. In Study 494-03 and P3T06, all subjects received Prevnar concomitantly with Pentacel at 2, 4 and 6 months of age. Subjects in Study 5A9908 did not receive Prevnar concomitantly with Pentacel.

In most instances, for the pivotal immunogenicity studies, the protocol specified criteria for non-inferiority for ratios of GMCs or GMTs and for differences in seroprotection or seroconversion rates were based on 2-sided 90% CIs. Although CBER currently recommends use of 2-sided 95% CIs for such analyses, the data presented in this document reflect the protocol specified statistical criteria for non-inferiority.

5.2 Effectiveness of Pentacel

Evaluation of the efficacy of the tetanus, diphtheria, polio and PRP-T components of Pentacel was based on a comparison of immune responses, using either established serologic correlates of protection or the GMCs, relative to separately administered

vaccines in U.S. children. There is no generally accepted serologic correlate of protection for pertussis vaccines. Evaluation of the efficacy of the pertussis component was based on a) a comparison of immune responses in U.S. children administered four doses of Pentacel to those in Swedish infants following three doses of DAPTACEL in a clinical endpoint efficacy study and b) a comparison of immune responses relative to separately administered vaccines in U.S. children.

The Pentacel immunogenicity data raise two issues for consideration by the Committee:

- The response to the PRP-T component of Pentacel, and
- The response to the pertussis component of Pentacel.

5.2.1 Effectiveness of the PRP-T component

Antibodies to PRP have been shown to correlate with protection against invasive 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 0.15 ug/mL has been accepted as a minimal protective level[1] and 1.0 ug/mL as a long term (one year) protective level[2,3]. 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.

Historically, administration of PRP conjugate vaccines in combination with DTaP vaccines has generally resulted in decreased PRP antibody responses in infants, although the reason for these diminished responses is unclear.

In Studies 494-01 and P3T06 effectiveness of the PRP-T component of Pentacel was based on anti-PRP seroprotection rates and GMCs following three doses of Pentacel compared to ActHIB control vaccine. However, these two studies showed inconsistent results with regard to the anti-PRP levels ≥1.0 ug/mL and GMCs.

The anti-PRP analyses from Study 494-01 are presented in Table 8. The proportion of subjects with anti-PRP levels ≥ 1.0 ug/mL and the GMC were lower following three doses of Pentacel compared to three doses of separately administered ActHIB.

Table 8. Study 494-01- Anti-PRP seroprotection rates and GMCs following three doses of Pentacel compared to three doses of ActHIB (+HCPDT + POLIOVAX), PPI population

	Pentacel N=1127	ActHIB N = 401	Non-inferiority analyses	
Anti-PRP ug/mL			**Difference ActHIB minus Pentacel**	**90% CI[1]**
% ≥0.15 (95% CI)	95.4 (94.0, 96.5)	98.3 (96.4, 99.3)	2.87	(1.38, 4.36)
% ≥1.0 (95% CI)	79.1 (76.7, 81.5)	88.8 (85.3, 91.7)	9.63	(6.36, 12.90)
			Ratio ActHIB/Pentacel	**90% CI[2]**
GMC (95% CI)	3.19 (2.91, 3.50)	6.23 (5.40, 7.18)	1.95	(1.68, 2.26)

[1]Non-Inferiority of seroprotection rates is achieved when the upper limit of the 90% CI of the rate difference (ActHIB-Pentacel) is <10%.
[2]Non-inferiority of GMCs is achieved when the UL 95% CI of the ratio Control/Pentacel is <1.5
Shaded cells indicate non-inferiority criteria were not met.
Source: 49401si.pdf page 98 and 100

In Study 494-01, three lots of Pentacel were administered to evaluate lot consistency. Subjects administered ActHIB separately received the same bulk lot of PRP-T as subjects administered Pentacel lot #3. Table 9 presents the anti-PRP seroprotection rates and GMC following administration of the same bulk lot of PRP-T as Pentacel or ActHIB. Non-inferiority analyses were not pre-specified.

Table 9. Study 494-01- Anti-PRP seroprotection rates and GMCs following three doses of Pentacel lot #3 or three doses of ActHIB. Both vaccines formulated with the same lot of PRP-T concentrate, PPI population

Anti-PRP ug/mL	**Pentacel lot #3**	**ActHIB**
	N=367	**N = 401**
% ≥0.15 (95% CI)	96.7 (94.4, 98.3)	98.3 (96.4, 99.3)
% ≥1.0 (95% CI)	81.7(77.4, 85.6)	88.8 (85.3, 91.7)
GMC	3.64 (3.12, 4.25)	6.23 (5.40, 7.18)

Source: 49401si.pdf page 92, 96, 98, 100

In contrast to Study 494-01, in Study P3T06 the anti-PRP seroprotection rates and GMC were similar following three doses of Pentacel or separately administered ActHIB (Table 10).

Table 10. Study P3T06 - Anti-PRP seroprotection rates and GMCs following three doses of Pentacel compared to three doses of ActHIB (+ DAPTACEL + IPOL), PPI population

	Pentacel N = 365	ActHIB N = 1128	Non-inferiority analyses	
Anti-PRP ug/mL			**Difference ActHIB minus Pentacel[1]**	**90% CI[1]**
% ≥ 0.15 (95% CI)	92.3 (89.1, 94.8)	93.3 (91.6, 94.7)	0.93	(-1.67, 3.53)
% ≥ 1.0 (95% CI)	72.1 (67.1, 76.6)	70.8 (68.1, 73.5)	-1.22	(-5.68, 3.24)
			Ratio ActHIB/Pentacel	
GMC (95% CI)	2.31 (1.94, 2.75)	2.29 (2.08, 2.53)	0.99	(0.84, 1.17)[2]

[1]Non-Inferiority is achieved when the upper limit of the 90% CI of the rate difference (ActHIB-Pentacel) is <10%.
[2] Non-inferiority criteria not specified in the protocol.
Source: p3t06si.pdf page 90 and 96

CBER also requested exploratory analyses of anti-PRP seroprotective level ≥0.15 ug/mL at 15 months of age prior to receipt of a fourth dose of Pentacel or ActHIB in Studies 494-01 and P3T06 (Table 11).

Table 11. Study 494-01 and Study P3T06 - Anti-PRP seroprotection rates at 15-16 months of age prior to receipt of a fourth dose of Pentacel or ActHIB, PPI populations

Anti-PRP	**Study 494-01**		**Study P3T06**	
	Pentacel	**ActHIB**	**Pentacel**	**ActHIB***
	N =829	**N= 276**	**N= 335**	**N= 323**
% ≥0.15ug/mL (95% CI)	68.6 (65.4, 71.8)	80.8 (75.6, 85.3)	65.4 (60.0, 70.5)	60.7 (55.1, 66.0)

*Study P3T06 dose 4 Group 1 .
Source: 49401sii.pdf page 102; p3t06sii.pdf page 945

In studies which did not include an ActHIB comparator, following the third dose of Pentacel, the anti-PRP GMC 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 12). In Study M5A07, subjects received four doses of Pentacel at 2, 4, 6, and 15 months of age, either concomitantly with Prevnar, or with Prevnar administered one month after each dose of Pentacel. The data from Study M5A07 presented in Table 12, as well as the accompanying non-inferiority analyses of anti-PRP seroprotection rates and GMCs (data not shown), demonstrated that concomitant administration of Prevnar with each of the first three doses of Pentacel did not interfere with the anti-PRP response following the third dose of Pentacel.

Table 12. Study 494-03 and Study M5A07 - Anti-PRP seroprotection rates and GMC one month following three doses of Pentacel in studies which did not include an ActHIB comparator, PPI populations

Study		Anti-PRP		
	N	% ≥0.15 ug/mL (95% CI)	% ≥1.0 ug/mL (95% CI)	GMC (95% CI)
494-03	270	94.4 (91.0, 96.9)	75.6 (70.0, 80.6)	2.80 (2.30, 3.41)
M5A07	433*	95.8 (93.5, 97.5)	77.1 (72.9, 81.0)	3.32 (2.85, 3.87)
	427+	95.3 (92.9, 97.1)	79.6 (75.5, 83.3)	3.60 (3.09, 4.20)

* Subjects were administered Pentacel concomitantly with Prevnar at 2, 4 and 6 months of age
+ Subjects were administered Pentacel at 2, 4 and 6m and Prevnar at 3, 5 and 7 months
Source: 49401si.pdf page 474 and478; is.pdf page 114 and 115

5.2.2 Effectiveness of the Pertussis Component

The following sections will present the pivotal data on the effectiveness of the pertussis component of Pentacel: 1) a comparison of the immune responses in U.S. children administered Pentacel in Study 494-01 to infants administered DAPTACEL in the Sweden I Efficacy Trial; and 2) a comparison of the immune responses in U.S. children administered Pentacel or DAPTACEL in Study P3T06. In addition, data on a comparison of the immune responses following Pentacel or HCPDT in Study 494-01 will be presented. Although these data are not considered pivotal to support the effectiveness of the pertussis component of Pentacel they do allow the immune response to the pertussis antigens administered as Pentacel to be directly compared to the response to the same antigens administered as HCPDT. Finally, data to evaluate the effect of co-administered Prevnar on the pertussis immune response following Pentacel will be presented.

5.2.2.1 Serology Bridge of Pentacel in U.S. Children to DAPTACEL in the Sweden I Efficacy Trial

To evaluate the effectiveness of the pertussis component of Pentacel, the immune responses of subjects administered four doses of Pentacel in study 494-01 were compared to the immune responses of infants administered three doses of DAPTACEL in the Sweden I Efficacy Trial. Because an earlier immunogenicity bridging analysis comparing U.S. and Swedish infants administered three doses of DAPTACEL showed diminished pertactin responses in U.S. infants (see Section 2.1), the primary bridging analyses to the Sweden I Efficacy Trial for Pentacel were based on Pentacel post-dose 4 responses.

In the U.S., concomitant administration of the first three doses of DTaP vaccine and Prevnar is recommended. The recommended ages for the fourth dose of DTaP (15-18 months) and the fourth dose of Prevnar (12-15 months) overlap. In view of the current recommended U.S. vaccination schedule and the potential for diminished responses to the pertussis antigens when Pentacel is administered concomitantly with Prevnar, sera from Study 494-01 used in the serology bridging analyses were obtained from children who had received Pentacel concomitantly with Prevnar at 2, 4 and 6 months of age. Since

Prevnar was introduced after Study 494-01 was initiated, some subjects did not receive the first three doses concomitantly with Pentacel. In Study 494-01, the fourth doses of Pentacel and Prevnar were administered on staggered schedules for the fourth dose (15 months and 12 months of age, respectively).

Sera from the Sweden I Efficacy Trial that were used in the bridging analyses were available stored sera that were re-assayed at the same time that the Study 494-01 sera were assayed.

Following four doses of Pentacel in U.S. Study 494-01 compared to three doses of DAPTACEL in the Sweden I Efficacy Trial, non-inferiority was demonstrated for GMCs for all pertussis antigens and for PT, FHA and FIM seroconversion rates. Non-inferiority was not demonstrated for pertactin seroconversion rates (Table 13 and 14). Of note is that for the comparison of pertactin GMCs, the non-inferiority criterion was marginally met (Table 14).

Although not pre-specified as non-inferiority analyses, the seroconversion rates and GMCs for PT, FHA and FIM following three doses of Pentacel in Study 494-01 were similar (non-overlapping 95% CIs) to those observed following three doses of DAPTACEL in the Sweden I Efficacy Trial (data not shown).

Table 13. Serology Bridge – Pertussis seroconversion rates following 4 doses of Pentacel in Study 494-01 compared to 3 doses of DAPTACEL in the Sweden I Efficacy Trial

Pertussis Antigen	**Post dose 3 DAPTACEL Sweden I % ≥4-fold rise[1] (95% CI)**	**Post dose 4 Pentacel Study 494-01* % ≥4-fold rise[1] (95% CI)**	**Non-Inferiority Difference DAPTACEL minus Pentacel (95% CI)[2]**
	N = 80	**N = 507-508**	
PT	86.3 (76.7, 92.9)	94.9 (92.6, 96.6)	-8.63 (-16.42, -0.85)
FHA	68.8 (57.4, 78.7)	91.7 (89.0, 94.0)	-22.97 (-33.40, -12.53)
FIM	86.3 (76.7, 92.9)	91.5 (88.7, 93.8)	-5.27 (-13.20, 2.66)
PRN	98.8 (93.2, 100.0)	89.2 (86.1, 91.7)	9.60 (5.96, 13.24)

*494-01 PPI population included subjects who had received three doses of Prevnar concomitantly with Pentacel at 2, 4 and 6 months of age; the fourth dose of Prevnar was administered at 12 months of age.
'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.
[1] The post dose 3 fold rise is calculated by post-Dose 3/pre-Dose 1 antibody level (EU/mL), the post dose 4 fold rise is calculated by post-Dose 4/pre-Dose 1 antibody level (EU/mL)
[2] Non-inferiority is achieved when the upper limit of the 95% CI for the difference in seroresponse rates was <10%.
The shaded cell indicates that the non-inferiority criterion was not met.
Source: bridge.pdf page 42

Table 14. Serology Bridge - Pertussis GMCs following 4 doses of Pentacel in Study 494-01 compared to 3 doses of DAPTACEL in the Sweden I Efficacy Trial

Pertussis antigen	Post dose 3 DAPTACELSweden I GMC (EU/mL) (95% CI)	Post dose 4 Pentacel Study 494-01* GMC (EU/mL) (95% CI)	Non-inferiority Ratio DAPTACEL/Pentacel (90% CI)[1]
	N = 80	N = 553-554	
PT	87.50 (73.30, 104.45)	195.10 (181.61, 209.59)	0.45 (0.38, 0.53)
FHA	40.70 (34.99, 47.36)	129.85 (121.83, 138.39)	0.31 (0.27, 0.36)
FIM	339.31 (266.46, 432.08)	506.57 (463.97, 553.08)	0.67 (0.54, 0.82)
PRN	111.26 (94.19, 131.44)	90.82 (83.46, 98.83)	1.23 (1.01, 1.49)

*494-01 PPI population included subjects who had received three doses of Prevnar concomitantly with Pentacel at 2, 4 and 6 months of age, the fourth dose of Prevnar was administered at 12 months of age.
[1]Non-inferiority is achieved when the upper limit of the 2-sided 90% CI of the ratio DAPTACEL/Pentacel is <1.5.
Source: bridge.pdf page 43

Effect of Pre-vaccination Antibody Levels on Seroconversion Rates and GMCs
The applicant noted that failure to demonstrate non-inferiority of anti-pertactin seroconversion rates following four doses of Pentacel in U.S. children as compared to three doses of DAPTACEL in Swedish infants may be because "subjects participating in Study 494-01 had a significantly higher mean anti-PRN pre-immunization (2 months of age) antibody level than did subjects who participated in the Sweden I Efficacy Trial (GMC 3.12 EU/mL in Study 494-01 vs. 2.17 EU/mL in Sweden I; p ≤0.0012 by t-test based upon log-concentrations, and on the upper limit of 90% for pre-Dose 1 GMC ratio [Pentacel/CPDT Vaccine Adsorbed] of 494-01 Stage I over Sweden I >1.5)." An uneven distribution of pre-immunization antibody levels may affect the number of subjects with a four fold rise over baseline.

To investigate whether an imbalance in pre-vaccination pertactin antibody levels may have contributed to the failure to demonstrate non-inferiority of anti-pertactin seroconversion rates the applicant provided an exploratory post-hoc analysis of seroconversion rates and GMCs following three doses of DAPTACEL in the Sweden I Efficacy Trial and four doses of Pentacel in Study 494-01, stratified by pre-vaccination antibody levels <20 EU/mL and ≥ 20 EU/mL. An anti-pertactin antibody level of 20 EU/mL corresponds to almost 6 times the lower limit of quantitation of the assay (3 EU/mL). However, the concentration of anti-pertactin required for protection is not known.

As shown in Table 15, 5.5% of U.S. subjects who received Pentacel in Study 494-01 and 1.3% of infants from the Sweden I Efficacy Trial had pre-vaccination anti-pertactin levels ≥20 EU/mL. Following Pentacel in Study 494-01, about 61% of the subjects with pre-vaccination values ≥20 EU/mL demonstrated a four-fold rise, compared to 91% of the

subjects with pre-vaccination values <20 EU/mL. The applicant noted that among Pentacel subjects with anti-pertactin pre-immunization levels >20 EU/mL, the post-immunization GMC (144.43 EU/mL) was higher than that observed for the overall PPI population of Pentacel subjects (90.82 EU/mL) or in the Sweden I Efficacy Trial subjects (111.26 EU/mL) (Table 14 above). However, among subjects with pre-vaccination anti-pertactin levels <20 EU/mL, which constitute ≥95% of the study populations, the anti-pertactin GMC following four doses of Pentacel in Study 494-01 (88.03 EU/mL) is lower than the GMC following three doses of DAPTACEL in the Sweden I Efficacy Trial (111.41 EU/mL).

Table 15. Sweden I Efficacy Trial and Study 494-01 - Pertactin GMCs and seroconversion rates stratified by pre-vaccination antibody level

	DAPTACEL Sweden I N = 80				Pentacel Study 494-01* N = 507			
	Pre-dose 1		Post-dose 3		Pre-dose 1		Post-dose 4	
Pre-dose 1 anti-pertactin level (EU/mL)	n (%)	GMC	GMC	% ≥ 4x rise	n (%)	GMC	GMC	% ≥ 4x rise
<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

*494-01 PPI population included subjects who had received three doses of Prevnar concomitantly with Pentacel at 2, 4 and 6 months of age, the fourth dose of Prevnar was administered at 12 months of age.
N represents number of subjects with a valid sera pair (Sweden I: pre-Dose 1 and post-Dose 3; or Study 494-01: pre-Dose 1 and post-Dose 4).
Source: bridge.pdf page 49, September 7, 2006 questions1_133.pdf page 267.

