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

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From: Karen M. Farizo, M.D.
Medical Officer
Vaccines Clinical Trials Branch

Subject: Clinical Review of the Safety of Pentacel

To: BLA STN# 125145

Through: Lucia Lee, M.D.
Team Leader
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Chief
Vaccines Clinical Trials Branch

cc: Theresa Finn, Ph.D.
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1 General Information

1.1 Medical Officer Review Identifiers and Dates

1.1.1 BLA #: 125145

1.1.2 Related INDs and BLA Supplements:

- IND #---- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine (Pentacel), Sanofi Pasteur Limited
- IND #---- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (DAPTACEL), Sanofi Pasteur Limited
- IND #---- Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (ADACEL), Sanofi Pasteur Limited
- DAPTACEL BLA Supplement STN #103666/5071: This Labeling Supplement (approved 11/8/06) included data from Study P3T06, which is a pivotal study for the evaluation of the safety and immunogenicity of Pentacel.
- DAPTACEL BLA Supplement #103666/5069: Under this Supplement, ---------- ---------- the acellular pertussis antigens contained in DAPTACEL was approved 8/23/06. This Supplement included data from Study M5A03 Stage I (doses 1-3), in which subjects received Pentacel containing an acellular pertussis component from the ---------- (N=2,260) or the ---------- ---------- (N=760). This study was not included in the Pentacel BLA.
- ADACEL BLA Supplement #125111/50: Under this Supplement, a ---------- to manufacture the acellular pertussis antigens contained in ADACEL was approved 8/23/06, based on Pentacel data from Study M5A03.
- DAPTACEL BLA Supplement #103666/5158: Under this Supplement, a fifth dose of DAPTACEL following four previous doses of DAPTACEL was approved 3/12/08.

1.1.3 Reviewer Name, Division, and Mail Code

Karen Farizo, M.D.
Division of Vaccines and Related Products Applications
HFM-475

1.1.4 Submission Received by FDA: 7/26/05

1.1.5 Review Completed: 6/13/08

1.2 Product

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

1.2.2 Tradename: Pentacel

1.2.3 Product Formulation (per 0.5 mL dose, after reconstitution):

Active ingredients:

- purified polyribosyl-ribitol-phosphate capsular

polysaccharide (PRP) of *Haemophilus influenzae* type b (Hib) covalently bound to 24 µg of tetanus toxoid	10 µg
• diphtheria toxoid	15 Lf
• tetanus toxoid	5 Lf
• acellular pertussis:	
pertussis toxin (PT) detoxified	20 µg
filamentous hemagglutinin (FHA)	20 µg
fimbriae types 2 and 3 (FIM)	5 µg
pertactin (PRN)	3 µg
• poliovirus vaccine inactivated:	
Type 1 (Mahoney)	40 D-antigen units
Type 2 (MEF1)	8 D-antigen units
Type 3 (Saukett)	32 D-antigen units

Other ingredients per dose include 3.3 mg (0.6% v/v) 2-phenoxyethanol (not as a preservative), 1.5 mg aluminum phosphate (0.33 mg aluminum) as the adjuvant, polysorbate 80 (approximately 10 ppm by calculation), ≤5 µg residual formaldehyde, <50 ng residual glutaraldehyde, <50 ng residual bovine serum albumin, ≤4 pg neomycin and ≤4 pg polymyxin B sulfate.

The Hib conjugate vaccine used to formulate Pentacel is ActHIB manufactured by Sanofi Pasteur SA. ActHIB is licensed and distributed in the U.S. The inactivated poliovirus vaccine component of Pentacel is POLIOVAX manufactured by Sanofi Pasteur Limited. POLIOVAX is licensed, but not distributed, in the U.S. The DTaP component of Pentacel is also referred to as HCPDT (hybrid component pertussis vaccine combined with diphtheria and tetanus toxoids adsorbed). HCPDT is manufactured by Sanofi Pasteur Limited. HCPDT contains the same antigens as U.S. licensed DAPTACEL but with twice the amount of detoxified PT and four times the amount of FHA as in DAPTACEL. HCPDT is not licensed in the U.S.

1.3 Applicant: Sanofi Pasteur Limited

1.4 Pharmacologic Class: Vaccine

1.5 Proposed Indication: The applicant has requested an indication for active immunization against invasive Hib disease, diphtheria, tetanus, pertussis and poliomyelitis in infants and children 6 weeks through 4 years of age (prior to fifth birthday).

1.6 Dosage Forms and Routes of Administration: Pentacel will be supplied in 5-dose packages containing 5 vials of the Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed Combined with Poliovirus Vaccine Inactivated (DTaP-IPV) component (0.5 ml per vial) and five single dose vials of lyophilized ActHIB. The content of each 0.5 ml vial of the DTaP-IPV component is used to reconstitute a single dose of ActHIB. The reconstituted vaccine, Pentacel, is to be administered intramuscularly.

2 Table of Contents

3 Executive Summary

This is a review of the clinical safety of Pentacel. CBER's review of the clinical effectiveness of Pentacel is included in a separate memorandum by Dr. Theresa Finn.

The Pentacel BLA included safety data from four pivotal studies, in which a total of 5,980 subjects received at least one dose of Pentacel.[*] Of these subjects, 4,198 were enrolled in one of three U.S. studies (494-01, 494-03, and P3T06) that evaluated four consecutive doses of Pentacel administered at 2, 4, 6 and 15-16 months of age. In Study 5A9908, conducted in Canada, 1,782 subjects previously vaccinated with three doses of Pentacel, received a fourth dose at 15-18 months of age. Overall, across the four studies, 17,021 doses of Pentacel were administered.

In two pivotal studies, the safety of Pentacel was compared to separately administered vaccines: HCPDT (DTaP manufactured by Sanofi Pasteur Limited; not licensed in the U.S.), POLIOVAX (Poliovirus Vaccine Inactivated, Sanofi Pasteur Limited) and ActHIB [Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Sanofi Pasteur SA] in Study 494-01; and DAPTACEL (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed, Sanofi Pasteur Limited), IPOL (Poliovirus Vaccine Inactivated, Sanofi Pasteur SA) and ActHIB in Study P3T06. With the exception of HCPDT, all control vaccines are licensed in the U.S. For Study 494-01, which was initiated prior to licensure of DAPTACEL in the U.S., CBER agreed to the use of HCPDT as the control DTaP vaccine. HCPDT is identical to the DTaP component of Pentacel and differs from DAPTACEL only in its higher content of detoxified PT and FHA. Safety data on HCPDT were considered supportive for licensure of DAPTACEL in the U.S. Under the DAPTACEL BLA, CBER reviewed data on serious adverse events from the Sweden II Efficacy Trial in which approximately 20,000 infants received HCPDT, predominantly at 3, 5, and 12 months of age; a subset of approximately 2,500 subjects received HCPDT at 2, 4, and 6 months of age. In addition, the DAPTACEL BLA included comparative safety data on more common adverse events following HCPDT or DAPTACEL from smaller studies. Data from the Sweden II Efficacy Trial on serious adverse events following HCPDT were included in the Pentacel BLA and are presented in Section 6.7.

In the three pivotal safety studies in which subjects received four consecutive doses of Pentacel, Prevnar [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), Wyeth Pharmaceuticals Inc.] was administered concomitantly with the first three doses of Pentacel in most subjects. The second and third doses of the hepatitis B vaccine series, using RECOMBIVAX HB (Hepatitis B Vaccine Recombinant, Merck & Co., Inc.), also were administered concomitantly with the first and third doses of Pentacel in most subjects. In one study, some subjects who had not previously received the first dose of hepatitis B vaccine received three doses of RECOMBIVAX HB concomitantly with the first three doses of Pentacel. Depending on the study design, in the pivotal safety studies, the fourth dose of Pentacel was given either alone, concomitantly with the first doses of MMR_{II} (Measles, Mumps, and Rubella Virus Vaccine Live, Merck & Co., Inc.) and VARIVAX [Varicella Virus Vaccine Live (Oka/Merck), Merck & Co., Inc.], or concomitantly with the fourth dose of Prevnar. The pivotal safety studies of Pentacel were conducted prior to licensure of the two currently licensed Rotavirus vaccines in the U.S., and thus, did not evaluate the safety of Pentacel administered concomitantly with either of these vaccines.

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[*] Among the 5,980 subjects who received at least one dose of Pentacel in the pivotal studies, one subject randomized to receive Control vaccines received Pentacel for the first dose and Control vaccines for Doses 2-4. In calculating rates of events across doses and across studies, this subject was included in the randomized Control group. Thus, for such analyses, 5,979 subjects are included in the Pentacel group.