5.2.2.2 Comparison of Pentacel to DAPTACEL in U.S. Children

In Study P3T06, non-inferiority of pertussis responses elicited by Pentacel relative to DAPTACEL was evaluated following three and four doses of each vaccine administered to U.S. children. As discussed in Section 2.1 four doses of DAPTACEL constitute a primary immunization course for pertussis in U.S. children. Thus, in the comparison of Pentacel to DAPTACEL in U.S. children in Study P3T06, CBER considers the immune responses post-dose 4 to be critical determinants of effectiveness.

Following three doses of each vaccine, non-inferiority of Pentacel relative to DAPTACEL was demonstrated for seroconversion rates and GMCs for all pertussis antigens (Table 16 and 17).

Table 16. Study P3T06 - Pertussis seroconversion rates following three doses of DAPTACEL compared to three doses of Pentacel, PPI population

Pertussis antigen	Post dose 3 DAPTACEL % ≥ 4-fold rise[2] (95%CI)	Post dose 3 Pentacel % ≥ 4-fold rise[2] (95%CI)	Non-inferiority Difference DAPTACEL minus Pentacel (90% CI)[1]
	N = 712-724	N = 218-221	
PT	86.1 (83.3, 88.6)	93.6 (89.5, 96.5)	-7.51 (-10.97, -4.06)
FHA	60.9 (57.2, 64.5)	81.9 (76.2, 86.7)	-20.99 (-26.19, -15.79)
FIM	86.3 (83.5, 88.7)	91.7 (87.3, 95.0)	-5.47 (-9.19, -1.74)
PRN	75.4 (72.1, 78.5)	74.2 (67.9, 79.8)	1.21 (-4.31, 6.73)

[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 antibody level (EU/mL).
Source: p3t06si.pdf page 86.

Table 17. Study P3T06 - Pertussis GMCs following three doses of DAPTACEL compared to three doses of Pentacel, PPI population

Pertussis Antigen	Post dose 3 DAPTACEL GMC (EU/mL) (95%CI)	Post dose 3 Pentacel GMC (EU/mL) (95%CI)	Non-inferiority Ratio DAPTACEL/Pentacel (90% CI)[1]
	N = 1015-1016	N = 318	
PT	63.82 (61.22, 66.53)	89.98 (84.19, 96.17)	0.71 (0.66, 0.76)
FHA	29.22 (27.91, 30.60)	73.68 (68.52, 79.23)	0.40 (0.37, 0.43)
FIM	267.18 (253.15, 282.00)	268.15 (247.21, 290.87)	1.00 (0.91, 1.09)
PRN	43.25 (40.68, 45.99)	36.05 (32.27, 40.27)	1.20 (1.08, 1.33)

[1]Non-inferiority is achieved when the upper limit of the 90% CI of the GMC Ratio (DAPTACEL/Pentacel) is <1.5.
Source: p3t06si.pdf page 88.

Following four doses of each vaccine, non-inferiority of Pentacel relative to DAPTACEL was demonstrated for seroconversion rates for all pertussis antigens and for anti-PT, -FHA and –FIM GMCs (Table 18 and 19). Although the quantity of pertactin in both vaccines is the same, the post-vaccination anti-pertactin GMC was significantly diminished in Pentacel recipients as compared to DAPTACEL recipients (Table 19).

Table 18. Study P3T06 - Pertussis seroconversion rates following four doses of DAPTACEL compared to four doses of Pentacel, PPI population

Pertussis Antigen	Post dose 4 DAPTACEL % ≥ 4-fold rise[1] (95% CI)	Post dose 4 Pentacel % ≥ 4-fold rise[1] (95% CI)	Non-inferiority Difference DAPTACEL minus Pentacel (90% CI)[2]
	N=237-242	N = 230-232	
PT	97.1 (94.0, 98.8)	97.4 (94.4, 99.0)	-0.34 (-2.84, 2.15)
FHA	79.3 (73.7, 84.3)	88.4 (83.5, 92.2)	-9.02 (-14.53, -3.52)
FIM	91.6 (87.3, 94.8)	93.5 (89.5, 96.3)	-1.92 (-5.92, 2.08)
PRN	98.3 (95.8, 99.5)	92.7 (88.5, 95.7)	5.67 (2.55, 8.79)

[1] Fold rise is calculated by post-dose 4/pre-dose 1 antibody level (EU/mL)
[2] Non-inferiority: Upper limit of the two-sided 90% CI of the seroresponse difference (DAPTACEL – Pentacel) is <10%.
DAPTACEL group 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 VARIVAX, and the 4th dose of Prevnar were given at 12 months.
Pentacel group received the 4th dose of Pentacel at 15-16 months of age. The 1st dose of MMR and VARIVAX, and the 4th dose of Prevnar were given at 12 months.
Source: p3t06sii.pdf page 92.

Table 19. Study P3T06 - Pertussis GMCs following four doses of Pentacel compared to four doses of DAPTACEL, PPI population

Pertussis Antigen	Post dose 4 DAPTACEL GMC (EU/mL) (95% CI)	Post dose 4 Pentacel GMC (EU/mL) (95% CI)	Non-inferiority Ratio DAPTACEL/Pentacel (90% CI)[1]
	N = 345-347	N = 366-367	
PT	168.48 (153.52, 184.89)	174.03 (159.27, 190.17)	0.97 (0.87, 1.08)
FHA	64.02 (58.81, 69.69)	107.94 (99.42, 117.20)	0.59 (0.54, 0.66)
FIM	513.54 (457.72, 576.17)	553.39 (496.11, 617.27)	0.93 (0.81, 1.06)
PRN	186.07 (168.16, 205.88)	93.59 (83.98, 104.31)	1.99 (1.76, 2.25)

[1]Non-inferiority is achieved when the upper limit of the two-sided 90% CI of the GMC ratio is <1.5.
DAPTACEL group 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 VARIVAX, and the 4th dose of Prevnar were given at 12 months.
Pentacel group received the 4th dose of Pentacel at 15-16 months of age. The 1st dose of MMR and VARIVAX, and the 4th dose of Prevnar were given at 12 months.
Shaded cell indicates non-inferiority criterion was not met.
Source: p3t06sii.pdf page 94.

5.2.2.3 Comparison of Pentacel to HCPDT in U.S. Children

A primary endpoint in Study 494-01 was non-inferiority of the pertussis component of Pentacel relative to the component equivalent DTaP, HCPDT. Since HCPDT is not licensed in the U.S. the comparison of Pentacel to HCPDT is not considered pivotal to support the efficacy of the pertussis component of Pentacel. Nevertheless, these data will be presented as a direct evaluation of the pertussis immune responses following vaccines containing the same amount of PT, FHA, pertactin and fimbriae, administered as either Pentacel or HCPDT.

Table 20 and 21 present the results of non-inferiority analyses (Pentacel versus HCPDT) for pertussis seroconversion rates and GMCs post dose 3. For all comparisons, non-inferiority was demonstrated. Following four doses of Pentacel or HCPDT non-inferiority of Pentacel relative to HCPDT was demonstrated for pertussis seroconversion rates to all antigens and GMCs for PT, FHA and FIM (Table 22 and 23). Non-inferiority was not demonstrated for anti-pertactin GMCs (Table 23).

Table 20. Study 494-01 - Pertussis seroconversion rates following three doses of Pentacel compared to three doses of HCPDT, PPI population

Antigen	Post dose 3 Pentacel % ≥ 4-fold rise[2] (95% CI)	Post dose 3 HCPDT % ≥ 4-fold rise[2] (95% CI)	Non-inferiority Difference Control minus Pentacel (90% CI)[1]
	N = 992-995	N = 339-341	
PT	90.3 (88.3, 92.1)	89.7 (86.0, 92.7)	-0.60 (-3.71, 2.52)
FHA	80.3 (77.7, 82.7)	78.0 (73.2, 82.3)	-2.30 (-6.53, 1.94)
FIM	86.2 (83.9, 88.3)	87.0 (83.0, 90.4)	0.83 (-2.67, 4.33)
PRN	73.2 (70.3, 75.9)	78.6 (73.9, 82.8)	5.43 (1.10, 9.75)

[1] Non-inferiority is achieved when the upper limit of the 90% CI for the difference in seroconversion rates was <10%

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

Source: 49401si.pdf, page 98- 99

Table 21. Study 494-01- Pertussis GMCs following three doses of Pentacel compared to three doses of HCPDT, PPI population.

Antigen	Post dose 3 Pentacel. GMC (EU/mL) (95% CI)	Post dose 3 HCPDT GMC (EU/mL) (95% CI)	Non-inferiority Ratio Control/Pentacel. (90% CI)[1]
	N = 1117-1119	N = 391-392	
PT	99.67 (95.49, 104.02)	84.45 (78.72, 90.60)	0.85 (0.79, 0.91)
FHA	76.24 (73.06, 79.56)	69.24 (64.18, 74.69)	0.91 (0.85, 0.97)
FIM	270.29 (256.83, 284.46)	245.98 (227.67, 265.76)	0.91 (0.84, 0.99)
PRN	39.55 (37.16, 42.10)	38.63 (34.93, 42.73)	0.98 (0.88, 1.08)

[1] Non-inferiority is achieved when the UL of the 90% CI for the GMC ratio (Control/Pentacel) is <1.5
Source: 49401si.pdf page 100.

Table 22. Study 494-01 - Pertussis seroconversion rates following four doses of Pentacel compared to four doses of HCPDT, PPI population

Antigen	Post dose 4 Pentacel % ≥ 4-fold rise[2] (95% CI)	Post dose 4 HCPDT % ≥ 4-fold rise[2] (95% CI)	Non-inferiority Difference Control minus Pentacel (90% CI)[1]
	N = 778-780	N = 247-250	
PT	95.4 (93.7, 96.7)	94.4 (90.8, 96.9)	-0.98 (-3.68, 1.71)
FHA	90.2 (87.9, 92.2)	86.3 (81.4, 90.4)	-3.90 (-7.88, 0.09)
FIM	91.3 (89.1, 93.1)	87.9 (83.1, 91.7)	-3.41 (-7.21, 0.40)
PRN	89.3 (87.0, 91.4)	92.8 (88.8, 95.7)	3.43 (0.17, 6.68)

[1] Non-inferiority is achieved when the upper limit of the 90% CI for the difference in seroconversion rates was <10%.
[2] The fold-rise is calculated by post-Dose 4/pre-Dose 1 antibody level (EU/mL)
Source: 49401sii.pdf page 87

Table 23. Study 494-01 - Pertussis GMCs following four doses of Pentacel compared to four doses of HCPDT, PPI population

Antigen	Post dose 4 Pentacel GMC (EU/mL) (95% CI)	Post dose 4 HCPDT GMC (EU/mL) (95% CI)	Non-inferiority Ratio Control/Pentacel (90% CI)[1]
	N = 853-854	N = 281-282	
PT	202.18 (190.84, 214.20)	188.62 (169.49, 209.92)	0.93 (0.85, 1.03)
FHA	134.59 (127.67, 141.89)	128.26 (116.77, 140.88)	0.95 (0.87, 1.04)
FIM	514.19 (477.80, 553.35)	350.29 (306.46, 400.39)	0.68 (0.60, 0.77)
PRN	94.91 (88.39, 101.90)	129.91 (114.13, 147.87)	1.37 (1.21, 1.54)

1 Non-inferiority is achieved when the upper limit of the 90% CI of the GMC ratio (Control/Pentacel) is <1.5.
The shaded cell indicates that the non-inferiority criterion was not met.
Source: 49401sii.pdf page 90

5.2.2.4 Effect of Co-administered Prevnar on Response to the Pertussis Component of Pentacel

Historically, some inconsistent differences in responses to acellular pertussis antigens have been observed when Prevnar was administered concomitantly with a DTaP vaccine manufactured by Wyeth Pharmaceuticals Inc. (Prevnar package insert). The following section will review and summarize the available data that evaluate the potential for reduced responses to the pertussis antigens when Pentacel and Prevnar are co-administered.

Prevnar was recommended for use in U.S. infants after Study 494-01 was initiated, and was administered to all subjects when available. In Study 494-01 approximately 80% of subjects received the first three doses of Pentacel concomitantly with Prevnar. The other subjects received 0, 1, or 2 doses of Pentacel concomitantly with Prevnar. The fourth dose of Pentacel and Prevnar (at 15 and 12 months of age, respectively) were administered at different times. Prospectively specified exploratory analyses examined pertussis responses following three and four doses of Pentacel or HCPDT stratified by the number of doses of Prevnar administered concomitantly with Pentacel. Although these analyses are inconclusive, the data suggest the possibility of interference in the post-dose 3 and post-dose 4 pertussis responses with increasing number of doses of Prevnar administered concomitantly (post dose 3 data not shown).

Table 24 presents pertussis GMCs following four doses of Pentacel or HCPDT, stratified by number of doses of Prevnar administered concomitantly. Although a formal statistical evaluation was not performed these data suggest that the anti-PT and anti-pertactin GMCs following four doses of Pentacel or HCPDT may be lower with increasing number of doses of Prevnar co-administered with Pentacel at 2, 4 and 6 months of age.

Table 24. Study 494-01 - Pertussis GMCs one month following the fourth dose of Pentacel or HCPDT 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	Post dose 4 Pentacel N = 852-853		Post dose 4 HCPDT N = 281-282	
	N	GMC (EU/mL) (95% CI)	N	GMC (EU/mL) (95% CI)
PT				
3	554	195.10 (181.61, 209.59)	175	181.69 (157.54, 209.53)
2	238	215.59 (193.92, 239.69)	87	199.04 (165.18, 239.84)
0-1	61	224.60 (176.42, 285.94)	20	207.26 (151.16, 284.18)
FHA				
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				
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				
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)

Source: 49401sii.pdf page 96 and 97,

Table 25 presents pertussis GMCs following the fourth dose of Pentacel administered at 15 months of age or at 15-16 months of age in a) Study 5A9908 subjects (no concomitant Prevnar with any dose of Pentacel); b) Study 494-01 subjects (0, 1, 2, or 3 doses of Prevnar concomitantly with Pentacel at 2, 4, and 6 months of age); c) Study 494-03 subjects (Group 1: concomitant Prevnar and Pentacel at 2, 4, and 6 months of age, and Group 3: concurrent Prevnar and Pentacel at 2, 4, 6 and 15 months of age); and d) Study P3T06 subjects (concomitant Prevnar and Pentacel at 2, 4, and 6 months of age). The anti-PT, -FHA, -FIM, and -pertactin GMCs in Study 5A9908 in which subjects were not administered Prevnar concomitantly with any dose of Pentacel, all appeared to be higher than in the other pivotal studies. All assays were performed in the same laboratory. While these data suggest that concomitant administration of Prevnar with Pentacel may interfere with the responses to the pertussis component they should be interpreted with caution since the studies were performed at different times and in different populations.

Table 25. Pertussis GMCs following a fourth dose of Pentacel across all pivotal studies, PPI populations

	Study				
Number of concurrent Prevnar doses:	**5A9908[1]**	**494-01**	**P3T06**	**494-03**	
	N=191	**N = 853-854**	**N = 366-367**	**Group 1 N = 203**	**Group 3 N = 202**
at 2, 4 and 6 months	**0**	**0-3**	**3**	**3**	**3**
at 15 months	**0**	**0**	**0**	**0**	**1**
Antigen	GMC (EU/mL) (95% CI)	GMC (EU/mL) (95% CI)	GMC (EU/mL) (95% CI)	GMC (EU/mL) (95% CI)	GMC (EU/mL) (95% CI)
PT	249.85 (220.48, 283.14)	202.18 (190.84, 214.20)	174.03 (159.27, 190.17)	161.87 (144.41, 181.44)	138.83 (123.06, 156.62)
FHA	172.42 (156.34, 190.16)	134.59 (127.67, 141.89)	107.94 (99.42, 117.20)	134.47 (120.76, 149.74)	128.12 (113.79, 144.24)
FIM	833.37 (723.10, 960.46)	514.19 (477.80, 553.35)	553.39 (496.11, 617.27)	434.35 (372.93, 505.89)	324.96 (273.72, 385.78)
Pertactin	187.52 (163.40, 215.19)	94.91 (88.39, 101.90)	93.59 (83.98, 104.31)	76.44 (66.01, 88.52)	69.63 (59.81, 81.06)

[1]Study 5A9908 group was administered a fourth dose of Pentacel at 15 months of age
Source: 5a9908.pdf page 480, 49403.pdf page 91, p3t06sii.pdf page 94, 49401sii.pdf page 90

Because available data from Study 494-01 suggested the possibility that concomitant administration of Prevnar with Pentacel could reduce the immune responses to some of the pertussis antigens, CBER requested that the applicant initiate a study to evaluate prospectively the effect of concomitant Prevnar on the immune responses to Pentacel. In Study M5A07, subjects received four doses of Pentacel at 2, 4, 6, and 15 months of age, either concomitantly with Prevnar, or with Prevnar administered one month after each dose of Pentacel. Summary data from Study M5A07, included in the BLA, demonstrate that co-administration of Prevnar with Pentacel does not interfere with the post-dose 3 response to the pertussis antigens compared with Pentacel administered one month prior to each dose of Prevnar (Tables 26 and 27). Although Study M5A07 evaluated the response to a fourth dose of Pentacel, post-dose 4 data have not been submitted to the BLA.