Overall, the quality of the safety data from the pivotal safety studies was adequate to assess the safety of Pentacel. The following issues will be addressed in the pivotal clinical trials sections of this review: data audits of already analyzed safety data with subsequent changes to the safety databases; two non-routine site audits due to non-conformance with Good Clinical Practices; data inconsistencies and coding errors (resolved in responses to a Complete Response Letter issued 5/26/06); missing data for solicited adverse events; and poor compliance with measuring temperatures rectally (as specified in all protocols for Doses 1-3 and in one protocol for Dose 4 of Pentacel or Control vaccines).

In the two controlled pivotal safety studies, overall rates of serious adverse events were similar in Pentacel and Control subjects. These studies were not designed to reliably evaluate differences between groups with regard to particular serious adverse events. Across the pivotal safety studies, following Doses 1-3 combined of Pentacel or Control vaccines, the most frequently reported serious adverse events were bronchiolitis, dehydration, pneumonia and gastroenteritis. Across the pivotal safety studies, following the fourth dose of Pentacel or Control vaccines, the most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and pneumonia.

A total of five deaths occurred during the pivotal safety studies: four among subjects who received Pentacel (N=5,979) (asphyxia due to suffocation, head trauma, SIDS, and neuroblastoma, respectively) and one in a subject who received DAPTACEL, IPOL and ActHIB separately (N=1,455) (aspiration and metastatic ependymoma).

Two cases of encephalopathy occurred during the pivotal safety studies. One case was secondary to cardiac arrest following cardiac surgery 30 days after Pentacel. One case occurred in an infant who developed neurological symptoms 8 days following Pentacel, had structural cerebral abnormalities on MRI, and was eventually diagnosed with congenital encephalopathy.

In the pivotal safety studies, there were no febrile seizures within seven days following any of Doses 1-3 of Pentacel (N=4,197 subjects) or Control vaccines (HCPDT, POLIOVAX and ActHIB: N=1,032 subjects; DAPTACEL, IPOL and ActHIB: N=1,455 subjects). One subject experienced a possible seizure on the same day as the third dose of Pentacel and also had fever reported the same day. Four subjects experienced a febrile seizure within seven days following the fourth dose of Pentacel or Control vaccines: 2 of 5,033 Pentacel subjects, 2 of 739 subjects who received HCPDT, POLIOVAX and ActHIB separately, and 0 of 418 subjects who received DAPTACEL, IPOL and ActHIB separately. Overall, there were three afebrile seizures within seven days following any of Doses 1-3 of Pentacel or Control vaccines: one each following Pentacel; HCPDT, POLIOVAX, and ActHIB administered separately; and DAPTACEL, IPOL, and ActHIB administered separately. There were no afebrile seizures within seven days following the fourth dose of Pentacel or Control vaccines.

Across the four pivotal safety studies, no cases of hypotonic hyporesponsive episodes (HHEs) meeting the pre-specified definition were reported following any dose of Pentacel (N=5,979 subjects) or Control vaccines (HCPDT, POLIOVAX and ActHIB: N=1,032 subjects; DAPTACEL, IPOL and ActHIB: N=1,455 subjects).

With regard to fever and other commonly occurring solicited local and systemic adverse events, no notable increases in rates following Pentacel relative to separately administered Control vaccines were identified. Compliance with measuring temperature rectally following Doses 1-3 of Pentacel or Control vaccines, as specified in the protocols, was relatively low (approximately 50% of measurements). In one study in which temperatures were also to be taken rectally

following the fourth dose, approximately one-third of measurements post-Dose 4 were rectal. In the two controlled studies, use of different routes of temperature measurement was similar in Pentacel and Control subjects. Whether infants had medical visits for fever was not specifically solicited or systematically assessed in the pivotal studies.

In addition to safety data from four pivotal studies, the BLA included supportive safety data from eight historical non-IND studies (six studies conducted in Canada and one each in Israel and Mexico). None of these studies included a control group that received a U.S. licensed DTaP vaccine or HCPDT. In three studies, a total of 996 subjects previously vaccinated with three doses of whole cell DTP vaccine received a single dose of Pentacel. In the other studies, a total of 1,694 subjects received three or four consecutive doses of Pentacel. The types of serious adverse events reported were generally similar to those reported in the pivotal studies.

The BLA also included supportive post-marketing safety data on Pentacel, reflecting a 9-year period between 5/1/97 and 4/30/06, during which a total of approximately 13.5 million doses of Pentacel were distributed outside the U.S., 92% of them in Canada. In Canada, Pentacel administered at 2, 4, 6, and 18 months of age and Sanofi Pasteur's DTaP-IPV administered at 4-6 years of age replaced whole-cell DTP vaccines and have been used exclusively since 1997-1998 to prevent pertussis, poliomyelitis and invasive Hib disease throughout early childhood. Post-marketing safety data presented in the BLA included spontaneous reports received by Sanofi Pasteur, the results of a retrospective survey for adverse events following the fourth dose of Pentacel conducted in approximately 3,000 children in British Columbia, and publications from an active surveillance system for adverse events following vaccination.

During the 9-year post-marketing period, Sanofi Pasteur received 288 adverse event reports following Pentacel. Most events reported in the post-marketing setting also have been reported in clinical trials of Pentacel. The five most frequently reported events in the post-marketing setting were injection site reaction, pyrexia, crying, injection site inflammation and irritability. During the 9-year period, there were 14 post-marketing reports of deaths, including five cases of SIDS, four other deaths without known cause, two deaths due to Hib meningitis following the first dose of Pentacel, and one death each due to Group B streptococcal sepsis, congenital anomalies, and seizures. For all 14 reported deaths, the interval since vaccination was between 1 and 25 days. There were five post-marketing reports of encephalopathy, with the time to onset of symptoms since the last dose of Pentacel reported as 1, 5, 7, 10, and 24 days, respectively. Most cases of encephalopathy had an identified plausible cause other than vaccination. In two cases, influenza A virus was isolated from nasopharyngeal secretions. One case each was associated with bloody diarrhea, atypical Kawasaki syndrome, and complex symptoms 24 days post-vaccination. In interpreting these data, the characteristics of passive surveillance systems should be considered. For example, passive surveillance for adverse events is subject to underreporting; serious, life-threatening events and fatal cases are more likely to be reported than minor events; and events with a shorter onset time after vaccination are more likely to be reported than those with a longer interval since vaccination.

The BLA also included publications from a hospital-based Canadian program of active surveillance for post-vaccination adverse events. Participating hospitals, of which there are currently 12, encompass approximately 90% of Canada's tertiary care pediatric beds and serve an immediate population base of 3 million children (approximately half of Canada's population under 15 years of age). Based on vaccine distribution data, vaccine coverage rates, and hospitalizations for encephalopathy and encephalitis at participating sites during the period 1993-2002, the risk, if any, of developing encephalopathy or encephalitis as a result of vaccination was estimated as <1 per 3 million doses of whole-cell pertussis vaccine and <1 per 3.5 million doses

of acellular pertussis vaccine (Pentacel for Doses 1-4 and Sanofi Pasteur's DTaP-IPV for Dose 5). In addition, data from this active surveillance system suggested a decreased risk of febrile seizures and HHEs with the introduction of Pentacel in Canada in place of whole-cell DTP vaccines.

Within the constraints of the sample sizes of the pivotal safety studies, the available data did not raise any particular concerns with regard to the occurrence of adverse events following Pentacel relative to separately administered Control vaccines and no concerning safety signals were identified. However, given the number of subjects evaluated, the ability of the pivotal studies safety database to evaluate rare adverse events is limited. While the limitations of passive surveillance systems, particularly underreporting, are well recognized, the available data on spontaneous post-marketing reports of adverse events following Pentacel provide some assurance of the overall safety of Pentacel in the general population. Data from the Canadian hospital-based program of active surveillance for certain targeted vaccine adverse events also provide some assurance of the safety of Pentacel with regard to febrile seizures, HHEs and encephalopathy.

In conclusion, the available safety data from the pivotal clinical studies and the supportive safety data from historical studies and from post-marketing use of Pentacel, primarily in Canada, support the safety of Pentacel in children 6 weeks to 4 years of age. The safety data in the BLA support use of Pentacel as a four dose series, with a single dose intramuscularly administered at 2, 4, 6 and 15-18 months of age. Use of Pentacel in children 19 months through 4 years of age is intended for catch-up immunization for unvaccinated children and children whose vaccinations have been delayed. Safety of Pentacel in children 19 months through 4 years of age is supported by clinical evidence of the safety of Pentacel in children 6 weeks to 18 months of age. Based on the justification provided in Section 8.3 of this review, waiver of the requirement, under the Pediatric Research Equity Act, to conduct studies of Pentacel in infants 0 to 5 weeks of age and children 5 to 16 years of age is recommended. FDA's Pediatric Review Committee concurred with this recommendation.

Based on current recommendations for DTaP vaccination, children who receive a four dose series with Pentacel will need a fifth dose of DTaP vaccine at age 4 to 6 years. Since some State immunization requirements for school entry specify receipt of the last dose of IPV after the fourth birthday, some children who receive the recommended four dose IPV series with Pentacel will likely be required to receive an extra dose of IPV.

The applicant has proposed to conduct a descriptive post-licensure passive surveillance study designed to detect serious adverse events and specified, medically-attended neurological conditions, hypersensitivity reactions, and new-onset autoimmune disease following Pentacel. The proposed study will accrue at least 10,000 children who receive Pentacel and an unspecified number of children who receive other DTaP vaccines. For each subject, passive surveillance for specified adverse events through 6 months following the fourth dose of Pentacel or other DTaP vaccine will be conducted by review of computerized medical records and state mortality tapes. This study will also provide safety data on concomitant use of Rotavirus vaccine and Pentacel. In view of the available pre-licensure clinical data on Pentacel and the post-marketing data on use of Pentacel outside the U.S., the proposed study, combined with routine pharmacovigilance activities, is considered sufficient for the post-marketing safety evaluation of Pentacel.

The applicant has committed to submit safety data to support the use of DAPTACEL in children 4-6 years of age following four previous doses of Pentacel.

4 Clinical and Regulatory Background

4.1 Diseases to be Prevented and Available Interventions

The requested indication for Pentacel is for the prevention of invasive Hib disease, diphtheria, tetanus, pertussis, and poliomyelitis in children ages 6 weeks through 4 years. For children in this age group, the following vaccines are licensed in the U.S. for prevention of diseases targeted by Pentacel:

- DTaP
  - DAPTACEL
  - Tripedia (Sanofi Pasteur Inc.)
  - INFANRIX (GlaxoSmithKline)

- Diphtheria and Tetanus Toxoids Adsorbed for Pediatric Use (DT)
  - DT, Sanofi Pasteur Inc. and Sanofi Pasteur Limited

- Hib conjugate vaccine
  - ActHIB
  - PEDVAXHIB (Meningococcal Protein Conjugate; Merck)

- Poliovirus Vaccine Inactivated (IPV)
  - IPOL (Sanofi Pasteur Inc.)
  - POLIOVAX (Sanofi Pasteur Limited; not distributed in the U.S.)

- DTaP, Hepatitis B (Recombinant) and IPV Combined
  - PEDIARIX (GlaxoSmithKline)

- Hib conjugate and hepatitis B (recombinant) vaccine
  - COMVAX (Merck)

- ActHIB reconstituted with Tripedia
  - TriHIBit, Sanofi Pasteur Inc. (for use in children 15-18 months of age only)

4.2 Previous Human Experience

Pentacel was first registered in Canada in May 1997, and is currently licensed in Argentina, Australia, Brazil, Canada, Colombia, Israel, Mexico, and Turkey. Between 5/1/97 and 4/30/06, a total of ---------- doses of Pentacel were distributed outside the U.S., ---------- of them in Canada. [source: postmarketing_clean.pdf, page 1].

4.3 Regulatory Background Information

Chronology of Review:
7/26/05 Application received
5/26/06 Complete Response Letter issued
9/7/06 Response to 5/26/06 Complete Response Letter submitted
1/25/07 Vaccines and Related Products Advisory Committee meeting
3/5/07 Major Amendment submitted (in response to an Information Request Letter issued 2/20/07)
4/23/07 Complete Response Letter issued

5/3/07 Response to 4/23/07 Complete Response Letter submitted
6/8/07 Complete Response Letter issued
12/21/07 Response to 6/8/07 Complete Response Letter submitted

5 Clinical Data Sources, Review Strategy and Data Integrity

5.1 Material Reviewed

The main data sources used in conducting this review were the final study reports for four pivotal IND studies that evaluated the safety of Pentacel (see section 5.2 Table 6), synopses of eight historical non-IND studies of Pentacel (see Section 6.6 Table 68), the report of a post-marketing survey following the fourth dose of Pentacel, a summary of spontaneous post-marketing reports of adverse events following Pentacel, and the applicant's integrated summary of safety. All of these data sources were included in the BLA.

5.1.1 BLA pdf Files Which Served as a Basis for the Clinical Safety Review

Safety data from the following files served as the basis for the clinical safety review.

Filename	Pages
clinsum.pdf	1-85
49401si.pdf	1-4593
49401si_d.pdf	12783-12851
49401sii.pdf	1-1893
49401sii_b.pdf	6622-6693
49403si.pdf	1-1460
49403si_a.pdf	5466-5524
49403sii.pdf	1-1740
49403sii_a.pdf	4298-4341
5a9908.pdf	1-1343
5a9908_a.pdf	4505-4536
p3t06si.pdf	1-4344
p3t06si_c.pdf	13077-13188
p3t06sii.pdf	1-1946
p3t06sii_c.pdf	8482-8586
swedenii.pdf	1-298
swedenii_a.pdf	1-118
5a9703infantseries.pdf	1-173
5a97034thdose.pdf	1-148
m5a08.pdf	1-1451
pb9402.pdf	1-63
pb9501.pdf	1-111
pb9502infantseries.pdf	1-210
pb95024thdose.pdf	1-182
pb9505.pdf	1-164
pb9506.pdf	1-283
pb9601infantseries.pdf	1-308
pb96014thdose.pdf	1-188
pnf35.pdf	1-404
iss.pdf (original and revised versions)	1-2653
49401_addnl_safetyanalyses.pdf	1-273
49403_addnl_safetyanalyses.pdf	1-198

5a9908_addnl_safetyanalyses.pdf	1-75
p3t06_addnl_safetyanalyses.pdf	1-273
iss.pdf (revised; submitted 9/7/06)	1-3198
iss_highlighted.pdf	1-184
questions1_133.pdf	1-650
questions157_164.pdf	4-8
postmarketingclean.pdf	1-25
response_fax09nov06.pdf	1-51
revised_q163.pdf	1-2
draft_pmc_07feb07.pdf	1-3
concept_protocol_m5a11.pdf	1-7

5.1.2 Post-marketing Experience

5.1.2.1 Spontaneous Reports of Adverse Events

During the period 5/1/97 through 4/30/06, 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 Limited 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 to the medically confirmed reports, there were 43 spontaneous reports received from consumers. The most frequently reported (N $\geq$3) adverse events, both serious and non-serious, are presented by Medical Dictionary for Regulatory Activities (MedDRA) system organ class in Table 1.

Table 1. 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
Oedema + Oedema peripheral	5 + 3
Therapeutic response decreased + vaccination failure	4 + 2
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
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 both medically confirmed and consumer cases
[3] Includes MedDRA Preferred Terms of Convulsion, Febrile Convulsion, Status Epilepticus and Convulsion Local
[4] Three of the hypotonic events met the criteria for HHE but were not coded as HHE and therefore are not included under the term "hypotonic hyporesponsive episode".
[5] A fourth case of encephalopathy was coded as Convulsions in this table. A fifth case of encephalopathy identified in a post-marketing safety survey conducted by the applicant was not included as a "spontaneous report". See text for further details.
Source: postmarketing_clean.pdf, pages 1-2

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

Deaths

Between 5/1/97 and 4/30/06, 14 deaths following Pentacel were identified by the applicant through spontaneous reports or in published literature (Table 2). Five deaths were classified as SIDS, four were reported as due to unknown cause, two were due to invasive Hib disease (both

post-Dose 1) and one each was reported as due to sepsis, congenital anomaly, and convulsions. Limitations of passive surveillance data preclude drawing conclusions from comparisons to population based incidence rates. Nevertheless, to place the data on SIDS in perspective, it is useful to note that the reported rate of SIDS in Canada in the late 1990s was 1 out of 2000 live births each year, or approximately 170 cases per year.

Table 2. Post-marketing reports of deaths following Pentacel, May 1997 through April 2006

Age at Death (months)	Interval Since Last Dose	Co-administered Vaccines	Events/Cause of Death
2	1 days	--	SIDS
2	2 days	--	SIDS
2	7 days	Prevnar	SIDS
2	8 days	Prevnar	SIDS
2	13 days	--	SIDS
4	24 hours	Meningococcal conjugate C	Sudden death
2	8 days	--	Sudden death
36	11 days	Hepatitis B, MMR, Meningococcal	Sudden death
19	25 days	--	Death
2	9 hours	--	Group B Streptococcal sepsis
2	3 days	--	Congenital anomaly; cardiac myopathy
5	3 months	--	Hib meningitis/pneumonia (post-Dose 1)
3	30 days	--	Hib meningitis (post-Dose 1)
20	n/a	--	Convulsions

n/a indicates not available
source: postmarketing_clean.pdf, pages 17-21

Encephalopathy

As shown in Table 1, the applicant received three spontaneous reports of encephalopathy following Pentacel. A fourth case of encephalopathy identified post-marketing from a literature report was coded as convulsions (status epilepticus) by the applicant. A fifth case of encephalopathy was identified in a post-marketing safety survey conducted by Sanofi Pasteur (see Section 5.1.2.2). Although this case was not included in the applicant's presentation of spontaneous post-marketing adverse event reports, a clinical description will be provided in this section, along with the spontaneous and literature reports of encephalopathy. Available clinical information on these five cases of encephalopathy identified in the post-marketing setting is presented below.