Table 26. Study M5A07 - Seroconversion rates following three doses of Pentacel co-administered with Prevnar (Group 1) or administered separately from Prevnar (Group 2), PPI population

Antigen	Group 1 % ≥ 4-fold rise[1] (95% CI)	Group 2 % ≥ 4-fold rise[1] (95% CI)	Non-inferiority Difference Group 2 minus Group 1 (95% CI)[2]
	N = 422-445	N = 436-438	
PT	89.7 (86.5, 92.3)	90.4 (87.2, 93.0)	0.73 (-3.23, 4.68)
FHA	81.6 (77.7, 85.1)	81.9 (77.9, 85.4)	0.25 (-4.86, 5.36)
FIM	87.6 (84.1, 90.5)	87.7 (84.2, 90.6)	0.11 (-4.24, 4.47)
PRN	73.6 (69.3, 77.7)	71.7 (67.2, 75.9)	-1.96 (-7.84, 3.92)

Group 1: Pentacel + Prevnar at 2, 4, and 6 months, Group 2: Pentacel at 2, 4, and 6 months with Prevnar at 3, 5 and 7 months.
[1]The fold rise is calculated by Post-Dose 3/Pre-Dose 1 antibody level (EU/mL).
[2]Non-inferiority is achieved when the upper limit of the 95% CI for the seroresponse rate Group 2 minus Group 1 is <10%
Source: isi.pdf page 113

Table 27. Study M5A07 - Pertussis GMCs following three doses of Pentacel co-administered with Prevnar (Group 1) or separately (Group 2), PPI population

Antigen	Group 1 GMC (EU/mL) (95% CI)	Group 2 GMC (EU/mL) (95% CI)	Non-Inferiority Ratio Group 2/Group 1 (90% CI)[1]
	N = 446-447	N = 439	
PT	103.58 (97.87, 109.63)	102.78 (96.86, 109.06)	0.99 (0.93, 1.06)
FHA	82.41 (77.40, 87.75)	77.80 (72.62, 83.35)	0.94 (0.87, 1.02)
FIM	272.47 (251.39, 295.32)	280.97 (258.02, 305.97)	1.03 (0.93, 1.14)
PRN	45.70 (41.59, 50.23)	44.28 (40.11, 48.89)	0.97 (0.86, 1.09)

Group 1: Pentacel + Prevnar at 2, 4, and 6 months, Group 2: Pentacel at 2, 4, and 6 months with Prevnar at 3, 5 and 7 months.
[1] Non-inferiority is achieved when the upper limit of the 90% CI for the GMC ratio (Group 2/Group 1) is <1.5.
Source: isi.pdf page 115

5.2.3 Effectiveness of the Diphtheria and Tetanus Toxoids

The evaluation of the effectiveness of the diphtheria and tetanus toxoids of Pentacel was based on comparison of immune responses using established protective levels, relative to

Control vaccines (HCPDT or DAPTACEL). As measured by the applicant's ELISA, anti-tetanus toxin levels ≥0.1 IU/mL are considered the minimum protective levels. Anti-diphtheria toxin levels were measured using a VERO neutralization assay. Anti-diphtheria toxin antibody levels ≥0.01 IU/mL are the minimum levels giving some degree of protection.

Since the immune response to the diphtheria and tetanus components of Pentacel and control vaccines was similar in both comparative studies this section will only present the data and non-inferiority analyses from Study P3T06. Following three doses of Pentacel or DAPTACEL 100% of subjects had seroprotective levels to each antigen (Table 28). Following a fourth dose of each vaccine administered at 15-16 months of age >92% of subjects had anti-tetanus levels ≥1.0 IU/mL and, >95% had anti-diphtheria levels ≥0.1 IU/mL (10 times the minimum protective levels). These data and the results of non-inferiority analyses are presented in Table 29.

Table 28. Study P3T06 - Anti-tetanus and diphtheria seroprotection rates following three doses of Pentacel compared to DAPTACEL, PPI Population

Endpoint	Vaccine Rate % (95% CI)		Difference Control minus Pentacel (95% CI)
	Pentacel	DAPTACEL	
	N = 331-345	N = 1037-1099	
Anti-diphtheria ≥0.01 IU/mL	100.0 (98.9, 100.0)	100.0 (99.7, 100.0)	0.00[1]
Anti-tetanus ≥0.1 IU/mL	99.7 (98.3, 100.0)	100.0 (99.6, 100.0)	0.30 (-0.29, 0.89)[2]

[1] Non-Inferiority is achieved when the upper limit of the 90% CI of the rate difference (DAPTACEL-Pentacel) is <10%.
[2] Non-inferiority criteria not prespecified
Source: p3t06si.pdf page 86, September 7, 2006 questions1_133.pdf page 319

Table 29. Study P3T06 - Anti-tetanus and anti-diphtheria seroprotection rates following four doses of Pentacel compared to DAPTACEL, PPI Population

Endpoint	Vaccine Rate % (95% CI)		Difference Control minus Pentacel (90% CI)
	Pentacel	DAPTACEL	
	N = 341-352	N = 328-334	
Anti-diphtheria			
≥0.1 IU/mL	100.0 (98.9, 100.0	100.0(98.9, 100.0)	0.00
≥1.0 IU/mL	96.5(93.9, 98.2)	95.7(92.9, 97.6)	-0.75 (-3.21, 1.71)*
Anti-tetanus			
≥0.1 IU/mL	100.0 (99.0, 100.0)	100.0(98.9, 100.0)	0.00
≥1.0 IU/mL	92.9 (89.7, 95.4)	99.4 (97.9, 99.9)	6.50 (4.15, 8.86)*

*Non-inferiority criteria were not pre-specified for the comparison of anti-tetanus and anti-diphtheria levels ≥1.0 IU/mL.
The 4th dose of DAPTACEL was administered concomitantly with the 4th dose of ActHIB at 15-16 months of age.
Source: p3t06sii.pdf page 92 and 93

The GMC response to diphtheria and tetanus toxoids following three and four doses of each vaccine is provided in Table 30. Although the post-dose 4 tetanus GMC following Pentacel is decreased as compared to that following DAPTACEL, all children had seroprotective levels of tetanus antibodies (Table 29).

Table 30. Study P3T06 - Tetanus and diphtheria GMCs following three and four doses of Pentacel compared to DAPTACEL, PPI population

GMC	Pentacel	DAPTACEL	Ratio Control/Pentacel (90% CI)[1]
Post dose 3	N= 331-345	N = 1037-1099	
Anti diphtheria	0.95 (0.86, 1.04)	0.94 (0.89, 0.99)	0.99 (0.91, 1.08)
Anti-tetanus	1.10 (1.01, 1.19)	1.24 (1.18, 1.29)	1.12 (1.04, 1.21)
Post dose 4	N=341-352	N = 328-334*	
Anti-diphtheria	5.15 (4.66, 5.70)	5.69 (5.11, 6.34)	1.10 (0.98, 1.25)
Anti-tetanus	3.19 (2.96, 3.44)	4.98 (4.61, 5.37)	1.56 (1.43, 1.71)

[1]Non-Inferiority is achieved when the upper 90% CI of the GMC Ratio (DAPTACEL/Pentacel) is <1.5.
*DAPTACEL group received the 4th dose of DAPTACEL concomitantly with the 4th dose of ActHIB at 15-16 months of age.
The shaded cell indicates that the non-inferiority criterion was not met.
Source: p3t06si.pdf page 88, p3t06sii.pdf page 94

5.2.4 Effectiveness of the Polio Component

Neutralizing antibodies to poliovirus are recognized as conferring protection against poliomyelitis disease. Effectiveness of the polio component of Pentacel was based on comparative evaluation of neutralizing titer to each polio virus type relative to separately administered POLIOVAX (Study 494-01) or IPOL (Study P3T06). Following three doses of Pentacel or control vaccines in Studies 494-01 and P3T06 >99% of subjects had protective neutralizing antibody levels (≥1:8) to each poliovirus serotype (data not shown).

As an indicator of longevity of protection, anti-poliovirus GMTs following a fourth dose of Pentacel or POLIOVAX administered at 15 months of age in Study 494-01 are presented in Table 31.

Table 31. Study 494-01 - Polio GMTs following a fourth dose of Pentacel or POLIOVAX, PPI population.

Antigen	POLIOVAX GMT (95% CI)	Pentacel. GMT (95% CI)	Ratio Control/Pentacel (90% CI) [1]
	N = 284-287	N = 851-857	
Polio 1 (1/dil)	2329.76 (2049.16, 2648.79)	2303.65 (2115.27, 2508.80)	1.01 (0.88, 1.16)
Polio 2 (1/dil)	2840.33 (2516.24, 3206.17)	4178.27 (3864.65, 4517.34)	0.68 (0.60, 0.77)
Polio 3 (1/dil)	3299.79 (2852.46, 3817.27)	4415.38 (4045.96, 4818.54)	0.75 (0.65, 0.86)

[1] Non-inferiority criteria were not pre-specified.
Source: 49401sii.pdf page 100.

5.3 Response to Co-Administered Vaccines

The responses to three doses of Prevnar and hepatitis B vaccine administered with control vaccines or Pentacel were assessed in the two comparative studies 494-01 and P3T06. The response to a fourth dose of Prevnar administered with Pentacel or with MMR and VARIVAX was assessed in Study 494-03. This study also evaluated the response to MMR and VARIVAX when administered with Pentacel.

5.3.1 Prevnar

The minimum serum antibody concentration necessary for protection against pneumococcal disease has not been determined for any pneumococcal serotype. In Studies 494-01, 494-03 and P3T06 however, using WHO standardized ELISA methods, antibody levels of ≥0.15 μg/mL and ≥0.50 μg/mL were pre-specified for the analyses of seroresponse to the pneumococcal serotypes contained in Prevnar.

Among children administered 3 doses of Prevnar with Pentacel or control vaccines in Studies 494-01 and P3T06 there was no evidence of interference of Pentacel with anti-pneumococcal seroresponse rates using the pre-specified antibody levels (data not shown).

The GMC to each pneumococcal serotype following three doses of Prevnar administered with Pentacel or control vaccines in Study 494-01 and Study P3T06 is shown in Table 32 and 33.

Table 32. Study 494-01 - Pneumococcal GMCs one month following a third dose of Prevnar administered with Pentacel or control vaccines (HCPDT + ActHIB + POLIOVAX), PPI population*

Antigen	Prevnar + Control	Prevnar +Pentacel
	GMC (EU/mL) 95% CI	GMC (EU/mL) 95% CI
	N = 165	N = 462
Serotype 4	2.23 (1.93, 2.58)	2.46 (2.26, 2.68)
Serotype 6B	0.72 (0.55, 0.95)	0.61 (0.52, 0.73)
Serotype 9V	1.79 (1.55, 2.06)	1.79 (1.63, 1.97)
Serotype 14	3.70 (3.02, 4.54)	3.95 (3.50, 4.45)
Serotype 18C	2.67 (2.23, 3.20)	2.56 (2.32, 2.84)
Serotype 19F	2.56 (2.14, 3.07)	2.65 (2.37, 2.95)
Serotype 23F	1.32 (1.04, 1.67)	1.31 (1.15, 1.49)

*PPI population who had received all three doses of Prevnar concomitantly with control vaccines or Pentacel
Source: 49401si.pdf page 108

Table 33. Study P3T06 - Pneumococcal GMCs one month following a third dose of Prevnar administered with Pentacel or control vaccines (DAPTACEL+ ActHIB + IPOL), PPI population

Antigen	Prevnar + Control	Prevnar +Pentacel
	GMC (EU/mL) 95% CI	GMC (EU/mL) 95% CI
	N = 1027-1029	N = 321
Serotype 4	3.23 (3.07, 3.39)	3.09 (2.82, 3.39)
Serotype 6B	1.75 (1.59, 1.93)	1.84 (1.55, 2.18)
Serotype 9V	2.35 (2.23, 2.47)	2.26 (2.06, 2.49)
Serotype 14	6.03 (5.66, 6.43)	5.19 (4.63, 5.83)
Serotype 18C	3.75 (3.56, 3.96)	3.72 (3.37, 4.10)
Serotype 19F	3.40 (3.19, 3.62)	3.32 (2.95, 3.74)
Serotype 23F	2.48 (2.30, 2.67)	2.65 (2.33, 3.01)

Source: p3t06si.pdf page 94

In Study 494-03 the response to a fourth dose of Prevnar administered at 15 months of age with Pentacel (Group 3) or with MMR and VARIVAX (Group 4) was assessed. In this study all subjects had received the first three doses of Prevnar concomitantly with Pentacel at 2, 4 and 6 months of age. One month following the fourth dose of Prevnar >95% of subjects in both groups had antibody levels ≥0.5ug/mL to each serotype and the pre-defined criteria for non-inferiority were met for each serotype (UL of the 90% CI for the rate difference Group 4 minus Group 3 <10%, data not shown).

Post dose 4 GMC for each serotype and non-inferiority analyses are shown in Table 34. Criteria for non-inferiority (UL 90% CI of GMC ratio <2.0) were met for each serotype.

Table 34. Study 494-03 - Pneumococcal GMCs following the fourth dose of Prevnar administered with Pentacel or MMR + VARIVAX, PPI population.

Antigen	Group 3 (Pentacel + Prevnar) N = 155		Group 4 (Prevnar + MMR + VARIVAX) N = 158		Ratio Group 4/Group 3	
	GMC	(95% CI)	GMC	(95% C)	ratio	(90% CI) [1]
Serotype 4	5.11	(4.44, 5.88)	6.55	(5.69, 7.54)	1.28	(1.09, 1.51)
Serotype 6B	9.46	(7.67, 11.66)	11.93	(9.92, 14.35)	1.26	(1.00, 1.59)
Serotype 9V	5.45	(4.76, 6.24)	7.01	(6.19, 7.93)	1.29	(1.10, 1.50)
Serotype 14	13.92	(12.02, 16.13)	15.43	(13.23, 17.99)	1.11	(0.93, 1.32)
Serotype 18C	5.26	(4.54, 6.09)	6.24	(5.38, 7.24)	1.19	(1.00, 1.41)
Serotype 19F	5.44	(4.62, 6.40)	6.96	(5.73, 8.46)	1.28	(1.04, 1.58)
Serotype 23F	6.16	(5.02, 7.55)	7.40	(6.16, 8.89)	1.20	(0.96, 1.51)

[1] Non-inferiority: Upper limit of the two-sided 90% CI of the GMC ratio is <2.0
All subjects received doses 1-3 of Prevnar co-administered with Prevnar. 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 98

5.3.2 Hepatitis B Vaccine

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 (from birth to 21 days of age). The hepatitis B vaccine children received as a first dose was not noted in the study reports. 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 (≥10mIU/mL) following the third dose of hepatitis B vaccine (Table 35 and 36). Within each comparative study the response to hepatitis B vaccine when co-administered with Pentacel or control vaccines appeared similar. Between these studies the GMC ranged from 121 IU/mL to 365 mIU/mL.

Table 35. Study 494-01 and P3T06 – Anti-hepatitis B seroprotection rates and GMCs one month following the third dose of hepatitis B vaccine administered with Pentacel or control vaccines at 2 and 6 months of age*, PPI population

	Hepatitis B vaccine administered with:	
	Pentacel	**Control**
Study 494-01*		
N	1076	386
% ≥10mIU/mL (95% CI)	98.0 (96.9, 98.7)	97.9(96.0, 99.1)
GMC (95% CI)	365.08 (330.96, 402.72)	303.25(260.29, 353.31)
Study P3T06*		
N	325	998
% ≥10mIU/mL (95% CI)	89.8 (86.0, 92.9)	92.4 (90.6, 94.0)
GMC (95% CI)	120.98 (97.05, 150.81)	126.97 (113.19, 142.44)

*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
Source: 49401si.pdf page 102, p3t06si.pdf page 94

Table 36. Study 494-03 - Anti-hepatitis B seroprotection rates and GMCs one month following the third dose of hepatitis B vaccine administered with Pentacel, PPI population

	0, 2, 6 months schedule*	**2, 4, 6 months schedule**	**All schedules**
	N = 169	N = 83	N = 252
% ≥10m IU/mL (95% CI)	98.2 (94.9, 99.6)	100 (95.7, 100)	98.8 (96.6, 99.8)
GMC 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 was not recorded, RECOMBIVAX HB was administered at the other doses
Source: 49401si.pdf page 98

5.3.3 MMR and Varicella Vaccine

A secondary endpoint of Study 494-03 was an evaluation of the response to MMR and VARIVAX when administered with Pentacel or Prevnar at 15 months of age. For all antigens non-inferiority was demonstrated for seroresponse rates when MMR and VARIVAX were administered with Pentacel vs. Prevnar at 15 months of age (Table 37).

Table 37. Study 494-03 - 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) % (95% CI)	Group 4** (MMR + VARIVAX + Prevnar at 15m) % (95% CI)	Non-inferiority Difference Group 4 minus Group 2 (90% CI)[1]
	N = 154	N = 144	
Measles			
ELISA ≥300 or Neutralization ≥120 mIU/mL	98.7 (95.4, 99.8)	97.9 (94.0, 99.6)	-0.78 (-3.25, 1.68)
Mumps			
ELISA ≥500 U/mL or Neutralization ≥60 (1/dil)	98.1 (94.4, 99.6)	97.2 (93.0, 99.2)	-0.83 (-3.73, 2.07)
Rubella			
≥10 IU/mL	96.8 (92.6, 98.9)	97.2 (93.0, 99.2)	0.47 (-2.79, 3.72)
Varicella			
ELISA ≥300 mIU/mL or FAMA ≥4 (1/dil)	92.9 (87.6, 96.4)	93.8 (88.5, 97.1)	0.89 (-3.87, 5.65)

*Group 2: Received 4th Dose of Pentacel concomitantly with the 1st Dose of MMR and VARIVAX 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.

[1]Non-inferiority: Upper limit of the two-sided 90% CI of Group 4–Group 2 <5% (except <10% for Varicella)

Source 49403sii.pdf page 93

6 Safety

6.1 Pivotal Studies

6.1.1 Safety Monitoring

Safety monitoring was similar across the four pivotal studies. Subjects were observed at the study site for 30 minutes post-vaccination. Solicited local reactions (redness, swelling, tenderness, and change in limb circumference [4th dose only]) and systemic events (fever, decreased activity, crying, diarrhea, fussiness, anorexia, vomiting, rash) were recorded daily on diary cards for Days 0-7 post-vaccination. In Study P3T06, the diary cards included questions pertaining to HHE. In the other studies, a question about the occurrence of fainting or change in mental status was asked during post-vaccination phone calls.