> Case 1 occurred in a 2-month old infant, with onset seven days following Pentacel. No other co-administered vaccines were reported. Adverse events noted included viral infection, fever, abnormal crying, cough, apnea, and seizures. There was no specific abnormality on cranial CT. Cerebrospinal fluid was normal. Influenza A virus was isolated from a nasopharyngeal aspirate. The outcome was reported as normal by Day 7.
>
> Case 2 occurred in an 18-month old child, with onset one day following Pentacel. No other co-administered vaccines were reported. Adverse events noted included viral infection, fever, coryza, focal seizures, status epilepticus, and cough. Cranial CT showed diffuse cerebral edema. Influenza A virus was isolated from a nasopharyngeal aspirate. The outcome was reported as right-sided weakness at discharge with improvement one month later.

Case 3 occurred in a 4 month old male approximately one month following the second dose of Pentacel. No other co-administered vaccines were reported. Adverse events noted included generalized spasm, developmental delay, convulsions, pneumonia, hepatomegaly, splenomegaly, and cyanosis. Specific information on diagnostic studies was not provided, but the subject was eventually diagnosed with 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.

Case 4 (coded as convulsions) occurred in a 4 month old infant five days following the second dose of Pentacel. Information was not provided on co-administered vaccines. Adverse events noted included fever, vomiting, bloody diarrhea, coryza, status epilepticus, coma, and elevated AST (335 units/L) and ALT (351 units/L). Cranial CT showed diffuse brain edema and laminar necrosis. MRI showed cortical bleeding. CSF was normal. No etiologic agent was identified. Viral and bacterial cultures of CSF and stool, viral cultures of the upper respiratory tract, and 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.

Case 5 (identified in post-marketing survey M5A08; see Section 5.1.2.2) occurred in an 18 month old female who developed lymphadenopathy, loss of coordination, conjunctivitis, puffiness, dry lips, and fever, 10 days following Pentacel and MMR, and was hospitalized for atypical Kawasaki syndrome with acute disseminating encephalopathy and hypotonia. Treatment included intravenous immunoglobulin, acetylsalicylic acid and clindamycin. Outcome was reported as improved.

Decreased Level of Consciousness

As shown in Table 1, there were three spontaneous reports of decreased level of consciousness following Pentacel. There was no overlap in these cases with either reports of HHEs or encephalopathy. The following information was provided on these cases.

Case 1 occurred in a 6 month old female who experienced persistent crying, fever of 39.7^{o}C and a fixed gaze two to twelve hours after the third dose of Pentacel.

Case 2 occurred in a 2 month old infant, five days following the first dose of Pentacel. The infant was difficult to arouse and was transferred to a tertiary care unit. Reportedly, the infant recovered by the following day.

Case 3 occurred in a 5 month old male, 26 hours following the second dose of Pentacel. The infant appeared absent and was staring. Seven to 10 days later, he had an unspecified seizure. He continued having intermittent staring episodes. He had two brief hospitalizations. Diagnostic tests to evaluate for meningitis and other infections, muscle biopsy, EEG, MRI, and CAT scans were performed, but the results were not provided. Initial treatment included phenytoin, lorazepam, carbamazepine and clobazan, as well as vitamin B6 and diet. The infant continued having 10-15 seizures a day for approximately 2 years. Reportedly the seizures stopped following homeopathic treatment. He also had developmental delay which reportedly improved.

Seizures

Of the 19 seizures reported post-marketing, 13 were medically confirmed events (reported in 11 children). Among the 13 medically confirmed events, there were 8 convulsions not otherwise specified, 2 febrile convulsions, 2 cases of status epilepticus, and 1 event coded as "convulsions local". The latency period following receipt of Pentacel ranged from 1 hour to 24 days. Eight of the events occurred within seven days following vaccination, including one febrile convulsion that occurred 12 hours after vaccination.

HHE

The definition of HHE used in the sponsor's presentation of post-marketing reports of HHE following Pentacel was the same as that published in a report of a U.S. Public Health Service workshop on HHE after pertussis immunization[1]:

> "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."

A total of 12 spontaneous post-marketing reports of HHE were received. In Table 1, nine of these are coded as HHE and three as hypotonia.

Therapeutic Response Decreased and Vaccination Failure

In Table 1, there were six spontaneous 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 three doses of Pentacel at appropriate ages. All six reports of "Therapeutic Response Decreased" or "Vaccination Failure" represented cases of invasive Hib disease, although not all cases were in children who had received three doses of Pentacel or another Hib vaccine (Table 3). Spontaneous reports of vaccination failure unlikely capture all vaccination failures. The BLA includes data on nationally reported cases of invasive Hib disease and pertussis in Canada. These Canadian national surveillance data are presented in a separate review (by Dr. Theresa Finn) of the immunogenicity data submitted to support the efficacy of Pentacel.

Table 3. 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	DPT-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.; 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

5.1.2.2 Post-Marketing Survey-- Study M5A08

The BLA contains a final report for a post-marketing retrospective safety survey conducted in British Columbia between 9/03 and 4/04. For this survey, the Public Health Information System of British Columbia provided a list of children who had received a fourth consecutive dose of Pentacel before their 2nd birthday. Parents or legally authorized representatives of 3,214 children were contacted by telephone 6 months after vaccination and asked if during this time their child had experienced any of the following: hospital admissions, life-threatening episodes, medical conditions that required 3 or more office or emergency room visits, or diagnosis of low blood cell count, low platelet count, swelling or redness of the joints, asthma, diabetes, or autism.

Of 3,213 subjects who provided data, 3,023 did not report any of the solicited events. Of the 190 subjects who had at least one of the solicited events, the data were confirmed by the primary care physician for 161 subjects. The Primary Analysis Population consisted of 3,184 subjects: 3,023 who reported none of the solicited events and 161 with confirmed adverse event data. Approximately half of subjects were female. The mean age at the fourth dose of Pentacel was 19.5 months (range 12.5-24.0 months). The majority of subjects (86.7%) were Caucasian. The second largest ethnic category was "other" (10.2%). Table 4 provides a summary of positive responses to the questionnaire. Table 5 presents a summary of reported life-threatening episodes reported. No deaths were reported.

Table 4. Study M5A08 Number (percentage) of subjects who had a positive response to the adverse events questionnaire, primary analysis population

	n	(%)
Primary Analysis Population	3184	(100.0)
Subjects with a Solicited Event	161	(5.1)
Admitted to Hospital	63	(2.0)
Life-threatening Episodes	33	(1.0)
3 or More Office or Emergency Room Visits	97	(3.0)
Physician Diagnosis of:		
Low Blood Count or Low Platelet Count	6	(0.2)
Swelling or Redness of the Joints	1	(<0.1)
Asthma	18	(0.6)
Diabetes	1	(<0.1)
Autism	3	(0.1)

Source: m5a08.pdf, page 72

Table 5. Study M5A08: Life-threatening episodes, primary analysis population

System Organ Class Preferred Term	Pentacel N=3184	
	n %	95% CI
IMMUNE SYSTEM DISORDERS	1 (<0.1)	(0.0, 0.2)
Hypersensitivity NOS	1 (<0.1)	(0.0, 0.2)
INFECTIONS AND INFESTATIONS	15 (0.5)	(0.3, 0.8)
Bronchiolitis	1 (<0.1)	(0.0, 0.2)
Bronchopneumonia NOS	1 (<0.1)	(0.0, 0.2)
Croup infectious	4 (0.1)	(0.0, 0.3)
Kawasaki's disease	3 (0.1)	(0.0, 0.3)
Lobar pneumonia NOS	1 (<0.1)	(0.0, 0.2)
Periorbital cellulitis	1 (<0.1)	(0.0, 0.2)
Pneumonia NOS	3 (0.1)	(0.0, 0.3)
Upper respiratory tract infection NOS	1 (<0.1)	(0.0, 0.2)
NERVOUS SYSTEM DISORDERS	11 (0.3)	(0.2, 0.6)
Convulsions NOS	2 (0.1)	(0.0, 0.2)
Febrile convulsion	10 (0.3)	(0.2, 0.6)
PSYCHIATRIC DISORDERS	1 (<0.1)	(0.0, 0.2)
Breath holding	1 (<0.1)	(0.0, 0.2)
RESPIRATORY, THORACIC, MEDIASTINAL DISORDERS	4 (0.1)	(0.0, 0.3)
Asthma NOS	4 (0.1)	(0.0, 0.3)

Notes: Solicited Adverse Events were coded using the MedDRA (Version 6.0) dictionary.
Each subject is counted once per System Organ Class or Preferred Term.
Source: questions1_133.pdf Table 78

Additional information was provided on three reported life-threatening episodes that were considered by the Investigator to be possibly or probably related to Pentacel.