Unsolicited adverse events that represented a change in health status were monitored through seven days post-vaccination; those that required health provider contact (phone call, office, emergency room or hospital visit) were monitored through 60 days post-vaccination. Serious adverse events were monitored through 60 days (Studies 494-01, 494-03, and 5A9908) or 180 days (Study P3T06) following the last dose of study vaccines.

Phone calls to inquire about adverse events were conducted at approximately Day 2-4 (depending on study), Day 8, Day 30, and Day 60 post-vaccination. Interviews at the study sites or review of computerized medical records (if available) may have substituted for the Day 30 and Day 60 phone calls. In Study P3T06, a phone call or review of computerized medical records (if available) was also conducted 180 days following the fourth dose to inquire about serious adverse events, chronic events, or events of possible autoimmune origin.

6.1.2 Definition of Safety Population

Safety analyses were based on the safety population which included all subjects who received at least one dose of Pentacel or Control vaccines, regardless of whether they adhered to the eligibility criteria or protocol-specified windows for study visits.

6.1.3 Completion of Follow-up and Reasons for Early Discontinuation

Table 38 provides a summary of subjects who completed the 60 day follow-up post-dose 3 and the 60 or 180 day follow-up (depending on study) post-dose 4. Percentages are based on subject participation by randomized treatment at Dose 1 (Studies 494-01, 494-03 and P3T06) or Dose 4 (Study 5A9908).

Table 38. Pivotal studies: Summary of subjects who completed the safety follow-up post-dose 3 and post-dose 4

	494-01		494-03	P3T06		5A9908
	Pentacel	Control[1]	Pentacel	Pentacel	Control[1]	Pentacel
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All randomized subjects for safety	2507	1036	1213	484	1457	1869
Participation by randomized treatment group	2506	1032	1207	484	1455	1782
Completed 60-day follow-up post-dose 3[2]	2251 (89.8)	880 (85.3)	1061 (87.9)	452 (93.4)	1350 (92.8)	NA
Completed 60 or 180-day follow-up post-dose 4[2, 3]	1882 (75.1)	698 (67.6)	947 (78.5)	416 (86.0)	1217[4] (83.6)	1773 (99.5)

[1] The Control vaccines were: HCPDT + POLIOVAX + ActHIB in Study 494-01; DAPTACEL + IPOL + ActHIB for Doses 1-3 and DAPTACEL + ActHIB for Dose 4 in Study P3T06.
[2] Subjects have been classified by the treatment to which they were randomized. Percentages are based on participation by randomized treatment at Dose 1 (Studies 494-01, 494-03 and P3T06) or Dose 4 (Study 5A9908). **Treatment errors**: In Study 494-01, 52 subjects randomized to Pentacel received Control vaccines for Dose 4; 19 subjects randomized to Control vaccines received Pentacel for Dose 4. In Study P3T06, one subject randomized to Control vaccines received Pentacel at Dose 1; 4 subjects randomized to Control vaccines received Pentacel for Dose 4; 2 subjects randomized to Pentacel received Control vaccines for Dose 4.
[3]Follow-up post-dose 4 was 60 days in Studies 494-01, 494-03, and 5A9908, and 180 days in Study P3T06.
[4]Includes DAPTACEL subjects from all three Dose 4 study groups. Of these, 406 received the fourth doses of DAPTACEL + ActHIB at 15-16 months of age without other concomitantly administered vaccines and served as the Control for the fourth dose of Pentacel.
NA indicates not applicable.
Source: iss.pdf (version 3.0), pages 54-57 and p3T06sii.pdf, page 86.

In the pivotal studies, in both Pentacel and Control subjects, the majority of early discontinuations were due to voluntary withdrawal or non-compliance. Across all doses in the pivotal studies, lost to follow-up accounted for approximately 11% of early discontinuations in Pentacel subjects, approximately 6% in HCPDT subjects, and approximately 22% in DAPTACEL subjects. Adverse events accounted for 1-6% of early discontinuations. The most common adverse events leading to withdrawal following Pentacel were seizures (15 subjects) followed by crying and/or fussiness (seven subjects). Of 15 Pentacel subjects who withdrew due to seizures, one subject had a seizure 29 days post-vaccination. The remaining 14 subjects who withdrew due to seizures following Pentacel experienced a seizure(s) between 45-296 days post-vaccination. Among Control subjects, the most common adverse events leading to withdrawal were seizures (three subjects) and chickenpox (three subjects). Of the three Control subjects who withdrew due to seizures, two experienced a seizure(s) on the day of vaccination and one experienced a seizure 290 days post-vaccination.

6.1.4 Serious Adverse Events

Serious adverse events were defined as events resulting in death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

6.1.4.1 Deaths

A total of five deaths occurred during the pivotal studies, four of them in subjects who had received Pentacel (N=5,980) and one in a subject who had received DAPTACEL (N=1,454). Table 39 presents a summary of deaths in the pivotal studies.

Table 39. Pivotal studies: Summary of deaths

Study/ Vaccine Group	Age (months) at death	Last dose of study vaccine	No. of days between last dose and death	Cause/circumstances of death
494-01/ Pentacel	15	3	256	Neuroblastoma
494-03/ Pentacel	2	1	23	Head trauma with intraventricular hemorrhage following motor vehicle accident
494-03/ Pentacel	4	1	52	SIDS
P3T06/ Pentacel	15	4	8	Asphyxia due to suffocation
P3T06/ DAPTACEL + IPOL + ActHIB	13	3	222	Aspiration in a subject with metastatic ependymoma

6.1.4.2 Overall Rates of Serious Adverse Events

Overall, rates of serious adverse events following Pentacel appeared to be lower in Study 494-01 than the other pivotal studies. For example, following any of Doses 1-3, the percentage of subjects who reported at least one serious adverse event within 60 days following Pentacel was 1.5% in Study 494-01; 4.1% in Study 494-03; and 5.2% in Study P3T06. Following Dose 4, the percentage of subjects who reported at least one serious adverse event within 60 days following Pentacel was 0.4% in Study 494-01, and ranged from 1.1% to 2.1% in the other pivotal studies. Different geographic distribution of study sites and varying proportions of subjects vaccinated during different seasons were offered by the applicant as potential explanations for this observation.

6.1.4.3 Most Frequently Occurring Serious Adverse Events

Tables 40 and 41 present the frequencies of serious adverse events (in descending order of frequency) that occurred in at least two subjects within 30 days following any of Doses 1-3 and Dose 4, respectively, across the pivotal studies.

Table 40. Pivotal studies: Serious adverse events occurring in at least two subjects within 30 days following any of the first three doses of Pentacel or Control vaccines

Preferred Term	Study 494-01				Study 494-03		Study P3T06				Pentacel (pivotal studies pooled) N=4197	
	HCPDT + POLIOVAX + ActHIB N=1032		Pentacel N=2506		Pentacel N=1207		DAPTACEL + IPOL + ActHIB N=1455		Pentacel N=484			
	n	%	n	%	n	%	n	%	n	%	n	%
Bronchiolitis	6	0.6	5	0.2	9	0.7	28	1.9	4	0.8	18	0.4
Dehydration	0	0.0	3	0.1	3	0.2	1	0.1	3	0.6	9	0.2
Pneumonia NOS	0	0.0	3	0.1	3	0.2	2	0.1	2	0.4	8	0.2
Gastroenteritis NOS	0	0.0	1	<0.1	1	0.1	3	0.2	2	0.4	4	0.1
Otitis media NOS	0	0.0	3	0.1	2	0.2	0	0.0	0	0.0	5	0.1
Bronchospasm NOS	1	0.1	3	0.1	1	0.1	0	0.0	0	0.0	4	0.1
Gastroenteritis rotavirus	0	0.0	2	0.1	1	0.1	0	0.0	1	0.2	4	0.1
Gastroesophageal reflux	0	0.0	1	<0.1	2	0.2	1	0.1	0	0.0	3	0.1
Constipation	0	0.0	1	<0.1	1	0.1	0	0.0	1	0.2	3	0.1
Otitis media chronic NOS	0	0.0	0	0.0	0	0.0	2	0.1	2	0.4	2	<0.1
Pneumonia, RSV	0	0.0	0	0.0	1	0.1	0	0.0	2	0.4	3	0.1
Lip repair	0	0.0	1	<0.1	0	0.0	1	0.1	1	0.2	2	<0.1
Pertussis	0	0.0	2	0.1	0	0.0	1	0.1	0	0.0	2	<0.1
Apnea	0	0.0	0	0.0	2	0.2	0	0.0	0	0.0	2	<0.1
Cellulitis	0	0.0	1	<0.1	1	0.1	0	0.0	0	0.0	2	<0.1
Viral infection NOS	2	0.2	0	0.0	1	0.1	0	0.0	0	0.0	1	<0.1

Serious Adverse Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 3.1.
Subject treatment groups are per randomization.
NOS indicates not otherwise specified.
Source: questions1_133.pdf, Table 79

Table 41. Pivotal studies: Serious adverse events occurring in at least two subjects within 30 days following the fourth dose of Pentacel or Control vaccines

	Study 494-01				Study 494-03		Study P3T06				Study 5A9908		Pentacel (pivotal studies pooled) N=5033	
Preferred Term	**HCPDT + POLIOVAX + ActHIB N=739**		**Pentacel N=1862**		**Pentacel N=958**		**DAPTACEL + ActHIB N=418[1]**		**Pentacel N=431**		**Pentacel N=1782**			
	n	%	n	%	n	%	n	%	n	%	n	%	N	%
Dehydration	0	0.0	0	0.0	1	0.1	2	0.5	0	0.0	4	0.2	5	0.1
Gastroenteritis NOS	0	0.0	0	0.0	0	0.0	1	0.2	1	0.2	4	0.2	5	0.1
Asthma NOS	0	0.0	1	0.1	0	0.0	0	0.0	1	0.2	2	0.1	4	0.1
Pneumonia NOS	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	3	0.2	4	0.1
Croup infectious	0	0.0	1	0.1	0	0.0	0	0.0	1	0.2	1	0.1	3	0.1
Pyrexia	0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	2	0.1	3	0.1
Viral infection NOS	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	2	0.1	3	0.1
Convulsions NOS	1	0.1	0	0.0	2	0.2	0	0.0	0	0.0	0	0.0	2	<0.1
Bronchiolitis	0	0.0	1	0.1	1	0.1	0	0.0	0	0.0	0	0.0	2	<0.1
Bronchospasm NOS	0	0.0	2	0.1	0	0.0	0	0.0	0	0.0	0	0.0	2	<0.1
Ear infection NOS	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1	2	<0.1
Febrile convulsion	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0	1	0.1	2	<0.1
Influenza	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.1	2	<0.1

Serious Adverse Events were coded using the MedDRA Version 3.1.
NOS indicates not otherwise specified.
[1] Includes only the study group that received DAPTACEL + ActHIB at 15-16 months of age, without other vaccines administered concomitantly.
Source: questions1_133.pdf, Table 80

6.1.4.4 Encephalopathy

In the pivotal studies, there were two cases of encephalopathy reported, both following Pentacel. For one of the cases (Subject ------ below), the term "encephalopathy" was not used to code the event in the database. Instead, the event was coded using the terms "tremor" and "developmental coordination disorder", based on the medical terms used to report the event. For this reason, neither case of encephalopathy was captured in the preceding tables of serious adverse events occurring in at least two subjects. Clinical case narratives for these two cases of encephalopathy are provided below.

> Subject ------ Study 494-01: After receipt of the first dose of Pentacel, this Black male infant was diagnosed with total anomalous pulmonary venous return and associated cardiac defects, for which he underwent extensive surgical repair 30 days post-vaccination. Post-operatively, he had two pulmonary hypertensive crises and a cardiac arrest, which led to anoxia and hypoxic ischemic encephalopathy resulting in a seizure disorder, severe neurological impairment, blindness and spastic quadriplegia.
>
> Subject------ , Study 494-03: This Hispanic male infant received the first dose of Pentacel at 43 days of age. Reported solicited systemic adverse events were irritability and inconsolable crying <1 hour duration, decreased activity (moderate) and refusal of a feeding on the evening of vaccination, and decreased activity (mild) and refusal of a feeding on Days 6 and 7 post-vaccination. His highest recorded temperature post-vaccination was 99.9°F rectally on the evening of vaccination. Eight days post-vaccination he developed an inability to hold up his head, loss of visual following which improved over time, and shaking or jitteriness in the legs. Several café au lait spots were noted on exam. An MRI showed left frontal horn enlargement and left frontal atrophy. An EEG was normal. Several months later, subtle left hemiparesis was noted and the subject was diagnosed with congenital encephalopathy by a neurologist. Information on a more specific diagnosis was not provided. Treatment included physical and occupational therapy. The event was reported as continuing.

6.1.5 Seizures

Since not all seizures were considered serious adverse events, the previous tables on serious adverse events do not include all seizures. Table 42 presents rates of all afebrile seizures, febrile seizures and possible seizures that occurred in the pivotal studies within 7 days and 30 days after any of Doses 1-3 and after Dose 4 of Pentacel or Control vaccines. In Table 42, Pentacel subjects were pooled across the pivotal studies. Seizures within 3 days post-vaccination were reported for two subjects who received Pentacel (one febrile seizure and one possible seizure), one subject who received HCPDT (afebrile seizure) and one subject who received DAPTACEL (afebrile seizure).

Table 42. Pivotal Studies: Incidence of seizures occurring within 30 days and within 7 days after any of Doses 1-3 and after Dose 4, Pentacel and Control vaccines, safety population

	Control								
	HCPDT + POLIOVAX + ActHIB[1] Doses 1-3 (any): N=1032 Dose 4: N=739			DAPTACEL + IPOL + ActHIB[2] Doses 1-3 (any): N=1455 DAPTACEL + ActHIB Dose 4: N=418[3]			Pooled Pentacel[4] Doses 1-3 (any): N=4197 Dose 4: N=5033		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Febrile Seizure									
0-30 Days									
Post Dose 1-3 (any)	1	0.1	(0.0, 0.5)	1	0.1	(0.0, 0.4)	0	0.0	(0.0, 0.1)
Post-Dose 4	2	0.3	(0.0, 1.0)	0	0.0	(0.0, 0.9)	9	0.2	(0.1, 0.3)
0-7 Days									
Post Dose 1-3 (any)	0	0.0	(0.0, 0.4)	0	0.0	(0.0, 0.3)	0	0.0	(0.0, 0.1)
Post-Dose 4	2	0.3	(0.0, 1.0)	0	0.0	(0.0, 0.9)	2	<0.1	(0.0, 0.1)
Afebrile Seizure									
0-30 Days									
Post Dose 1-3 (any)	1	0.1	(0.0, 0.5)	2	0.1	(0.0, 0.5)	3	0.1	(0.0, 0.2)
Post-Dose 4	1	0.1	(0.0, 0.8)	0	0.0	(0.0, 0.9)	4	0.1	(0.0, 0.2)
0-7 Days									
Post Dose 1-3 (any)	1	0.1	(0.0, 0.5)	1	0.1	(0.0, 0.4)	1	<0.1	(0.0, 0.1)
Post-Dose 4	0	0.0	(0.0, 0.5)	0	0.0	(0.0, 0.9)	0	0.0	(0.0, 0.1)
Possible Seizure[5]									
0-30 Days									
Post Dose 1-3 (any)	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.3)	3	0.1	(0.0, 0.2)
Post-Dose 4	0	0.0	(0.0, 0.5)	0	0.0	(0.0, 0.9)	0	0.0	(0.0, 0.1)
0-7 Days									
Post Dose 1-3 (any)	0	0.0	(0.0, 0.4)	0	0.0	(0.0, 0.3)	1	<0.1	(0.0, 0.1)
Post-Dose 4	0	0.0	(0.0, 0.5)	0	0.0	(0.0, 0.9)	0	0.0	(0.0, 0.1)

[1]HCPDT + POLIOVAX + ActHIB data are from Study 494-01.
[2]DAPTACEL + IPOL + ActHIB and DAPTACEL + ActHIB data are from Study P3T06.
[3]Includes only the study group that received DAPTACEL + ActHIB at 15-16 months of age, without other vaccines administered concomitantly.
[4]Pentacel subjects are pooled from Studies 494-01, 494-03, and P3T06 for Doses 1-3 and from Studies from Studies 494-01, 494-03, P3T06, and 5A9908 for Dose 4.
[5]Possible seizures: events that elicited the suspicion of seizures but that the Investigator did not feel confident making the diagnosis or reporting as seizures.
Subjects are classified by randomized treatment for Post Dose 1-3 (any).
Source: iss.pdf (version 3.0), Tables 9.119-9.121

For historical perspective, in the Sweden I Efficacy Trial, no seizures were reported among 2,587 subjects within 72 hours following any of doses 1-3 of DAPTACEL administered at 2, 4, and 6 months of age. Over the entire study period of the Sweden I Efficacy Trial from Dose 1 through 2 months post-dose 3, seizures were reported in 6 subjects who received DAPTACEL for an overall rate of 0.23%. (These data are from the DAPTACEL package insert.)

6.1.6 HHE and Hypotonia

In the pivotal studies analyses, HHE was defined as per published criteria from a U.S. Public Health Service workshop on HHE[4]:

> "An event of sudden onset occurring within 48 hours of immunization, with duration of the episode ranging from 1 minute to 48 hours, in children younger than 10 years of age. All of the following must be present: 1) limpness or hypotonia, 2) reduced responsiveness or hyporesponsiveness, and 3) pallor or cyanosis or failure to observe or to recall skin coloration. HHE is not considered to have occurred if there is a known cause of these signs (e.g., postictal), if urticaria is present during the event, if normal skin coloration is observed throughout the episode, or if the child is simply sleeping."

In the four pivotal studies, there were no reports of HHE in either Pentacel subjects (N=5,980) or Control subjects (N=2,486). One subject who received DAPTACEL reported an event that met the criteria for HHE except that it occurred 16 days post-vaccination.

In the pivotal studies, within seven days post-vaccination, four subjects who received Pentacel and one subject who received DAPTACEL experienced hypotonia that did not meet the criteria for HHE. All cases in Pentacel subjects occurred on the day of vaccination (one post-dose 1 and three post-dose 3). Specific information on duration of hypotonia in these subjects was not provided. The case following DAPTACEL occurred four days post-dose 1 and lasted two days. All cases were graded by the investigator as mild (easily tolerated) in severity. For the case in a DAPTACEL subject and one case following Pentacel, the outcome was reported as recovered without sequelae. For one case following Pentacel, a medical record review indicated that the hypotonia had resolved. For the other two cases following Pentacel, information on outcome was not available.

For historical perspective, as described previously, in the Sweden II Efficacy Trial, a higher than expected rate of HHE within 48 hours post-vaccination (14 per 10,000 subjects or 0.47 per 1000 doses) was observed following HCPDT, administered at 3, 5 and 12 months of age in most subjects. In that trial, HHE was prospectively defined as loss of muscle tone and a diminished or absent response to stimulation. In the Sweden I Efficacy Trial, among 2,587 subjects who received 7,703 doses of DAPTACEL at 2, 4 and 6 months of age, within 24 hours post-vaccination, there was one report of HHE. In the Sweden I Efficacy Trial HHE was not prospectively defined, but was described in the study report as an episode of pallor, lack of muscle tone and a diminished or absent response to stimulation.

6.1.7 Events of Possible Autoimmune Origin

In Study P3T06, the final safety follow-up 6 months following the fourth dose of Pentacel or Control vaccines was conducted, in part, to capture events of possible autoimmune origin that occurred since the previous contact (Day 60 post-dose 4). The follow-up was conducted by review of computerized medical records or telephone

interview. During interviews, parents were asked whether their child had been diagnosed as having low blood or platelet count, swelling or redness of the joints, asthma, diabetes, or autism. Table 43 presents a listing of reported events that were considered by the applicant to have a possible autoimmune origin.

Table 43. Study P3T06 Events of possible autoimmune origin occurring 61 to 180 days following the fourth dose of Pentacel or Control vaccines.

Subject	Vaccine Group[1]	Preferred Term	Latency[2] (Days)	Duration (Days)	Severity	Outcome
------	Pentacel	Serum Sickness	70	1	Severe	Recovered without sequelae
------	Pentacel	Asthma NOS	119	12	Severe	Recovered without sequelae
------	Pentacel	Leucopenia NOS	151	Not Reported	Mild	Ongoing at end of study
		Thrombocytopenia	151	Not Reported	Mild	Ongoing at end of study
------	Pentacel	Asthma Aggravated	169	30	Moderate	Recovered without sequelae
------	DAPTACEL	Bronchospasm NOS	127	17	Severe	Recovered without sequelae

[1]Data are presented for the Pentacel Group and for the group that received DAPTACEL + ActHIB without other concomitantly administered vaccines at 15-16 months of age.
[2] Days to onset after Dose 4.
NOS indicates not otherwise specified.
Source: questions1_133.pdf, page 141

6.1.8 Solicited Systemic and Local Adverse Events

In this document, the presentation of data on solicited adverse events will primarily focus on the two comparative pivotal studies, Study 494-01 and Study P3T06.

6.1.8.1 Fever

In the pivotal studies, antipyretics were not to be given routinely post-vaccination. Use of antipyretics within 7 days post-vaccination was to be recorded in the diary cards. In Studies 494-01 and P3T06, antipyretics were used within 3 days following Doses 1-3 of Pentacel or Control vaccines in approximately 40-50% of subjects and within 3 days following Dose 4 in approximately 33% of subjects. There were no notable differences between vaccine groups with regard to use of antipyretics.

In Study 494-01, parents and guardians were instructed to measure subjects' temperatures rectally following Doses 1-3 of Pentacel or Control vaccines and via the axillary route following the fourth dose. In Study P3T06, temperatures were to be measured rectally following all four doses of Pentacel or Control vaccines. Before the analyses of fever were conducted, it was determined that in some pivotal studies, nearly half of temperature measurements in infants were obtained by the axillary route, rather than rectally as specified in the protocols. The applicant proposed converting axillary temperature measurements to rectal equivalents by the addition of 0.6°C, a less conservative conversion than the addition of 1.0°C that CBER had historically accepted for clinical studies of some other pediatric vaccines. Because of the difficulty in determining a reliable standard number by which to convert axillary to rectal temperatures, as recently reviewed by the Brighton Collaboration,[5] CBER subsequently

recommended that the analyses of fever be conducted without conversion of axillary measurements and that information on routes of temperature measurement be presented in the BLA.

Table 44 presents the frequency by which temperature measurements were obtained rectally and axillary following Doses 1-3 and Dose 4 of Pentacel and Control vaccines in Studies 494-01 and P3T06. Overall, tympanic and oral routes and route unspecified (not shown in table) accounted for <2% of temperature measurements following Doses 1-3 and for approximately 4.5% of temperature measurements following Dose 4.

Table 44. Frequency by which temperature measurements were obtained rectally and axillary, Studies 494-01 and P3T06

	Study 494-01				Study P3T06			
	Pentacel		Control[1]		Pentacel		Control[1]	
	Doses 1-3	Dose 4	Doses 1-3	Dose 4	Doses 1-3	Dose 4	Doses 1-3	Dose 4
Number of temperature measurements	50107	12781	19712	4958	10698	3112	31920	2999
Route:	%	%	%	%	%	%	%	%
Axillary	45.3	70.3	45.6	66.7	46.3	63.0	45.1	61.0
Rectal	53.0	25.6	52.7	27.7	52.7	34.4	53.7	36.6

[1]The Control vaccines were HCPDT + POLIOVAX + ActHIB in Study 494-01 and DAPTACEL + IPOL + ActHIB (doses 1-3) and DAPTACEL + ActHIB (dose 4) in Study P3T06.
Source: 49401si.pdf page 123; 49401si.pdf page 116 ; p3t06si.pdf page 493; p3t06sii.pdf page 117.

Table 45 provides the rates of fever within 3 days following Pentacel or Control vaccines in Studies 494-01 and P3T06. Fever category is based on actual temperatures recorded without adjustment for route of measurement. In general, in both studies, the rate of fever tended to increase with successive doses from Dose 1 to Dose 3 following Pentacel or Control vaccines. While the data did not indicate an increase in rates of fever from Dose 3 to Dose 4, as noted above in Table 44, axillary rather than rectal temperature measurements were more frequent following the fourth dose than following the first three doses. In the pivotal studies, information on medical visits for fever and diagnostic studies performed to evaluate the cause of fever was not specifically solicited or systematically assessed.

Table 45. Studies 494-01 and P3T06: Number (percentage) of subjects with fever within 3 days after vaccination, safety population

Fever[1]	494-01		P3T06	
	Pentacel	HCPDT + POLIOVAX + ActHIB	Pentacel	DAPTACEL + IPOL + ActHIB (doses 1-3); DAPTACEL + ActHIB (dose 4)[2]
	(%)	(%)	(%)	(%)
Post-Dose 1	N=2296	N=920	N=466	N=1390
≥38.0°C	186 (8.1)	127 (13.8)	27 (5.8)	129 (9.3)
≥38.0°C - ≤38.5°C	151 (6.6)	106 (11.5)	21 (4.5)	107 (7.7)
>38.5°C - ≤39.5°C	27 (1.2)	20 (2.2)	4 (0.9)	21 (1.5)
>39.5°C	8 (0.3)	1 (0.1)	2 (0.4)	1 (0.1)
Post-Dose 2	N=2130	N=836	N=451	N=1346
≥38.0°C	304 (14.3)	131 (15.7)	49 (10.9)	217 (16.1)
≥38.0°C - ≤38.5°C	230 (10.8)	90 (10.8)	38 (8.4)	159 (11.8)
>38.5°C - ≤39.5°C	69 (3.2)	36 (4.3)	11 (2.4)	53 (3.9)
>39.5°C	5 (0.2)	5 (0.6)	0 (0.0)	5 (0.4)
Post-Dose 3	N=-1988	N=767	N=435	N=1301
≥38.0°C	383 (19.3)	158 (20.6)	71 (16.3)	205 (15.8)
≥38.0°C - ≤38.5°C	261 (13.1)	123 (16.0)	52 (12.0)	139 (10.7)
>38.5°C - ≤39.5°C	107 (5.4)	30 (3.9)	16 (3.7)	62 (4.8)
>39.5°C	15 (0.8)	5 (0.7)	3 (0.7)	4 (0.3)
Post-Dose 4	N=1630	N=634	N=389	N=379
≥38.0°C	174 (10.7)	83 (13.1)	52 (13.4)	33 (8.7)
≥38.0°C - ≤38.5°C	132 (8.1)	58 (9.1)	32 (8.2)	21 (5.5)
>38.5°C - ≤39.5°C	31 (1.9)	22 (3.5)	19 (4.9)	9 (2.4)
>39.5°C	11 (0.7)	3 (0.5)	1 (0.3)	3 (0.8)

[1]Fever is based upon actual temperatures recorded with no adjustment for route of measurement. See text and Table 44 for information on routes of temperature measurement.
[2]Includes only the study group that received DAPTACEL + ActHIB at 15-16 months of age, without other vaccines administered concomitantly.
Source: iss.pdf (version 1.0) Table 5.12

6.1.8.2 Other Solicited Systemic Adverse Events

Tables 46 and 47 present data on the occurrence of selected solicited systemic adverse events other than fever that occurred within 3 days following Pentacel or Control vaccines in Studies 494-01 and P3T06, respectively.

Table 46. Study 494-01: Frequency of selected solicited systemic adverse events within 3 days following Pentacel or Control vaccines

Adverse Event/Severity	Pentacel				HCPDT + POLIOVAX + ActHIB			
	Dose 1 N=2330-2332	Dose 2 N=2179-2180	Dose 3 N=2028-2030	Dose 4 N=1662	Dose 1 N=935	Dose 2 N=851	Dose 3 N=792	Dose 4 N=643
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Less Active[1]								
Any	1004 (43.1)	689 (31.6)	598 (29.5)	441 (26.5)	520 (55.6)	329 (38.7)	274 (34.6)	186 (28.9)
Mild	537 (23.0)	409 (18.8)	396 (19.5)	299 (18.0)	236 (25.2)	181 (21.3)	160 (20.2)	108 (16.8)
Moderate	434 (18.6)	254 (11.7)	180 (8.9)	121 (7.3)	246 (26.3)	135 (15.9)	104 (13.1)	72 (11.2)
Severe	33 (1.4)	26 (1.2)	22 (1.1)	21 (1.3)	38 (4.1)	13 (1.5)	10 (1.3)	6 (0.9)
Inconsolable Crying								
Any	1215 (52.1)	1045 (48.0)	858 (42.3)	600 (36.1)	612 (65.5)	448 (52.6)	364 (46.0)	259 (40.3)
<1 hour	850 (36.5)	767 (35.2)	628 (30.9)	446 (26.8)	402 (43.0)	308 (36.2)	244 (30.8)	186 (28.9)
1-3 hours	314 (13.5)	239 (11.0)	197 (9.7)	128 (7.7)	176 (18.8)	118 (13.9)	101 (12.8)	60 (9.3)
>3 hours	51 (2.2)	39 (1.8)	33 (1.6)	26 (1.6)	34 (3.6)	22 (2.6)	19 (2.4)	13 (2.0)
Fussiness (Irritability)								
Any	1590 (68.2)	1370 (62.8)	1204 (59.3)	886 (53.3)	714 (76.4)	574 (67.5)	532 (67.2)	380 (59.1)
<1 hour	915 (39.2)	814 (37.3)	721 (35.5)	541 (32.6)	367 (39.3)	320 (37.6)	316 (39.9)	235 (36.5)
1-3 hours	556 (23.8)	454 (20.8)	405 (20.0)	272 (16.4)	265 (28.3)	210 (24.7)	172 (21.7)	114 (17.7)
>3 hours	119 (5.1)	102 (4.7)	78 (3.8)	73 (4.4)	82 (8.8)	44 (5.2)	44 (5.6)	31 (4.8)
Anorexia[2]								
Any	538 (23.1)	428 (19.6)	436 (21.5)	436 (26.2)	295 (31.6)	205 (24.1)	200 (25.3)	193 (30.0)
Mild	417 (17.9)	313 (14.4)	320 (15.8)	306 (18.4)	212 (22.7)	150 (17.6)	136 (17.2)	130 (20.2)
Moderate	110 (4.7)	97 (4.5)	98 (4.8)	105 (6.3)	75 (8.0)	46 (5.4)	58 (7.3)	50 (7.8)
Severe	11 (0.5)	18 (0.8)	18 (0.9)	25 (1.5)	8 (0.9)	9 (1.1)	6 (0.8)	13 (2.0)

[1]Less Active: Mild = usual daily activity not affected; Moderate = interferes with and limits usual daily activity; Severe = disabling, not interested in usual daily activity.
[2]Anorexia: For Doses 1-3, Mild = Refuses 1 feed; Moderate = Refuses 2 feeds; Severe = Refuses 3 feeds. For Dose 4, Mild = Refuses 50% of a meal; Moderate = Skips a meal; Severe = Skips 2 or more meals.
Source: 49401si.pdf pages 125-127; 49401sii.pdf page 118; subject diary card (Amendment 20).

Table 47. Study P3T06: Frequency of selected solicited systemic adverse events within 3 days following Pentacel or Control vaccines

Adverse Event/Severity	Pentacel				DAPTACEL + IPOL + ActHIB for Doses 1-3 DAPTACEL + ActHIB for Dose 4[1]			
	Dose 1 N=467 n (%)	Dose 2 N=452 n (%)	Dose 3 N=440-441 n (%)	Dose 4 N=398 n (%)	Dose 1 N=1406 n (%)	Dose 2 N=1360 n (%)	Dose 3 N=1312 n (%)	Dose 4 N=381 n (%)
Less Active[2]								
Any	214 (45.8)	148 (32.7)	143 (32.5)	96 (24.1)	718 (51.1)	508 (37.4)	436 (33.2)	92 (24.1)
Mild	107 (22.9)	92 (20.4)	87 (19.8)	57 (14.3)	377 (26.8)	293 (21.5)	269 (20.5)	57 (15.0)
Moderate	97 (20.8)	53 (11.7)	55 (12.5)	29 (7.3)	324 (23.0)	196 (14.4)	159 (12.1)	34 (8.9)
Severe	10 (2.1)	3 (0.7)	1 (0.2)	10 (2.5)	17 (1.2)	19 (1.4)	8 (0.6)	1 (0.3)
Inconsolable Crying								
Any	277 (59.3)	225 (49.8)	208 (47.3)	143 (35.9)	822 (58.5)	699 (51.4)	629 (47.9)	138 (36.2)
<1 hour	185 (39.6)	177 (39.2)	148 (33.6)	96 (24.1)	592 (42.1)	482 (35.4)	469 (35.7)	98 (25.7)
1-3 hours	83 (17.8)	44 (9.7)	55 (12.5)	38 (9.5)	199 (14.2)	171 (12.6)	142 (10.8)	33 (8.7)
> 3 hours	9 (1.9)	4 (0.9)	5 (1.1)	9 (2.3)	31 (2.2)	46 (3.4)	18 (1.4)	7 (1.8)
Fussiness (Irritability)								
Any	359 (76.9)	322 (71.2)	299 (68.0)	213 (53.5)	1066 (75.8)	962 (70.7)	881 (67.1)	205 (53.8)
<1 hours	198 (42.4)	200 (44.2)	183 (41.6)	119 (29.9)	598 (42.5)	547 (40.2)	537 (40.9)	131 (34.4)
1-3 hours	141 (30.2)	104 (23.0)	94 (21.4)	73 (18.3)	389 (27.7)	340 (25.0)	288 (22.0)	57 (15.0)
>3 hours	20 (4.3)	18 (4.0)	22 (5.0)	21 (5.3)	79 (5.6)	75 (5.5)	56 (4.3)	17 (4.5)
Anorexia								
Any	119 (25.5)	88 (19.5)	103 (23.4)	93 (23.4)	341 (24.3)	328 (24.1)	311 (23.7)	95 (24.9)
Mild	94 (20.1)	66 (14.6)	73 (16.6)	56 (14.1)	259 (18.4)	248 (18.2)	219 (16.7)	63 (16.5)
Moderate	23 (4.9)	20 (4.4)	24 (5.5)	28 (7.0)	73 (5.2)	69 (5.1)	77 (5.9)	27 (7.1)
Severe	2 (0.4)	2 (0.4)	6 (1.4)	9 (2.3)	9 (0.6)	11 (0.8)	15 (1.1)	5 (1.3)

[1]Includes only the study group that received DAPTACEL + ActHIB at 15-16 months of age, without other vaccines administered concomitantly.
[2]Less Active: Mild: usual daily activity is not affected; Moderate: interferes with and limits usual daily activity; Severe: disabling, not interested in usual daily activity.
[3]Anorexia: For Doses 1-3, Mild = Refuses 1 feed; Moderate = Refuses 2 feeds; Severe = Refuses $\geq$3 feeds. For Dose 4, Mild = Refuses 50% of a meal; Moderate = Skips a meal; Severe = Skips 2 or more meals.
Source: p3t06si.pdf, pages 126-127 ; p3t06sii.pdf, page 119; subject diary card (Amendment 20).