- Atypical Kawasaki Syndrome with associated encephalopathy, with onset of symptoms 10 days post-vaccination (previously described in Section 5.1.2.1).

- At age 18 months, a female subject developed swelling around the nose, lips, cheeks, and heavy breathing within hours after Pentacel and MMR. The event did not progress to anaphylaxis. She recovered without sequelae following Benadryl.

- At age 20 months, a female subject experienced a febrile seizure on the same day she received Pentacel, MMR, and Prevnar. She was taken to an emergency room, treated with acetaminophen, and recovered.

Of the 97 events that required three or more office or emergency room visits, most were otitis media (56 cases), asthma (15 cases) or upper respiratory tract infection (11 cases).

Additional available information was provided for the six cases of low blood or platelet count.

- One subject was diagnosed with acute lymphoblastic leukemia approximately 75 days post-vaccination.

- One subject presented with severe anemia 33 days post-vaccination and was diagnosed with transient erythoblastopenia of childhood.

- One subject developed atypical Kawasaki disease with associated encephalopathy, with onset of symptoms 10 days post-vaccination (same subject as described in Section 5.1.2.1).

- One subject who had ongoing neutropenia and thrombocytosis (duration not specified) developed fever, conjunctivitis, and erythema with desquamation of hands and feet, 19 days post-vaccination, and was diagnosed with Kawasaki disease. Echocardiogram was normal and blood cultures negative. The subject recovered without sequelae following treatment with intravenous immunoglobulin and acetylsalicylic acid.

- One subject was diagnosed with anemia 12 days post-vaccination.

- One subject was diagnosed with anemia 124 days post-vaccination and was treated with supplemental iron. Reportedly the anemia resolved 138 days after initial onset.

The report of swelling or redness of the joints was in a subject who developed atypical Kawasaki disease 91 days post-vaccination.

The report of diabetes was in a 24-month old male who developed an upper respiratory tract infection 36 days post-vaccination. One week later, he developed thirst, lethargy and increased urine output. Four days later, he was hospitalized with vomiting and diagnosed with diabetic ketoacidosis. He improved following treatment with insulin and intravenous fluids.

Three cases of autism were reported. A 20 month-old female who had signs of developmental delay since 4 months of age, was diagnosed with autism four months after the fourth dose of Pentacel. A 27 month-old female who had signs of developmental delay since infancy was diagnosed with autism seven months after the fourth dose of Pentacel. A 25 month-old female who developed speech delay at 12 months of age was eventually diagnosed with autism.

The applicant indicated that rates of asthma, autism and diabetes reported following the fourth dose of Pentacel in the retrospective survey were lower than estimated background rates. In Study M5A08, a total of 23 subjects (7.2 per 1,000) reported asthma (confirmed or unconfirmed). The applicant cited data from Health Canada, indicating that from 1995-1996 (prior to licensure of Pentacel in Canada), there were 17,582 hospitalizations due to asthma in children aged 0-4 years (8.9 per 1000). In Study M5A08, there were three cases of autism reported (<1/1000). The applicant cited data from a study in metropolitan Atlanta that found a prevalence of Autistic Spectrum Disorder of 3.4/1000 children 3-10 years of age in 1996. In Study M5A08, there was one case of diabetes mellitus (0.31/1000). The applicant cited an estimated prevalence rate for diabetes of 0.21/1000 children aged 0-4 years during 1985-1993, based on a population-based database in Manitoba. The background rates cited by the applicant provide some perspective for interpreting the data from Study M5A08. However, direct comparisons between Study M5A08 and population based data may not be valid for several reasons including the potential for underreporting in Study M5A08, as well as differences in geographic areas and age groups.

5.1.2.3 Immunization Monitoring Program, Active (IMPACT)

The Immunization Monitoring Program, Active, also referred to as IMPACT, is a nationwide Canadian hospital-based program that conducts active surveillance for post-vaccination adverse events.[2,3] The twelve participating hospitals encompass approximately 90% of Canada's tertiary care pediatric beds and serve an immediate population base of three million children (approximately half of Canada's population under 15 years of age). IMPACT centers also

receive referrals from outside the immediate catchment areas. At participating sites, all admissions for acute neurological illness are screened for recent immunization.

Based on an IMPACT publication cited by the applicant, from 1993 to 1997, Canadian children received an estimated six million doses of vaccines containing whole cell pertussis; whereas from 1997 to 2002, they received an estimated seven million doses containing acellular pertussis vaccine. At IMPACT centers, between 1993 and 2002, there were seven cases of encephalopathy or encephalitis with onset within seven days after receiving a pertussis-containing vaccine, three after whole cell and four after acellular vaccine (of these, three were after Pentacel and one was after DTaP-IPV). A plausible (though not necessarily proven) cause other than vaccination was identified in most cases. The cases following Pentacel also were included in the applicant's summary of post-marketing spontaneous reports of adverse events (Section 5.1.2.1). The authors concluded that if any risk of developing encephalopathy or encephalitis exists as a result of vaccination, it would be <1 per 3 million administered doses of whole cell pertussis vaccine and <1 per 3.5 million administered doses of acellular pertussis vaccine.

The applicant also summarized data on seizures and HHEs from IMPACT. At IMPACT centers, active surveillance was conducted to identify children hospitalized with seizures or HHEs and children seen in the emergency department for HHEs. Using Poisson regression models, the average monthly admissions for seizures and reports of HHEs were compared between a whole-cell DTP period (1995-1996) and a period when Pentacel was used in all Canadian provinces (1998-2001). Between the two periods, hospitalizations for febrile seizures within 72 hours after a pertussis-containing vaccine decreased 79% (P=0.0000084) and reports of HHEs within 48 hours after pertussis vaccination decreased 60% (P=0.018). In contrast, in a control analysis, admissions for febrile seizures within 5-30 days after MMR vaccine did not change significantly between the two periods.

5.2 Table of Clinical Studies

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

Table 6. Summary of Pentacel pivotal safety studies

Protocol Number	Overview of Objectives	Pentacel and Control Vaccines Schedule	Designation of Study Groups/ Vaccines Administered Concomitantly with Pentacel or Control Vaccines	Country	Study Design	Number of Subjects in Safety Population[1]
494-01	Safety and immunogenicity; Pentacel lot consistency; Comparison to separate administration of formulation-equivalent component vaccines	Pentacel: 2, 4, 6, 15 months HCPDT + POLIOVAX + ActHIB: 2, 4, 6, 15 months	Doses 1-3 of Pentacel or Control vaccines: Group 1: Pentacel Lot 1 Group 2: Pentacel Lot 2 Group 3: Pentacel Lot 3 Group 4: HCPDT + POLIOVAX + ActHIB Dose 4 of Pentacel or Control vaccines: Group 1: Pentacel (includes subjects from Dose 1-3 Lot 1, Lot 2 and Lot 3) Group 2: HCPDT + POLIOVAX + ActHIB Concomitant vaccines: Prevnar at 2, 4, and 6 mo. (introduced after study initiation); RECOMBIVAX HB at 2 and 6 mo. (1st dose of Hepatitis B vaccine administered from birth to 21 days of age)	U.S.	Randomized, controlled, multi-center	Pentacel: 2506 Control: 1032
494-03	Safety and immunogenicity; Assessment of co-administration of Dose 4 with other recommended vaccines	Pentacel: 2, 4, 6, and 15 or 16 months	Concomitant vaccines: Prevnar + RECOMBIVAX HB at 2, 4, 6 months (RECOMBIVAX HB not given at 4 months if prior dose of Hepatitis B vaccine). Dose 4 Pentacel Study Groups/Concomitant Vaccines: Group 1: Pentacel at 15 mo. Group 2: Pentacel + MMR_{II} + VARIVAX at 15 mo. Group 3: Pentacel + Prevnar at 15 mo. Group 4: Pentacel at 16 mo.; MMR_{II} + VARIVAX + Prevnar at 15 mo.	U.S.	Randomized (for Dose 4 Groups), controlled (for Dose 4 co-administration) multi-center	Pentacel: 1207
5A9908	Safety and immunogenicity of fourth dose in subjects who previously received three doses of Pentacel	15 to 18 months	Dose 4 Pentacel Study Groups: Group 1: Pentacel at 15 mo. Group 2: Pentacel at 16 mo. Group 3: Pentacel at 17 mo. Group 4: Pentacel at 18 mo. Concomitant vaccines: none	Canada	Randomized, multi-center	Pentacel: 1782

P3T06	Safety and immunogenicity; Comparison to separate administration of licensed-components; DAPTACEL lot consistency; Assessment of co-administration of Dose 4 DAPTACEL with other recommended vaccines	Pentacel: 2, 4, 6, 15-16 months; DAPTACEL + ActHIB: 2, 4, 6, 15-16 months; IPOL: 2, 4, 6 months	<u>Doses 1-3 of Pentacel or Control vaccines</u>: Group 1: DAPTACEL Lot 1 + IPOL + ActHIB Group 2: DAPTACEL Lot 2 + IPOL + ActHIB Group 3: DAPTACEL Lot 3 + IPOL + ActHIB Group 4: Pentacel <u>Concomitant vaccines administered with Doses 1-3 of Pentacel or Control vaccines</u>: Prevnar at 2, 4, 6 mo.; RECOMBIVAX HB at 2 and 6 mo. (1st dose of Hepatitis B vaccine administered from birth to 21 days of age) <u>Dose 4 Study Groups/Concomitant Vaccines</u>: Group 1: MMR II + VARIVAX + Prevnar at 12 mos; DAPTACEL + ActHIB at 15-16 mos. Group 2: DAPTACEL + ActHIB + MMR II + VARIVAX + Prevnar at 15-16 mos. Group 3: ActHIB + MMR II + VARIVAX + Prevnar at 15-16 mo; DAPTACEL at 16-17 mos. Group 4: MMR II + VARIVAX + Prevnar at 12 mos Pentacel at 15-16 mos.	U.S.	Randomized, controlled, multi-center	Pentacel: 485 Control: 1454 for Doses 1-3; 418 for Dose 4 (only Dose 4 Group 1 served as the control for the fourth dose of Pentacel)

[1]The Intent-to-Treat (ITT) Safety Population is defined as all subjects who received at least one dose of study vaccine (Pentacel, HCPDT, or DAPTACEL per study design). For studies 494-01 and P3T06, subjects are classified according to the actual vaccine received at Dose 1.
Source: iss.pdf, pages 180-181

In addition to the pivotal safety studies, the BLA also contains safety data from eight historical non-IND studies of Pentacel. Across these eight studies, approximately 2,500 subjects were enrolled to receive 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 1500 subjects). None of these studies included a control group that received a U.S. licensed DTaP vaccine or HCPDT. Data on serious adverse events from these studies are summarized in Section 6.6 and are considered supportive in the evaluation of the safety of Pentacel.

As supportive safety data for Pentacel, the BLA also contains the Technical Reports for the Sweden I Efficacy Trial, the pivotal pertussis efficacy study for DAPTACEL, and the Sweden II Efficacy Trial which evaluated the efficacy of HCPDT against pertussis. Both of these studies were previously reviewed by CBER under the DAPTACEL BLA (STN 103666). Brief descriptions of these studies and a review of the safety data from the Sweden II Efficacy Trial will be presented Sections 6.6 and 6.7.

5.3 Review Strategy

The four pivotal safety studies of Pentacel, the eight historical supportive studies, the post-marketing safety survey (Study M5A08), and the summary of post-marketing reports of adverse events, all of which are included in the BLA, were reviewed. The Technical Reports for the Sweden I Efficacy Trial and the Sweden II Efficacy Trial, which contain safety data on DAPTACEL and HCPDT, respectively, were previously reviewed by CBER under the DAPTACEL BLA (STN 103666). Since HCPDT was used as the control DTaP vaccine in pivotal Study 494-01, a summary of data on serious adverse events following HCPDT in the Sweden II Efficacy Trial is presented in this review (Section 6.7).

5.4 Good Clinical Practices and Data Integrity

Overall, the quality of the safety data in the BLA was adequate to assess the safety of Pentacel. The following issues regarding data quality will be addressed in subsequent sections on the pivotal studies: data audits of already analyzed safety data with subsequent changes to the safety databases; two non-routine site audits due to non-conformance with Good Clinical Practices; data inconsistencies and apparent data errors particularly with regard to coding of some serious adverse events (resolved in responses to 5/26/06 Complete Response Letter); and missing data on solicited adverse events in as many as 20% of subjects.

6 Clinical Studies

6.1 Pivotal Trial # 1

6.1.1 Applicant's Protocol # and Protocol Title

Study 494-01: Safety, Immunogenicity and Lot Consistency Study of Hybrid Pertussis Vaccine in Combination with Diphtheria and Tetanus Toxoids and Inactivated Poliomyelitis Vaccine Used to Reconstitute Lyophilized *Haemophilus influenzae* Type b Tetanus Toxoid Conjugate Vaccine (Hybrid $CP_{20/20/5/3}$DT-mIPV//PRP-T, (PENTACEL™) in Infants and Toddlers

6.1.1.1 Objective/Rationale

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

6.1.1.2 Design Overview

Study 494-01 was a randomized, controlled, multi-center study designed to assess the safety, immunogenicity, and lot consistency of Pentacel. Subjects were randomized to receive one of three lots of Pentacel or Control vaccines (planned enrollment 800 subjects per Pentacel lot group and 1000 subjects in the Control group) for Doses 1-3. All subjects who received Pentacel for Doses 1-3 received a single lot of Pentacel for Dose 4. Subjects who received Control vaccines for Doses 1-3 received Control vaccines for Dose 4. The safety evaluation of lot consistency was blinded. The safety evaluation of Pentacel vs. separately administered Control vaccines was open-label.

6.1.1.3 Population

Inclusion Criteria

- Healthy infants 2 months (42-89 days) of age
- At least 36 weeks gestation at delivery
- Informed consent from parent or legal guardian
- Able to attend the scheduled visits and to comply with study procedures
- Received one dose of hepatitis B vaccine (from birth to 21 days of age and at least 28 days before the first dose of Pentacel or Control vaccines)

Exclusion Criteria

- Clinically significant findings on review of systems
- Known or suspected hypersensitivity to any component of the study vaccines
- Known or suspected impairment of immunologic function or receipt of immunosuppressive therapy or blood products (including immunoglobulin) since birth
- Known HIV-positive mother
- Personal or immediate family history of congenital immune deficiency
- History of developmental delay or neurological disorders (including seizures of any etiology)
- History of chronic underlying medical, congenital, developmental, or surgical disease
- Participation in any other experimental drug or vaccine trial since birth
- Any condition, which in the opinion of the investigator, would interfere with evaluation of the vaccine or pose a health risk to the subject
- Recent (<72 hours) febrile illness with rectal (or equivalent) temperature >38.0°C
- Previous therapy with cadaveric pituitary derived human growth hormone in infant or mother
- Prior receipt of any DTaP, DTwP, Hib-conjugate, poliovirus, or pneumococcal conjugate vaccine

Contraindications to Subsequent Doses

- Rectal (or equivalent) temperature >40.5° C within 48 hours following a previous vaccination
- Seizures within 3 days following a previous vaccination
- Encephalopathy within 7 days following a previous vaccination
- Hypotonia and/or hyporesponsiveness within 48 hours following a previous vaccination
- Hypersensitivity to any vaccine component or anaphylactic reaction following a previous vaccination
- Persistent inconsolable crying (>3 hours) following a previous vaccination
- Serious adverse events possibly, probably or definitely related to the vaccine
- Known or suspected impairment of the immune system

6.1.1.4 Products Mandated by the Protocol

Schedule of Study Vaccines

Table 7 presents the schedule of study vaccines.

Table 7. Study 494-01 Schedule of study vaccines

	Age (months)				
	2	4	6	12	15
Pentacel groups (lot 1, 2, or 3)	Pentacel RECOMBIVAX HB Prevnar	Pentacel Prevnar	Pentacel RECOMBIVAX HB Prevnar	MMR II VARIVAX Prevnar	Pentacel
Control Group	HCPDT POLIOVAX ActHIB RECOMBIVAX HB Prevnar	HCPDT POLIOVAX ActHIB Prevnar	HCPDT POLIOVAX ActHIB RECOMBIVAX HB Prevnar	MMR II VARIVAX Prevnar	HCPDT POLIOVAX ActHIB

Notes:
All subjects were to have received the first dose of hepatitis B vaccine (manufacturer not specified) from birth to 21 days of age, and at least 28 days prior to the first dose of study vaccines.
Refusal to accept vaccines offered at 12 months of age did not constitute a protocol violation.
Prevnar was introduced after the study was initiated. For subjects who did not receive their first or second dose of Prevnar at 2 and 4 months of age, respectively, catch-up doses could be administered at least 30 days after the last dose of Pentacel or Control vaccines and 30 days before the next dose(s).

Formulation of Study Vaccines

- Pentacel

For the formulation of Pentacel, see Section 1.2.3. In Study 494-01, lots of Pentacel used for Doses 1-3 also contained <0.05% human serum albumin. HCPDT-IPV Lots C0155A, C0154B, and C0094A and ActHIB Lots P1394, P1332, and UA480A (R0181 [bulk lot]) were used to formulate the three Pentacel lots. Appendix 1 presents the combinations of monovalent component lots including the intermediate lots, which were used to formulate the three HCPDT-IPV vaccine consistency lots.