6.1.8.3 Local Reactions

In the pivotal studies, solicited local reactions included injection site redness, swelling and tenderness following all doses of Pentacel or Control vaccines and increase in limb circumference following the fourth dose. Tables 48 and 49 present data on the occurrence of injection site redness, swelling and tenderness that occurred within 3 days following each dose of Pentacel or Control vaccines in Studies 494-01 and P3T06, respectively. For Control vaccines, data are presented for reactions that occurred at the DTaP (HCPDT in Study 494-01; DAPTACEL in Study P3T06) injection sites, as well as for reactions that occurred at any of the Control vaccine injection sites (HCPDT, POLIOVAX or ActHIB for Study 494-01; DAPTACEL, IPOL or ActHIB for Study P3T06). In general, in both studies, the frequency of solicited local reactions was higher following the fourth consecutive dose of either Pentacel or Control vaccines compared to the first three doses.

Table 48. Study 494-01 Solicited local reactions within 0-3 days after each dose of study vaccines: Pentacel injection site, HCPDT injection site, and any Control injection site

Event/ Severity	Pentacel Injection Site				Control: HCPDT Injection Site				Any Control Injection Site[1]: HCPDT, POLIOVAX, or ActHIB			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Redness	**N=2295**	**N=2146**	**N=1988**	**N=1616**	**N=927**	**N=849**	**N=787**	**N=632**	**N=928**	**N=850**	**N=787**	**N=632**
>5 mm	121 (5.3)	95 (4.4)	81 (4.1)	346 (21.4)	43 (4.6)	30 (3.5)	26 (3.3)	123 (19.5)	80 (8.6)	48 (5.6)	48 (6.1)	146 (23.1)
>5-<25 mm	84 (3.7)	83 (3.9)	67 (3.4)	173 (10.7)	33 (3.6)	26 (3.1)	22 (2.8)	66 (10.4)	62 (6.7)	43 (5.1)	42 (5.3)	80 (12.7)
25-50 mm	33 (1.4)	12 (0.6)	13 (0.7)	131 (8.1)	8 (0.9)	4 (0.5)	4 (0.5)	44 (7.0)	13 (1.4)	5 (0.6)	6 (0.8)	52 (8.2)
>50 mm	4 (0.2)	0 (0.0)	1 (0.1)	42 (2.6)	2 (0.2)	0 (0.0)	0 (0.0)	13 (2.1)	5 (0.5)	0 (0.0)	0 (0.0)	14 (2.2)
Swelling	**N=2295**	**N=2145**	**N=1987**	**N=1598**	**N=927**	**N=849**	**N=786**	**N=633**	**N=928**	**N=850**	**N=787**	**N=633**
>5 mm	111 (4.8)	69 (3.2)	43 (2.2)	187 (11.7)	47 (5.1)	25 (2.9)	14 (1.8)	72 (11.4)	66 (7.1)	34 (4.0)	26 (3.3)	88 (13.9)
>5-<25 mm	68 (3.0)	56 (2.6)	33 (1.7)	114 (7.1)	37 (4.0)	20 (2.4)	12 (1.5)	45 (7.1)	54 (5.8)	29 (3.4)	24 (3.0)	58 (9.2)
25-50 mm	35 (1.5)	12 (0.6)	10 (0.5)	52 (3.3)	10 (1.1)	4 (0.5)	2 (0.3)	19 (3.0)	11 (1.2)	4 (0.5)	2 (0.3)	22 (3.5)
>50 mm	8 (0.3)	1 (0.0)	0 (0.0)	21 (1.3)	0 (0.0)	1 (0.1)	0 (0.0)	8 (1.3)	1 (0.1)	1 (0.1)	0 (0.0)	8 (1.3)
Tenderness[2]	**N=2309**	**N=2155**	**N=2008**	**N=1642**	**N=932**	**N=853**	**N=790**	**N=639**	**N=933**	**N=854**	**N=791**	**N=640**
Any	918 (39.8)	723 (33.5)	669 (33.3)	754 (45.9)	482 (51.7)	357 (41.9)	330 (41.8)	319 (49.9)	546 (58.5)	386 (45.2)	370 (46.8)	360 (56.3)
Mild	561 (24.3)	532 (24.7)	517 (25.7)	523 (31.9)	252 (27.0)	232 (27.2)	226 (28.6)	223 (34.9)	268 (28.7)	244 (28.6)	240 (30.3)	225 (35.2)
Moderate	286 (12.4)	154 (7.1)	121 (6.0)	176 (10.7)	159 (17.1)	95 (11.1)	79 (10.0)	81 (12.7)	193 (20.7)	108 (12.6)	96 (12.1)	102 (15.9)
Severe	71 (3.1)	37 (1.7)	31 (1.5)	55 (3.3)	71 (7.6)	30 (3.5)	25 (3.2)	15 (2.3)	85 (9.1)	34 (4.0)	34 (4.3)	33 (5.2)

[1]Subjects are counted as having the specified reaction if it was present at any of the control injection sites. The highest severity/measurement of all injection sites is reported for each subject.
[2]Mild = subject whimpers when site is touched; Moderate = subject cries when site is touched; Severe = subject cries when leg or arm is moved.
Source: 49401si.pdf, pages 119-120; 49401sii.pdf, page 115

Table 49. Study P3T06 Solicited local reactions within 0-3 days after each dose of study vaccines: Pentacel injection site, DAPTACEL injection site, and any Control injection site

Reactions	Pentacel Injection Site				Control: DAPTACEL Injection Site				Any Control Injection Site[1] Doses 1-3: DAPTACEL, ActHIB , or IPOL Dose 4: DAPTACEL or ActHIB			
	Dose 1 n(%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4 n (%)	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4[2] n (%)	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4[2] n (%)
Redness	**N=467**	**N=451**	**N=438**	**N=392**	**N=1400**	**N=1358**	**N=1311**	**N=379**	**N=1401**	**N=1358**	**N=1311**	**N=379**
>5 mm	33 (7.1)	38 (8.4)	38 (8.7)	68 (17.3)	87 (6.2)	97 (7.1)	126 (9.6)	62 (16.4)	173 (12.3)	157 (11.6)	186 (14.2)	69 (18.2)
>5 - <25 mm	20 (4.3)	30 (6.7)	30 (6.8)	32 (8.2)	73 (5.2)	89 (6.6)	101 (7.7)	32 (8.4)	139 (9.9)	130 (9.6)	144 (11.0)	37 (9.8)
25 – 50 mm	10 (2.1)	7 (1.6)	8 (1.8)	27 (6.9)	9 (0.6)	7 (0.5)	25 (1.9)	21 (5.5)	26 (1.9)	25 (1.8)	42 (3.2)	23 (6.1)
>50 mm	3 (0.6)	1 (0.2)	0 (0.0)	9 (2.3)	5 (0.4)	1 (0.1)	0 (0.0)	9 (2.4)	8 (0.6)	2 (0.1)	0 (0.0)	9 (2.4)
Swelling	**N=467**	**N=451**	**N=439**	**N=392**	**N=1400**	**N=1358**	**N=1311**	**N=378**	**N=1401**	**N=1358**	**N=1311**	**N=378**
>5 mm	35 (7.5)	33 (7.3)	22 (5.0)	38 (9.7)	56 (4.0)	54 (4.0)	85 (6.5)	39 (10.3)	84 (6.0)	71 (5.2)	102 (7.8)	44 (11.6)
>5 - <25 mm	21 (4.5)	24 (5.3)	15 (3.4)	23 (5.9)	33 (2.4)	45 (3.3)	71 (5.4)	24 (6.3)	50 (3.6)	58 (4.3)	85 (6.5)	29 (7.7)
25 – 50 mm	10 (2.1)	9 (2.0)	7 (1.6)	12 (3.1)	17 (1.2)	8 (0.6)	13 (1.0)	10 (2.6)	28 (2.0)	12 (0.9)	16 (1.2)	10 (2.6)
>50 mm	4 (0.9)	0 (0.0)	0 (0.0)	3 (0.8)	6 (0.4)	1 (0.1)	1 (0.1)	5 (1.3)	6 (0.4)	1 (0.1)	1 (0.1)	5 (1.3)
Tenderness[3]	**N=465**	**N=451**	**N=440**	**N=396**	**N=1404**	**N=1359**	**N=1312**	**N=380**	**N=1405**	**N=1359**	**N=1312**	**N=380**
Any	221 (47.5)	177 (39.2)	188 (42.7)	222 (56.1)	685 (48.8)	519 (38.2)	537 (40.9)	194 (51.1)	766 (54.5)	588 (43.3)	601 (45.8)	204 (53.7)
Mild	130 (28.0)	129 (28.6)	137 (31.1)	156 (39.4)	395 (28.1)	353 (26.0)	376 (28.7)	134 (35.3)	422 (30.0)	399 (29.4)	416 (31.7)	138 (36.3)
Moderate	66 (14.2)	41 (9.1)	45 (10.2)	53 (13.4)	232 (16.5)	135 (9.9)	139 (10.6)	51 (13.4)	274 (19.5)	150 (11.0)	156 (11.9)	55 (14.5)
Severe	25 (5.4)	7 (1.6)	6 (1.4)	13 (3.3)	58 (4.1)	31 (2.3)	22 (1.7)	9 (2.4)	70 (5.0)	39 (2.9)	29 (2.2)	11 (2.9)

[1]Subjects are counted as having the specified reaction if it was present at any of the control injection sites. The highest severity/measurement of all injection sites is reported for each subject.
[2]Includes only the study group that received DAPTACEL + ActHIB at 15-16 months of age, without other vaccines administered concomitantly.
[3]Mild: subject whimpers when site is touched; Moderate: subject cries when site is touched; Severe: subject cries when leg or arm is moved.
Source: p3t06si.pdf, page 114, p3t06sii.pdf, pages 113, 116, and 183

Extensive local reactions, including entire proximal limb swelling, have been reported following DTaP vaccines, particularly the fourth and fifth consecutive doses. In the pivotal studies of Pentacel, information on the occurrence and characteristics of entire proximal limb swelling was not specifically solicited. Fourteen subjects reported unsolicited adverse events or had notes in the case report form that potentially may have represented entire proximal limb swelling involving one or more injected limbs. However, the available information is difficult to interpret because in some cases the vaccination site involved was not specified and for most cases, the reported comments or terms used (e.g., "swelling", "arm enlargement") were non-specific with regard to the size and extent of the swelling. In at least two subjects, the description of the event was indicative of entire proximal limb swelling: "whole thigh swelled" was noted for one subject who received Pentacel and Prevnar in the right thigh (dose number not specified); and "patients legs are swollen more than twice the normal size" was noted for one subject who received the first dose of Pentacel in the left thigh and the first dose of Prevnar in the right thigh.

Although information on entire proximal limb swelling was not solicited, in each of the Pentacel pivotal studies, the circumference of the Pentacel-, HCPDT- (Study 494-01), or DAPTACEL- (Study P3T06) injected arms was monitored daily by parents for seven days following the fourth dose. In each of the studies, the fourth dose of Pentacel, HCPDT (Study 494-01) or DAPTACEL (Study P3T06) was injected in the left deltoid. No other concomitantly administered vaccines were specified to be given in the left deltoid. In Study P3T06, the fourth dose of ActHIB was administered in the right deltoid and the circumference of the right upper arm also was monitored. Data on increase in arm circumference following the fourth dose of Pentacel or Control vaccines from all four pivotal studies are presented in Table 50.

As shown in Table 50, across all pivotal studies, a limb circumference increase of >40 mm within 3 days following the fourth dose was reported in 25 Pentacel subjects (N=4,534), no HCPDT subjects (N=605) and 4 DAPTACEL + ActHIB subjects (N=376). For the 25 Pentacel subjects with an increase in limb circumference >40 mm, the maximum reported percent increase over baseline measurement was between 20%-49% in 23 subjects and was 111% and 133%, respectively, in two subjects. For three DAPTACEL + ActHIB subjects for whom information was available, the largest percent increase over baseline measurement for the DAPTACEL injected arm (2 subjects) was 29% and 33%, respectively and for the ActHIB injected arm (1 subject) was 30%. For one DAPTACEL + ActHIB subject who reported a >40 mm increase in both the DAPTACEL and ActHIB injected arms, there was an apparent error in the baseline measurement (reported as 10 mm) so that the percent increase over baseline could not be calculated.

Table 50. Pivotal studies: Increase in upper arm circumference within three days following the fourth dose of Pentacel or Control vaccines

	494-01		494-03	P3T06			5A9908	All Studies Combined
	Pentacel-injected arm N=1563	HCPDT-injected arm N=605	Pentacel-injected arm N=870	Pentacel-injected arm N=387	DAPTACEL-injected arm[1] N=376	DAPTACEL- or ActHIB-injected arm[1] N=376	Pentacel-injected arm N=1714	Pentacel-injected arm N=4534
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Increase in Arm Circumference[2]								
>5 mm	396 (25.3)	131 (21.7)	242 (27.8)	130 (33.6)	115 (30.6)	141 (37.5)	647 (37.7)	1415 (31.2)
>20 mm	74 (4.7)	19 (3.1)	54 (6.2)	18 (4.7)	26 (6.9)	35 (9.3)	148 (8.6)	294 (6.5)
>40 mm	3 (0.2)	0 (0.0)	2 (0.2)	2 (0.5)	3 (0.8)	4 (1.1)	18 (1.1)	25 (0.6)

[1]Includes only the study group that received DAPTACEL + ActHIB at 15-16 months of age, without other vaccines administered concomitantly.
[2]Increase in arm circumference was calculated by subtracting the baseline circumference (Day 0) of the pre-vaccination injected arm from the circumference of the injected arm post-vaccination. The circumference was measured at the level of the axilla.
Source: iss.pdf (version 3.0) Table 5.16, page 94

6.2 Supportive Safety Data

6.2.1 Safety of DAPTACEL: Sweden I Efficacy Trial

The BLA contains supportive safety data on approximately 2,500 infants who received three doses of DAPTACEL in the Sweden I Efficacy Trial. These data were pivotal safety data for the licensure of DAPTACEL in the U.S. and will not be presented in this document.

6.2.2 Safety of HCPDT: Sweden II Efficacy Trial

The BLA contains supportive safety data on monitored serious adverse events in approximately 20,000 subjects who received three doses of HCPDT in the Sweden II Efficacy Trial. These data were summarized previously in Section 2.2.

6.2.3 Historical non-IND Studies of Pentacel

The BLA contains safety synopses from eight historical non-IND studies conducted in Canada, Israel, or Mexico. Overall, approximately 2,600 subjects received either a single dose of Pentacel following three previous doses of whole-cell DTP (approximately 1000 subjects) or three or four consecutive doses of Pentacel (approximately 1600 subjects). None of the studies included a control group that received U.S.-licensed vaccines. In all but one study, no other vaccines were administered concomitantly with Pentacel. In Study PNF35, subjects received oral poliovirus vaccine concomitantly with the second and third doses of Pentacel, and one group (half of subjects) received a non-U.S. licensed 11-valent pneumococcal conjugate vaccine concomitantly with each dose of Pentacel.

Across these eight historical studies, there was one death reported following Pentacel - a case of SIDS approximately 40 days post-dose 2 in a 23-week old infant.

While the definition for a serious adverse event varied across studies, it generally included deaths, life-threatening experiences, events that resulted in a permanent or substantial disability, and events that resulted in or prolonged hospitalization. Serious adverse events were monitored for at least 30 days following vaccination. In most studies, monitoring included phone calls within 72 hours post-vaccination and in some cases, phone calls or personal interviews at 7 days and/or 30 days post-vaccination. Parents were also queried about serious adverse events at each dose and were to report such events anytime during the study. Table 51 provides a summary of serious adverse events within 30 days following Pentacel in each of these historical studies.

Table 51. Historical non-IND studies: Serious adverse events within 30 days following Pentacel

Protocol Number	Country	Study Period	Pentacel Group (ITT) N	Pentacel Schedule	Serious Adverse Events
PERTB9402	Canada	1/95-5/95	33	1 dose at 18-19 mo.[1]	None
PERTB9501	Canada	3/95-9/95	295	1 dose at 18-19 mo.[1]	2 febrile seizures (Days 7 and 16), 2 circumcisions, 1 each of lung infection, ear infection, hospitalization (unknown reason)
PERTB9502	Canada	3/95-3/97	335	2, 4, 6, 18-19 mo.	1 each of febrile seizure (Day 0), afebrile seizure (Day 2), asthma, craniopharyngioma, parapertussis, myringotomy, adenoidectomy
PERTB9505	Canada	1/96-5/96	668	1 dose at 16-20 mo.[1]	4 pneumonias, 1 each of febrile seizure (Day 24), otitis media, myringotomy, pertussis, asthma
PERTB9506	Canada	1/96-10/96	661	2, 4, 6 mo.	2 HHEs (both on Day 0), 1 seizure (Day 0), 5 bronchiolitis, 2 apnea episodes in same subject (Days 4 and 18), 1 each of circumcision, anal fistula and excision, upper respiratory tract infection, RSV pneumonia, colitis, otitis media, pyelonephritis, ear operation, nasolacrimal duct repair
PERTB9601	Canada	8/96-7/98	118	2, 4, 6, and 18 mo.	3 bronchiolitis, 1 each of allergic reaction (Day 12), gastroesophageal reflux with apnea and cyanosis, urinary tract infection/rule out sepsis, otitis media
5A9703	Mexico	1/97-4/99	110	2, 4, 6, and 18 mo.	"paroxystic movements"/convulsions (Day 19), pertussis syndrome (age 10 wks), severe cough with cyanosis and vomiting (age 10 wks), 2 gastroenteritis, 2 bronchopenumonia, 1 dehydration
PNF35	Israel	1/00-2/02	470	2, 4, and 12 mo.; (DTaP/PRP-T[2] at 6 mo.)	6 bronchiolitis, 2 gastroenteritis, 2 pneumonia, 2 otitis media, 1 each of asthma aggravated, respiratory distress, stridor, wheezing, pneumonitis, pyrexia (Day 0), irritability (Day 0), convulsions (Day 7), herpangia, gastroesophageal reflux disease, inguinal hernia, animal bite, skull fracture, arthritis, hypocalcemia

[1]Subjects previously received DTwP, Hib conjugate vaccine, and IPV or OPV
[2]DTaP/PRP-T not licensed in the U.S.
Source: pb9402.pdf, pages 1-63; pb9501.pdf, pages 1-111; pb9502infantseries.pdf, pages 1-210; pb95024thdose.pdf, pages 1-182; pb9505.pdf, pages 1-164; pb9506.pdf, pages 1-283; pb9601infantseries.pdf, pages 1-308; pb96014thdose.pdf, pages 1-188; 5a9703infantseries.pdf, pages 1-173; 5a97034thdose.pdf, pages 1-148; pnf35.pdf, pages 1-404; questions1_133.pdf pages 159, 479, and 480.