- Control Vaccine 1: HCPDT manufactured by Sanofi Pasteur Limited (not U.S. licensed); composition per 0.5 ml dose:

  Active Ingredients:

detoxified PT	20 µg
FHA	20 µg
FIM types 2 & 3	5 µg
PRN	3 µg
Diphtheria toxoid	15 Lf
Tetanus toxoid	5 Lf

  Adjuvant: 1.5 mg aluminum phosphate (0.33 mg aluminum)

  Excipient: 0.6% 2-phenoxyethanol

  HCPDT Lot C0123A was used for Doses 1-3. HCPDT Lot C0756AA was used for Dose 4.

- Control Vaccine 2: POLIOVAX, poliovirus vaccine, inactivated, manufactured by Sanofi Pasteur Limited (licensed, but not distributed, in the U.S.); composition per 0.5 ml dose:

  Active Ingredients:
  40 DAU Poliovirus Type 1 Mahoney
  8 DAU Poliovirus Type 2 MEF-1

32 DAU Poliovirus Type 3 Saukett

Preservative: 0.6% 2-phenoxyethanol

Other ingredients: ---------- (by calculation) (note: POLIOVAX without ---------- was used for the fourth dose) --------- Tween 80 (by calculation), 1 ppm bovine serum (by calculation), and traces of polymyxin B and neomycin.

POLIOVAX Lot 8445-12 was used for Doses 1-3. POLIOVAX Lot C0880AB was used for Dose 4.

- Control Vaccine 3: ActHIB, Hib conjugate vaccine manufactured by Sanofi Pasteur SA (licensed in the U.S.); composition per 0.5 ml dose:

  10 µg of lyophilized purified PRP capsular polysaccharide of Hib covalently bound to 24 µg of inactivated tetanus toxoid

  Other ingredients: 8.5% sucrose

  Diluent: 0.5 ml saline

  ActHIB lot UA480A (R0181 [bulk lot)] was used for Doses 1-3. Lot R0181 (bulk lot) was used for Dose 4.

- Other Vaccine 1: Prevnar [Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein), Wyeth Pharmaceuticals Inc.] was licensed in the U.S. in February 2000. Each 0.5 ml dose of Prevnar contains 2 µg of each polysaccharide for *Streptococcus pneumoniae* serotypes 4, 9V, 14, 18C, 19F, and 23F and 4 µg of serotype 6B (16 µg total polysaccharide); approximately 20 µg of CRM_{197} protein; and 0.125 mg of aluminum as aluminum phosphate adjuvant. Prevnar lots 471-212 and 474-723 were used in this study.

- Other Vaccine 2: RECOMBIVAX HB [Hepatitis B Vaccine (Recombinant), Merck & Co., Inc] is licensed in the U.S. Each 0.5 ml dose contains 5 µg of purified HBsAg without preservative. Lot Numbers 1948H, 0134J, 1032K, 1423K, and 1381J were used in this study.

- Other Vaccine 3: MMR_{II} (Measles, Mumps, and Rubella Virus Vaccine Live, Merck & Co., Inc.) is licensed in the U.S. Each 0.5 ml dose contains not less than 1,000 TCID50 (tissue culture infectious doses) of measles virus; -------- TCID50 of mumps virus; and 1,000 TCID50 of rubella virus. Each dose contains approximately 25 µg of neomycin; sorbitol and hydrolyzed gelatin as stabilizers. The product contains no preservative. Lot numbers MMR 1179K and MMR Diluent M1012K and M1013K were used in this study.

- Other Vaccine 4: VARIVAX [Varicella Virus Vaccine Live (Oka/Merck); Merck & Co., Inc.] is licensed in the U.S. Each 0.5 ml dose contains a minimum of 1350 plaque forming units of Oka/Merck varicella virus. The vaccine contains no preservative. Lot numbers were identified at the time of use.

Sites and Route of Vaccine Administration

The sites and routes of administration of study vaccines were as follows:
Pentacel: intramuscular, left upper thigh for doses 1-3; left upper arm for dose 4

HCPDT: intramuscular, left upper thigh for doses 1-3, left upper arm for dose 4
POLIOVAX: intramuscular, left lower thigh for doses 1-3, right lower thigh for dose 4
ActHIB: intramuscular, right upper thigh
RECOMBIVAX HB: intramuscular, right lower thigh
Prevnar: intramuscular, right upper thigh (at least one inch away from ActHIB site in control group) for doses 1-3; site not specified for dose 4
MMR_{II}: subcutaneous; site not specified
VARIVAX: subcutaneous; site not specified

6.1.1.5 Safety Endpoints

There were no pre-specified primary safety endpoints. Secondary analyses of lot consistency of Pentacel and non-inferiority of Pentacel vs. Control vaccines with regard to rates of fever were prospectively defined, and are described in Table 8. All other safety analyses were observational, without predefined evaluation criteria.

Table 8. Study 494-01 Prospective secondary safety endpoints and evaluation criteria

Endpoint	Comparisons for each indicated dose	Evaluation criteria
Rate of fever ≥38.0°C within 72 hours following Pentacel	Doses 1, 2, and 3: Lot 2 – Lot 1 Lot 3 – Lot 1 Lot 3 – Lot 2	Lot equivalence: For each difference, upper limit of 90% confidence interval <10% and lower limit of 90% confidence interval >-10%
Rate of fever ≥38.0°C within 72 hours following Pentacel or control vaccines	Doses 1, 2, and 3: Pooled Pentacel Lots – Control Dose 4: Pentacel – Control	Non-inferiority: For each difference, upper limit of 90% confidence interval <10%

6.1.1.6 Safety Surveillance/Monitoring

Overview of Safety Monitoring Procedures

Safety was monitored following all study vaccines except those administered at 12 months of age. Safety monitoring, as summarized in Table 9, included on-site observation of subjects, use of diary cards, and telephone interviews. Completed diary cards were mailed to the study site and served as the source document for events that occurred on Days 0-7 post-vaccination.

Table 9. Study 494-01: Summary of safety monitoring procedures following each dose of study vaccines except those administered at 12 months of age

Type of adverse event/Interval since vaccination	Monitoring
immediate events within 30 minutes post- vaccination	• observation at study site
solicited local and systemic events Days 0-7 post-vaccination	• events recorded daily on diary cards • phone calls at approximately Day 4 and Day 8 following each vaccination
unsolicited events that represent a change in health status Days 0-7 post-vaccination	• events recorded daily on diary cards • phone calls at approximately Day 4 and Day 8 following each vaccination
medically attended (phone consultation, office visit, ER visit, hospitalization) unsolicited events through Day 60 post-vaccination	• events recorded daily on diary cards for Days 0-7 • phone calls at approximately Day 4 and Day 8 following each vaccination • phone call, interview at study site, or review of computerized records (if available) at Day 30 and Day 60 following each vaccination[1]
serious events	• events recorded daily on diary cards for Days 0-7 • phone calls at approximately Day 4 and Day 8 following each vaccination • phone call, interview at study site, or review of computerized records (if available) at Day 30 and Day 60 following each vaccination[1], at age 12 months, and at the fourth dose visit • parents instructed to call the study site to report serious adverse events at any time during the study period

[1]For the first 478 recruited Pentacel subjects/lot (1434 total Pentacel subjects) and the first 478 Control subjects, visits at the study site for blood sampling were scheduled 28-48 days following the third and fourth doses of study vaccines. These visits may have served as the 30-day safety follow-up.

Solicited Local and Systemic Adverse Events

The diary cards solicited information on the occurrence and severity of local and systemic adverse events. Local reactions were assessed at the Pentacel, HCPDT, POLIOVAX, ActHIB, and RECOMBIVAX HB injection sites. Solicited local reactions included injection site redness, swelling, and tenderness. Increase in arm circumference relative to baseline was also assessed following the fourth dose of Pentacel or HCPDT. Rulers were provided to measure the diameter of redness and swelling. Measuring tapes were provided for measuring arm circumference. The occurrence of whole limb swelling was not solicited.

Solicited systemic reactions included fever, decreased activity, inconsolable crying, diarrhea, fussiness, anorexia, vomiting, and rash. Monitoring for rash was intended to capture allergic reactions manifested as hives. The definition used for rash was "well-circumscribed wheals or welts with red raised irregular borders with blanched centers that may coalesce to become giant wheals". Digital thermometers were provided for measuring temperature. Parents/guardians were instructed to take rectal temperatures following Doses 1-3 of Pentacel or Control vaccines and axillary temperatures following the fourth dose. Actual routes of temperature measurement were recorded on the diary cards.

Whether infants with fever post-vaccination had medical visits for fever was not solicited.

Unsolicited Adverse Events

Unsolicited adverse events were monitored as described in Table 9.