6.2.4 Post-Marketing Safety Data

Sanofi Pasteur collects pharmacovigilance data for adverse events following Pentacel from spontaneous reports, health authority reports, literature publications, and clinical trials cases. The applicant provided a review of cases received from 5/1/97 through 4/30/06 that represent spontaneous reports, health authority reports and literature data. During this period, in which a total of approximately 13.5 million doses of Pentacel were distributed in other countries (approximately 12.5 million in Canada), Sanofi Pasteur received 245 new medically confirmed adverse event reports after Pentacel administration: 237 spontaneous reports from health care professionals and health authorities and 8 from literature sources. In addition, there were 43 spontaneous reports from consumers. The most frequently reported (N $\geq$3) adverse events, both serious and non-serious, from these sources are presented in Table 52.

Table 52. Post-marketing experience May 1997 through April 2006: most frequently reported (N$\geq$3) adverse events following Pentacel

System Organ Class[1] / Adverse Event Preferred Term	Number of Adverse Events[2]
Cardiac disorders	
Cyanosis	12
Eye disorders	
Eye rolling	4
Gastrointestinal disorders	
Vomiting	24
Diarrhea	7
General disorders and administration site conditions	
Injection site reaction	65
Pyrexia	64
Injection site inflammation	35
Irritability	31
Injection site mass	16
Injection site abscess sterile	9
Edema	5
Edema peripheral	3
Therapeutic response decreased or vaccination failure	6
Injection site pain	5
Sudden infant death syndrome	5
Sudden death	4
Infections and infestations	
Injection site abscess	13
Meningitis	3
Rhinitis	3
Viral infection	3
Metabolism and nutrition disorders	
Decreased appetite	3
Nervous system disorders	
Convulsion[3]	19
Somnolence	14
Hypotonic-hyporesponsive episode	9[4]
Hypotonia	8[4]
Lethargy	6
Encephalopathy	3[5]
Depressed level of consciousness	3

Psychiatric disorders	
Crying	51
Screaming	8
Apathy	3
Respiratory, thoracic and mediastinal disorders	
Cough	4
Apnea	3
Skin and subcutaneous tissue disorders	
Urticaria	25
Rash	20
Rash maculo-papular	4
Skin discoloration	3
Vascular disorders	
Pallor	9

[1] MedDRA coding dictionary version 9.0
[2] Includes spontaneous reports (medically confirmed and consumer cases), health authority reports and literature reports.
[3] Includes MedDRA Preferred Terms of Convulsion, Febrile Convulsion, Status Epilepticus and Convulsion Local
[4] Three events coded as hypotonia that met the criteria for HHE were not counted as HHE in the table.
[5] A fourth case of encephalopathy from a literature report was coded in the table as Convulsions.
Source: postmarketing_clean.pdf, 1-2

Post-marketing reports of deaths, encephalopathy, decreased level of consciousness, seizures, HHE, therapeutic response decreased and vaccination failure will be described in more detail below.

6.2.4.1 Deaths

Between 5/1/97 and 4/30/06, 14 deaths following Pentacel were identified through spontaneous reports or published literature. Information on these deaths is provided in Table 53.

Table 53. Summary of information on deaths following Pentacel identified by Sanofi Pasteur through spontaneous reports or literature reports, May 1, 1997-April 30, 2006

Age at Death	Interval Since Last Dose of Pentacel	Co-administered Vaccines	Preferred Term of Adverse Events	Selected Additional Information
2 mo	1 day	None reported	SIDS	--
2 mo	2 days	None reported	SIDS	--
2 mo	7 days	Prevnar	SIDS Vomiting	--
2 mo	8 days	Prevnar	SIDS Vomiting	--
2 mo	13 days	None reported	SIDS Vomiting	--
4 mo	24 hours	Meningococcal conjugate C	Sudden death	Died during nap, positioned prone. Cause of death not determined. Autopsy report not provided.
2 mo	8 days	None reported	Sudden death	Autopsy not performed.
36 mo	11 days	Hepatitis B Meningococcal MMR	Sudden death	Came to Canada from an orphanage in Haiti. Sickle-cell disease carrier with high fever, receiving antibiotics. Left home alone during the day. Sudden Unexpected Death per autopsy report.
19 mo	25 days	None reported	Death Vomiting	Did not wake from sleep. Per parental report, autopsy showed "slight swelling of the brain, maybe related to a virus".
2 mo	9 hours	None reported	Streptococcal sepsis Sudden death Irritability	Infant previously had been hospitalized for 3 weeks due to prematurity (32 weeks gestation). Sudden infant death due to invasive Group B streptococcal infection.
2 mo	1 day[1]	None reported	Death Congenital anomaly Tachycardia	Autopsy findings included cardiac myopathy, cardiomegaly, endocardial fibroelastosis, pericardial effusion, pulmonary/hepatic congestion, ascites.
5 mo	3 months	None reported	Pneumonia Meningitis	Hib isolated from blood and CSF. Had received 1 dose of Pentacel.
3 mo	30 days	None reported	Meningitis Therapeutic response decreased	Severe Hib infection with shock and meningitis. Had received 1 dose of Pentacel.
20 mo	Not reported	None reported	Convulsions	Non-febrile seizure. No information available regarding autopsy.

[1]This infant was admitted to the hospital one day post-vaccination and died 2 days later.
Source: postmarketing_clean.pdf, Table 5.31

6.2.4.2 Encephalopathy

Table 52 includes three events following post-marketing use of Pentacel that were coded as encephalopathy. A fourth case of encephalopathy identified in a literature report post-marketing was coded as Convulsions (status epilepticus) in Table 52. A fifth post-marketing case of encephalopathy, identified in a post-marketing study was not included in Table 52, but was presented in the BLA. This latter case was identified in a non-IND post-marketing retrospective safety survey (Study M5A08) conducted between 9/03 and 4/04 among 3,214 children in British Columbia. In this survey, during telephone interviews, parents were asked about adverse events that their child had experienced during the six months following the last dose of Pentacel.

For these five cases of encephalopathy identified during post-marketing use of Pentacel, the time to onset of symptoms since the last dose of Pentacel was 1 day, 5 days, 7 days, 10 days, and 24 days, respectively. Available information on each of these cases is provided below.

> Case 1 occurred in an 18 month old child, with onset one day following Pentacel. No other co-administered vaccines were reported. Viral infection, fever, coryza, focal seizures, status epilepticus, and cough were noted. Cranial CT showed diffuse cerebral edema. Influenza A virus was isolated from a nasopharyngeal aspirate. Outcome was reported as improving right-sided weakness.
>
> Case 2 occurred in a 4 month old infant 5 days following the second dose of Pentacel. No other co-administered vaccines were reported. Fever, vomiting, prominent bloody diarrhea, coryza, status epilepticus, coma, elevated AST (335 units/l) and elevated ALT (351 units/l) were noted. Cranial CT showed diffuse brain edema and laminar necrosis. MRI indicated cortical bleeding. CSF was reportedly normal. Viral and bacterial cultures of CSF and stool, viral cultures of the upper respiratory tract, CSF PCR for HSV, enterovirus and *Mycoplasma* were negative. Outcome was reported as improved, with ongoing need for anticonvulsants. The final diagnosis was probable gastrointestinal infection. *(Note: This case was coded as convulsions in Table 52. Clinical information was obtained, in part, from a literature report cited by the applicant.)*
>
> Case 3 occurred in a 2 month old infant, with onset 7 days following Pentacel. No other co-administered vaccines were reported. Viral infection, fever, abnormal crying, cough, apnea, and seizures were noted. Cranial CT and cerebrospinal fluid were normal. Influenza A virus was isolated from a nasopharyngeal aspirate. Outcome was reported as normal by day 7 after onset.
>
> Case 4 occurred in an 18 month old Caucasian female who developed loss of coordination, lymphadenopathy, conjunctivitis, puffiness, dry lips, and fever 10 days following Pentacel and MMR. She was hospitalized for atypical Kawasaki syndrome with acute disseminating encephalopathy and hypotonia. She improved

after treatment with intravenous immunoglobulin, clindamycin and acetylsalicylic acid. *[Note: This case was identified in post-marketing Study M5A08.]*

Case 5 occurred in a 4 month old male with onset of symptoms 24 days following the second dose of Pentacel. No other co-administered vaccines were reported. Until that time, the parents felt that the infant's development had been normal. Noted adverse events included convulsions, infantile spasms, pneumonia, hepatomegaly, splenomegaly, cyanosis, encephalopathy and developmental delay. Following parental decision to stop therapy, the seizures subsided, with clusters replaced by individual seizures. The patient underwent several hospitalizations due to complications.

The applicant cited a publication on the risk of encephalopathy related to pertussis vaccination based on a Canadian system of active surveillance for post-immunization adverse events (the Immunization Monitoring Program, Active or IMPACT).[6] (See Appendix 1.) Participating IMPACT hospitals encompass nearly 90% of Canada's tertiary care pediatric beds and serve a population base of 3 million children, approximately one-half of Canada's population younger than 15 years of age. At participating hospitals, all admissions for acute neurological illness are screened for recent immunization. From 1993-1997 Canadian children received an estimated 6 million doses of vaccines containing whole cell pertussis; from 1997-2002, they received an estimated 7 million doses containing acellular pertussis vaccine (Pentacel or DTaP-IPV manufactured by Sanofi Pasteur Limited). From 1993-2002, there were 7 cases of encephalopathy or encephalitis with onset within 7 days after receiving a pertussis-containing vaccine, 3 after whole-cell and 4 after acellular vaccine (3 after Pentacel and 1 after DTaP-IPV). Direct evidence of brain infection with herpes simplex virus was obtained in 1 case following whole-cell pertussis vaccine. In 3 children influenza A virus was isolated from the upper airway (1 following whole-cell pertussis vaccine; 2 following Pentacel). In 1 child who had received whole-cell pertussis vaccine, parainfluenza virus was isolated from the upper airway. One case of encephalopathy was associated with presumed gastrointestinal infection in a subject who had received Pentacel. One case following DTaP-IPV resulted from hypoglycemia secondary to adrenal insufficiency. The authors concluded that conservative estimates of any risk of encephalopathy or encephalitis attributable to vaccination in the population under surveillance by IMPACT were <1 per 3 million doses of whole cell pertussis vaccine and <1 per 3.5 million doses of acellular pertussis vaccine. The 3 cases of encephalopathy following Pentacel that were reported in this IMPACT publication were among the 5 cases identified by Sanofi Pasteur during post-marketing use of Pentacel and described earlier in this section.

6.2.4.3 Decreased Level of Consciousness

The following clinical information was provided for cases of decreased level of consciousness following Pentacel that were identified through post-marketing reports (Table 52).

- A 6 month old female experienced persistent crying, fever of 39.7°C and a fixed gaze 2-12 hours after the third dose of Pentacel. Symptoms resolved within 12 hours.

- A 2 month old infant was difficult to arouse 5 days after the first dose of Pentacel. The event resolved by the following day.

- A 5 month old male appeared absent and was staring 26 hours after the second dose of Pentacel. Seven to 10 days later, he had an unspecified seizure. Intermittent staring episodes continued. Results of diagnostic tests for infectious causes, muscle biopsy, EEG, MRI, and CT scans were not provided. Despite anticonvulsants, vitamin B6 and diet, he continued having 10-15 seizures daily for approximately 2 years. Reportedly the seizures resolved with homeopathic treatment. He also had developmental delay which improved.

6.2.4.4 Seizures

Of the 19 seizures reported post-marketing, 13 were medically confirmed events (in 11 children). Among the 13 medically confirmed seizures, 8 were not otherwise specified, 2 were febrile seizures, 2 were cases of status epilepticus, and 1 was reported as "convulsions local". The interval since the last dose of Pentacel ranged from 1 hour to 24 days, with 8 of the medically confirmed events occurring within 7 days after vaccination.

The applicant summarized IMPACT data on seizures.[7] (See Appendix 2.) An overview of the IMPACT system was previously provided in Section 6.2.4.2. Based on IMPACT data, the average number of reports per month of febrile seizures within 72 hours after a pertussis-containing vaccine decreased from 1.21 for 1995–1996 (whole-cell pertussis vaccine era) to 0.25 for 1998–2001 (use of Pentacel in all Canadian provinces) (P= .0000084), a 79% decrease between periods. The average number of reports per month of afebrile seizures within 72 hours after a pertussis-containing vaccine decreased from 0.46 for 1995–1996 to 0.19 for 1998–2001 (P=.053).

6.2.4.5 HHE

The definition of HHE used in the sponsor's report of post-marketing adverse events following Pentacel was the same as that used in the pivotal studies of Pentacel. A total of 12 post-marketing adverse event reports met the criteria for HHE. In Table 52, nine of these are coded as HHE and three as hypotonia.

The applicant cited a publication from IMPACT that found a 60-67% reduction (depending on case definition) in HHE that resulted in emergency department visits or hospitalization within 48 hours following pertussis-containing vaccines upon adoption of Pentacel in Canada in place of whole-cell pertussis vaccine.[7] (See Appendix 2.) An overview of the IMPACT system was previously provided in Section 6.2.4.2.

6.2.4.6 Therapeutic Response Decreased and Vaccination Failure

In Table 52, there were six post-marketing reports coded as "Therapeutic Response Decreased" or "Vaccination Failure". These terms were used interchangeably to capture reports of biologically confirmed infection in patients who had received 3 doses of Pentacel (or another acellular pertussis combination vaccine) at appropriate ages. All six reports of "Therapeutic Response Decreased" or "Vaccination Failure" included in Table 52 represented cases of invasive Hib disease, although not all cases had received 3 doses of Pentacel (or another acellular pertussis combination vaccine). Information on Hib vaccination history for these six cases of invasive Hib disease is provided in Table 54.

Table 54. Summary of post-marketing reports of adverse events coded as "Therapeutic Response Decreased" or "Vaccination Failure"

Age at time of event	Event	Hib Vaccination History
15 months	Hib meningitis	DTwP-IPV/PRP-T at 2 and 4 mo., Pentacel at 6 mo.
16 months	Hib septic arthritis	Pentacel at 2, 4, and 6 mo.
3 months	Hib meningitis, shock, death	Pentacel at 2 mo.
12 months	fever and Hib bacteremia	Pentacel at 2, 4, and 8 mo.
19 months	Hib meningitis	DTaP-IPV-Hib-HepB (Hexavac) at ~3.5 mo.; DTaP-IPV-Hib (Pentacel or Poliacel) at ~6.5 mo; DTaP-IPV-Hib-HepB (Hexavac) at ~9 mo.
6 years	Pneumonia Blood culture positive for Hib	Pentacel at 2, 4, and 5 mo; Investigational PRP-T-HepB-DTaP-IPV at 16 mo.

Source: questions1_133, page 184-185; response_fax09nov06.pdf, page 21

7 Epidemiology of Invasive Hib Disease and Pertussis in Canada

The following sections will provide an overview of data on the epidemiology of invasive Hib disease and pertussis in Canada that were included in the Pentacel BLA.

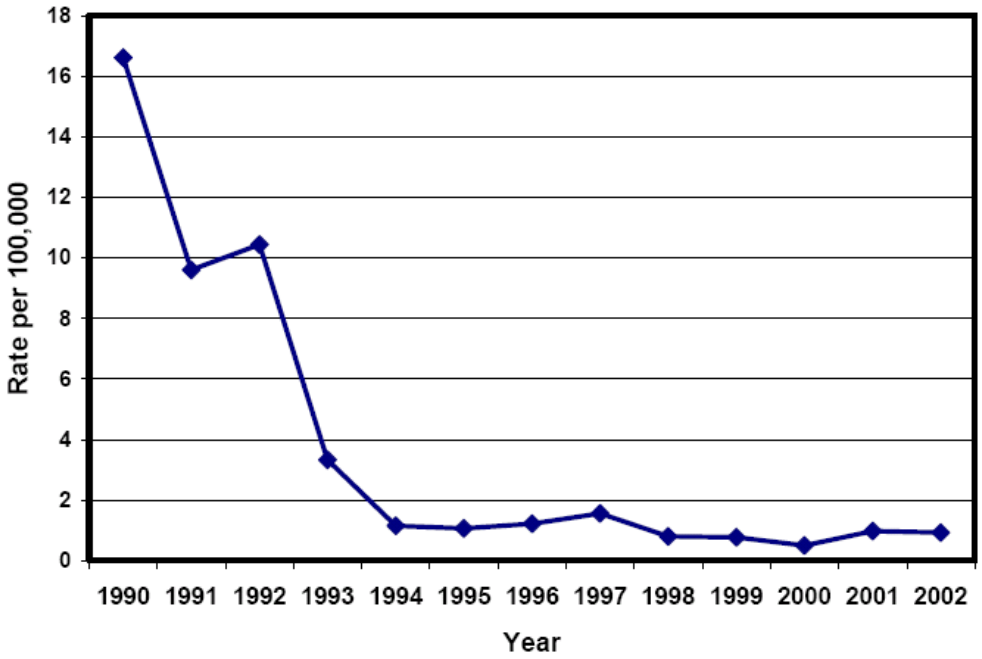
Some of the available immunogenicity data on concomitant administration of Pentacel and Prevnar that were presented in Section 5.2.2.4 suggest the possibility that Prevnar may interfere with the immune response to some of the pertussis antigens. As noted in the Prevnar package insert, historically, some inconsistent differences in responses to acellular pertussis antigens also have been observed when Prevnar was administered concomitantly with a DTaP vaccine manufactured by Wyeth Pharmaceuticals Inc. Therefore, it is of note that the available Canadian surveillance data on pertussis (as well as on invasive Hib disease) obtained after the introduction of Pentacel are largely from a period prior to the widespread use of Prevnar in Canada, and thus, generally do not reflect concomitant use of Pentacel with Prevnar. Prevnar was licensed in Canada in July 2001 but initially was administered to a limited number of children. The first two provinces to add Prevnar to the routine immunization schedule were Alberta and Nunavut in the summer and fall of 2002, respectively, followed by British Columbia in September 2003. Most other provinces did not begin using Prevnar routinely until late 2004 or in 2005.

7.1 Invasive Hib Disease

Prior to the use of Hib conjugate vaccines, the incidence of invasive Hib disease in Canada was similar to rates reported in the U.S. Hib conjugate vaccines were licensed for use in infants in Canada in 1992. Beginning in the mid-1990s, all Canadian provinces used DTwP-IPV//PRP-T manufactured by Sanofi Pasteur Limited. In 1997-1998, all provinces transitioned to Pentacel.

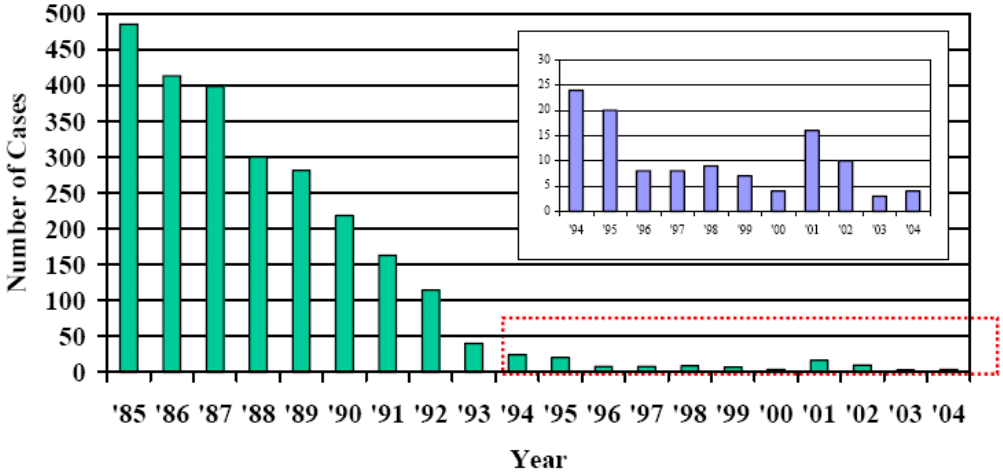
In Canada, cases of invasive Hib disease are reported for children aged <5 years with a positive culture for *H. influenzae* from a normally sterile body site (e.g., blood or CSF) or demonstration of Hib antigen in CSF. Hospitals and clinics report cases to the provincial health authorities and, in turn, to Health Canada. *H. influenzae* isolates are serotyped at provincial health authority laboratories. Figure 1 shows National Notifiable Disease data from Health Canada on the incidence rates of invasive Hib disease in children aged <5 years during 1990-2002.

Figure 1. Incidence of invasive Hib disease in children aged <5 years, Canada, 1990-2002



Since 1992, invasive Hib infections also have been monitored in IMPACT centers. An overview of the IMPACT system was previously provided in Section 6.2.4.2. At each participating IMPACT center, a nurse performs active surveillance for invasive Hib infections by monitoring daily hospital admissions, working with the microbiology laboratory and reviewing charts with specific discharge diagnoses. The numbers of cases of invasive Hib disease among children of all ages identified by IMPACT for the period 1985-2004 are shown in Figure 2. Data prior to 1992 were obtained retrospectively.

Figure 2. Invasive Hib disease among children admitted to hospitals in the IMPACT surveillance network, 1985-2004



The BLA contains a summary of the 29 cases of invasive Hib disease reported during 2001-2003 among children admitted to IMPACT hospitals. The summary was based on a literature publication[8] which is provided as Appendix 3. According to the applicant, of the 29 cases, 24 were in children <5 years of age; 15 in 2001, 8 in 2002 and 1 in 2003. Eleven children were aged <6 months, too young to have received three doses of Pentacel. Of the remaining 18 cases, all but 2 were incompletely immunized or had chronic underlying medical conditions including hypo- or dysgammaglobulinemia, nephrotic syndrome (chronic treatment with systemic steroids), HIV, prematurity, ventriculoperitoneal shunt, and transnasal hypophysectomy. Seven of the 29 children resided in the Yukon Territory, Nunavut or the Northwest Territories. However, information was not provided on whether any of these children were of Native Canadian Indian ancestry, and therefore at increased risk for developing invasive Hib disease.

In 2004, four cases of invasive Hib disease occurred in children aged <5 years in IMPACT facilities. One child each had previously received zero, one, two, or three doses of Pentacel. The child who had received three doses was diagnosed with an immunodeficiency.

To examine the impact of Prevnar on the clinical effectiveness of Pentacel against invasive Hib disease, the applicant presented incidence data in children <5 years of age in Alberta, where Prevnar was integrated into the standard immunization program as a four-dose series (at 2, 4, 6, and 18 months of age) in July 2002. In the first year after introduction, overall vaccination coverage rates in Alberta for three doses of Prevnar by age 12 months was approximately 92%. During 1999-2004, the average birth cohort (number of live births) reported for Alberta was 38,314. Incidence rates per 100,000 persons (based on 2001 census data) of invasive Hib disease in children <5 years of age in Alberta were reported as follows: 0.89 for 1999, 0.44 for 2000, 0.44 for 2001, 0.89 for 2002, 0.44 for 2003, and 0.00 for 2004.

7.2 Pertussis

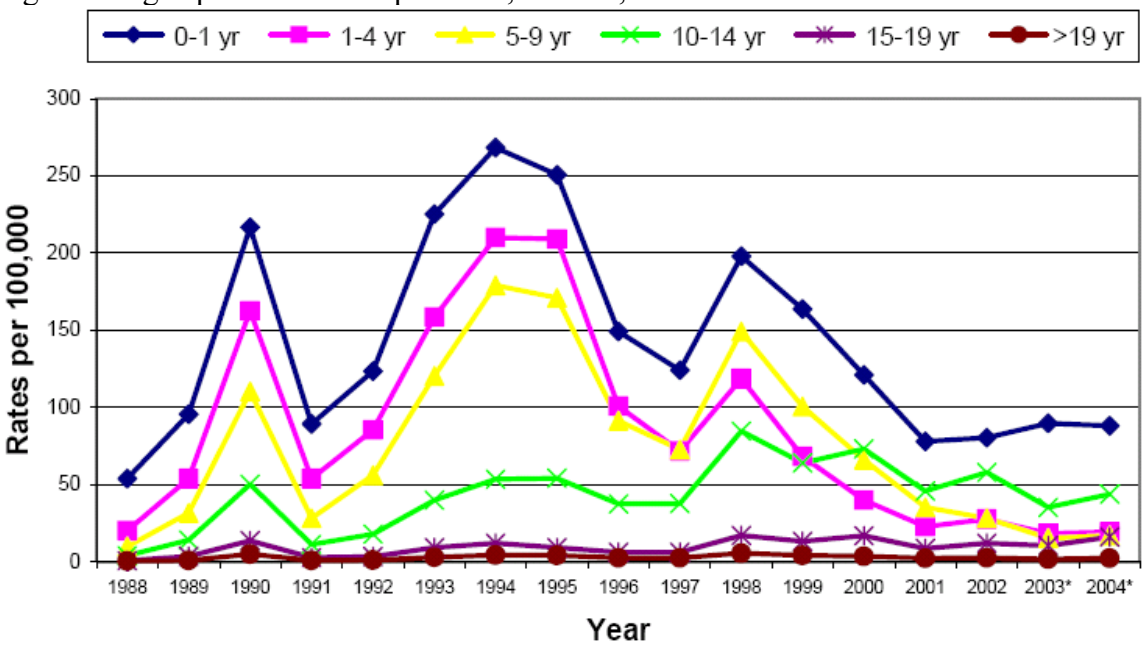
Whole-cell pertussis vaccines were introduced in Canada in 1943. Between July 1997 and April 1998, all Canadian provinces replaced DTwP-containing vaccines with Pentacel (2, 4, 6 and 18 months of age) and DTaP-IPV manufactured by Sanofi Pasteur Limited (4-6 years of age) and these vaccines have been used exclusively to prevent pertussis in Canada since their introduction.

Pertussis is nationally reportable in Canada. Cases identified by health care providers are reported to local authorities, who in turn, report to Health Canada. Cases of pertussis are confirmed for persons from whom *B. pertussis* is isolated by culture or identified by PCR from appropriate clinical specimens, or for persons who are epidemiologically linked to a laboratory-confirmed case and they have one or more of the following symptoms without another cause: paroxysmal cough of any duration, cough ending in vomiting or associated with apnea, or cough with inspiratory whoop. Prior to 1999, laboratory confirmation was by culture alone. Since 1999, confirmation has been by culture or PCR.

After introduction of whole-cell pertussis vaccines, the overall incidence of pertussis in Canada declined 90% over a 40-year period, with a nadir of 4.3 cases/100,000 persons in 1988. In the 1990s, the annual rate increased to 9.7-35.0 cases/100,000 persons (average of 6,358 cases reported per year in the 1990s) with increases primarily in infants <6 months of age and adolescents.

Figure 3 presents age-specific incidence rates of pertussis in Canada, from 1988-2004.

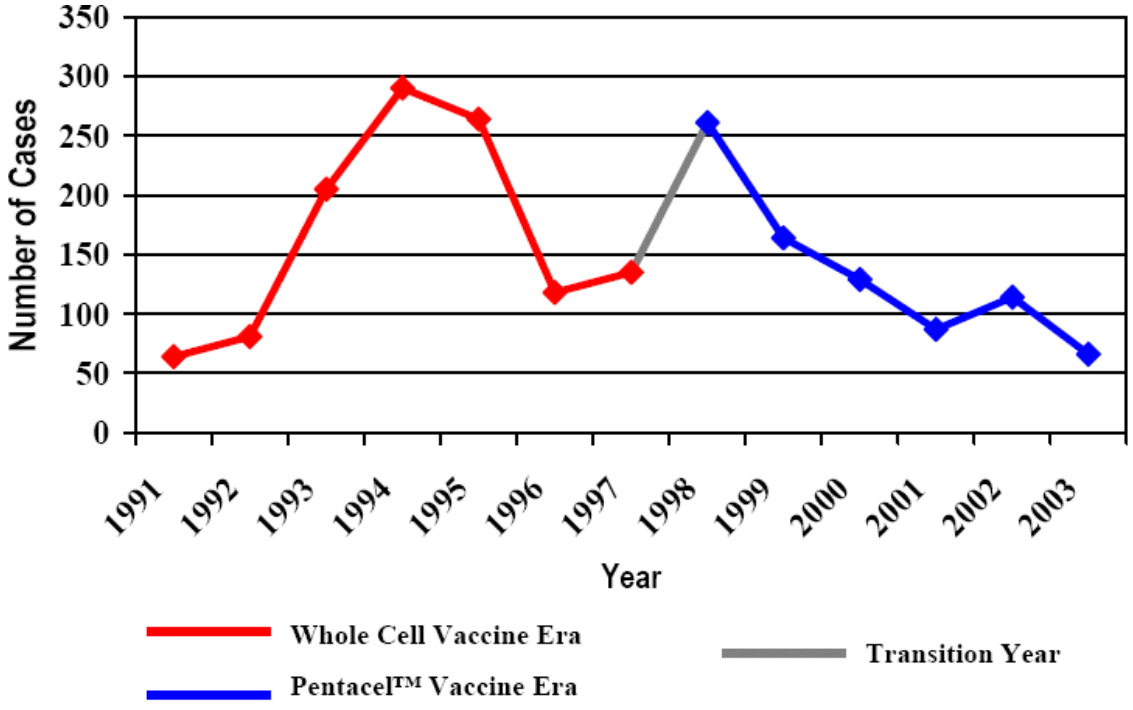
Figure 3. Age-specific rates of pertussis, Canada, 1988-2004*



*Provisional data for 2003 and 2004

Like invasive Hib disease, hospitalized cases of pertussis have been actively monitored in the IMPACT hospital network in Canada, using pertussis case definitions as detailed above for Health Canada. In an evaluation of pertussis surveillance data collected from IMPACT centers for the period of 1991-2004, the investigators evaluated pertussis cases during two time periods since 1991. They referred to the period 1991-1996 as the whole-cell vaccine era and the period 1998-2004 as the acellular pertussis (Pentacel) vaccine era. Data collected during the transition year (1997-1998) were not included in the analyses. During the 13.5-year surveillance period, 2000 cases of pertussis were diagnosed in IMPACT centers: 1,172 cases (mean of 195 cases/year) in the whole-cell vaccine era and 748 cases (mean of 115 cases/year) in the Pentacel era, representing a 41% decline in annual cases. (See Figure 4). Sixty-three percent of cases were laboratory-confirmed, 34% were clinically compatible, and 3% were clinically compatible and linked to a confirmed case. At IMPACT centers the proportion of hospitalized cases of pertussis who were <6 months of age was 74.8% in the whole-cell vaccine era and 92.4% in the Pentacel era.

Figure 4. Annual number of hospitalized cases of pertussis, IMPACT centers, 1991-2003



As described above for invasive Hib disease, to examine the impact of Prevnar on the effectiveness of Pentacel against pertussis, the applicant presented data on the incidence of pertussis in Alberta where Prevnar was integrated into the standard childhood immunization program in July 2002. (See Table 55).

Table 55. Incidence rates for pertussis in children, Alberta, Canada, 1999-2004

Age Group	Incidence Rate per 100,000 Persons					
	1999	2000	2001	2002	2003	2004
< 1 year	198.0	156.1	103.1	80.8	80.8	172.9
1-4 years	62.2	32.1	13.9	16.0	25.2	26.2
5-9 years	123.7	55.1	27.8	20.1	25.9	27.3

Source: hib_epidemiology.pdf, page 28

Among cases of pertussis <1 year of age reported in Alberta, the proportion 0-5 months of age ranged from 66-73% for 1999-2003 and was 84% for 2004.

8 Other Pentacel IND Studies not in the BLA

Table 56 presents a summary of three IND studies of Pentacel in the U.S. that are either ongoing, or if completed, the final study report(s) is pending. With the exception of post-dose 3 immunogenicity data from Study M5A07 that evaluated concomitant administration of Pentacel and Prevnar, data from these studies were not included in the BLA. A summary of post-dose 3 immunogenicity data from Study M5A07 (described in Section 5.2.2.4) was included in the BLA. Across the three studies listed in Table 56, a total of approximately 5,000 subjects are expected to receive Pentacel.

Table 56. Other IND studies of Pentacel not included in the BLA[1]

Protocol Number	Study Description	Vaccination Schedule	Study Groups	Number of Subjects (Safety Population)	Status
M5A03	Lot consistency of Pentacel containing pertussis antigens manufactured in new facility (NF); safety and immunogenicity comparison to Pentacel from current facility (CF)	Pentacel: 2, 4, 6, 15 mo. Prevnar: 2, 4, 6, 12 mo. RECOMBIVAX HB: 0, 2, 6 mo. MMR_{II}, VARIVAX: 12 mo.	Pentacel NF lot 1 Pentacel NF lot 2 Pentacel NF lot 3 Pentacel CF	Pentacel NF (pooled lots): 2260 Pentacel CF: 760 Total: 3020	Doses 1-3: final report reviewed by CBER under DAPTACEL Supplement for new manufacturing facility for pertussis antigens (approved 8/06) Dose 4: study completed.
M5A07	Safety and immunogenicity of Pentacel administered at different times from or concurrently with Prevnar	Pentacel: 2, 4, 6, 15 mo. Prevnar: Group 1: 2, 4, 6, 15 mo. Group 2: 3, 5, 7, 16 mo. RECOMBIVAX HB or ENGERIX B: 0, 2, 7 mo. MMR_{II}, VARIVAX: 12 mo.	Group 1: Pentacel and Prevnar concomitant Group 2: Pentacel and Prevnar staggered	Group 1: 587 Group 2: 579 Total: 1166	Doses 1-3: summary immunogenicity data included in BLA; final study report submitted to IND Jan 06. Dose 4: study completed; final report pending
M5A10	Comparative immunogenicity and safety of different multivalent vaccines based on a 5-component acellular pertussis vaccine	Pentacel, DAPTACEL, DTaP-IPV, ActHIB: see study groups IPOL: 2, 4, 6 mo *(Group 1 only)* Prevnar: 2, 4, 6, 12 mo. RECOMBIVAX HB or ENGERIX B: 0, 2, 6 mo. MMR_{II}, VARIVAX: 12 mo.	Group 1: DAPTACEL + ActHIB at 2, 4, 6, 15 mo. Group 2: Pentacel at 2, 4, 6 mo.; DAPTACEL + ActHIB at 15 mo. Group 3: HCPDT + ActHIB at 2, 4, 6, 15 mo. Group 4: Pentacel at 2, 4, 6, 15 mo.	540 per group (planned)	Ongoing

[1] A summary of post-dose 3 immunogenicity data from Study M5A07 was included in the Pentacel BLA.

9 Studies of DAPTACEL Following Four Doses of Pentacel

Two studies, Study P3T10 and P3T11, were designed to evaluate the safety and immunogenicity of DAPTACEL administered to children 4-6 years of age following four previous doses of Pentacel. In Study P3T10, approximately 980 subjects who received four doses of Pentacel in either pivotal Study 494-01 or 494-03 were enrolled. This study has been completed and the final report is pending. In Study P3T11, which was ongoing as of June 2006, available subjects from pivotal Study P3T06 who received either four doses of Pentacel or Control vaccines are to receive DAPTACEL at 4-6 years of age.

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