Information on the occurrence of seizures and HHEs was not specifically solicited on the diary cards. The Day 4 and 8 phone calls included a question about the occurrence of seizures, fainting or change in mental status since vaccination.

The severity of unsolicited adverse events was established by the investigator using the following definitions:
0 = None
1 = Mild: easily tolerated.
2 = Moderate: discomfort enough to cause interference with usual activity.
3 = Severe: incapacitating with inability to do usual activity.

Serious Adverse Events
A serious adverse event was defined as per 21CFR§312.32(a) as "any adverse drug experience occurring at any dose that resulted in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may have not resulted in death, been life-threatening, or required hospitalization may have been considered a serious adverse drug experience when, based upon appropriate medical judgment, they may have jeopardized the patient or subject and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalization, or the development of drug dependency or drug abuse."

6.1.1.7 Statistical Considerations Related to the Safety Evaluation
Sample Size
The planned sample size of 3,400 subjects randomized to receive either Pentacel (one of three lots) or Control vaccines (Pentacel: 2,400 subjects, Control: 1,000 subjects) was based on safety considerations. The sample size confers 81-84% power to rule out a 3-fold increase in adverse events (Pentacel vs. Control) occurring in 1% of Control subjects ($\alpha = 0.05$), following each of the first three doses, assuming an attrition rate of 10% by dose 3.

For each of the secondary lot consistency and non-inferiority analyses of fever, assuming an attrition rate of 10% to dose 3 and of 10% from dose 3 to dose 4, the planned sample size provides approximately 100% statistical power (assuming a 0.05 significance level). For these calculations, the fever rate within 24 hours post-immunization in historical trials was used, although fever rates within 72 hours post-immunization were evaluated in this study.

Analysis Population for Safety
The intent-to-treat (ITT) analyses for safety included subjects who received at least one dose of vaccine, regardless of whether they adhered to the study eligibility criteria or their visits were within the protocol-specified windows. The safety analyses are based on the ITT population only. For per-dose analyses, each lot/treatment group represents what subjects actually received. For safety analyses across more than one dose combined, the subject group is defined as per randomization.

Analyses of Fever
Before analyses of fever were conducted, the applicant submitted information to the IND indicating that in Study 494-01 and other pivotal studies of Pentacel in which the protocol recommended that temperatures be measured rectally following the first three doses of Pentacel

or Control vaccines, approximately half of these measurements were axillary. 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 other vaccines. Because the applicant did not accept CBER's recommendation to use a 1.0°C conversion and 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[4], CBER subsequently recommended that the main analyses of fever be conducted without conversion of axillary measurements.

HHE Definition
Although a definition for HHE was not included in the protocol, the criteria used for reporting HHE in the final study report were those published in a report of a U.S. Public Health Service workshop on HHE after pertussis immunization. (See section 5.1.2.1)

Classification of Seizures and Related Diagnoses
Although not specified in the protocol, seizures and related diagnoses were classified in the final study report as follows:

- Non-febrile Seizures: Events that were reported as seizures, convulsions or epilepsy without the association of fever. This category also included seizures associated with fever, but for which a primary cause of seizures was identified (e.g., seizures in a subject with meningitis).
- Febrile Seizures: Events reported as "febrile seizures" or synonymous.
- Possible Seizures: Events indicated as such by the investigator.
- Other Possible Neurological Events: Events identified in the clinical database and categorized as such by the Medical Monitor; includes symptoms that may have a possible neurological origin but for which no further information was available to make a diagnosis (e.g., tremors, shaking). This category was specifically intended to capture events that may have raised the suspicion of seizures yet were not considered seizures or possible seizures by Investigators. Neurological events not associated with seizure-like symptoms were not included in this category.

6.1.2 Results

6.1.2.1 Changes to the Data Resulting from Audit of Safety Database
During analysis of the safety data, the applicant noted inconsistencies in reporting of subject termination status and protocol violations. As a result, an audit of the safety database was performed using a special protocol for the audit of already analyzed data. The special protocol included an audit review board to assess the results of the audit. The auditors were blinded to treatment group. Following the audit, the database was unlocked and corrected. Changes to the safety data resulted from re-categorization of solicited adverse events that were incorrectly reported as unsolicited, removal of duplicate reports, and queries for clarification. A summary of changes to the database as a result of the audit is presented in Appendices 2-5.

6.1.2.2 Populations Enrolled/Analyzed
Study Sites and Study Period
Subjects were enrolled from 16 U.S. sites. The study period from the first subject visit to the last subject visit was 12/29/99 through 4/23/02.

Subject Disposition and Follow-up

Table 10 presents a summary of subject disposition with regard to the safety evaluation, from randomization through 60 days post-Dose 3. There was one treatment error involving receipt of an unintended lot of Pentacel. In addition, at Dose 2, two subjects who were randomized to receive Pentacel received HCPDT and two subjects who were randomized to receive HCPDT received Pentacel.

Table 10. Study 494-01 Summary of subject disposition for safety evaluation from randomization through 60 days post-Dose 3

Disposition	Pentacel Lot 1 n (%)	Pentacel Lot 2 n (%)	Pentacel Lot 3 n (%)	Pooled Pentacel Lots n (%)	Control n (%)
All Randomized Subjects	836	835	836	2507	1036
Randomized but did not Receive Dose 1	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)	4 (0.4)
Subject Participation by Randomized Treatment	836	835	835	2506	1032
Intent-to-Treat (ITT) Safety Population[1]	836 (100.0)	836 (100.0)	834 (100.0)	2506 (100.0)	1032 (100.0)
Received Dose 1 of Pentacel or HCPDT[2]	836 (100.0)	836 (100.0)	834 (100.0)	2506 (100.0)	1032 (100.0)
Received Doses 1 and 2 of Pentacel or HCPDT[3]	796 (95.2)	795 (95.1)	783 (93.9)	2374 (94.7)	945 (91.6)
Received 3 doses of Pentacel or HCPDT[4]	772 (92.3)	768 (91.9)	754 (90.4)	2294 (91.5)	900 (87.2)
Completed 60-day Safety Follow-up Post-Dose 3[5]	757 (90.6)	754 (90.3)	740 (88.6)	2251 (89.8)	880 (85.3)
Did not complete 60-day Safety Follow-up[5, 6]	79 (9.4)	81 (9.7)	95 (11.4)	255 (10.2)	152 (14.7)
Did not complete 60-day Safety Follow-up[5, 6]	79 (100.0)	81 (100.0)	95 (100.0)	255 (100.0)	152 (100.0)
Adverse event	1 (1.3)	2 (2.5)	1 (1.1)	4 (1.6)	2 (1.3)
Contraindication	2 (2.5)	0 (0.0)	2 (2.1)	4 (1.6)	1 (0.7)
Lost to follow-up	12 (15.2)	7 (8.6)	8 (8.4)	27 (10.6)	8 (5.3)
Non-compliance	22 (27.8)	33 (40.7)	28 (29.5)	83 (32.5)	54 (35.5)
Voluntary withdrawal	42 (53.2)	39 (48.1)	56 (58.9)	137 (53.7)	87 (57.2)

[1]Safety Population: All subjects enrolled who received at least 1 dose of Pentacel or HCPDT and have been classified according to the actual treatment received at Dose 1. One subject who was randomized to receive Pentacel lot 3 received lot 2 at dose 1. This subject was analyzed for safety according to the lot received at each dose.
[2] Subjects have been classified by the actual treatment received at Dose 1.
[3] Subjects have been classified by the actual treatment received at Dose 2.
[4] Subjects have been classified by the actual treatment received at Dose 3.
[5] Subjects have been classified by the randomized treatment.
[6] Subjects terminated anytime between receipt of Dose 1 and the post-Dose 3 60-day safety follow-up telephone call; only the primary reason for termination per subject is selected in the order listed.
Source: 49401si.pdf, pages 87-88.

Table 11 presents a summary of disposition for safety through the end of the study for subjects who completed the 60-day safety follow-up post-Dose 3. Of note are Dose 4 treatment errors in

71 subjects (see table footnotes). All but two errors occurred at the same investigator site. All subjects who did not receive ActHIB at the scheduled study visit were recalled and given the 4th dose of ActHIB as soon as the treatment error was identified.

Table 11. Study 494-01 Summary of subject disposition for safety evaluation through the end of study for subjects who completed the 60-day follow-up post-Dose 3

Disposition	Pentacel n (%)	Control n (%)
Completed 60-Day Safety Follow-up Post-Dose 3[1]	2251	880
Completed 60-day safety follow-up post-Dose 3 but terminated before Dose 4[1,2]	356 (15.8)	175 (19.9)
Completed 60-Day Safety Follow-up Post-Dose 3 But Terminated Before Dose 4[1,2]	356 (100.0)	175 (100.0)
Adverse event	9 (2.5)	2 (1.1)
Contraindication	0 (0.0)	1 (0.6)
Lost to follow-up	18 (5.1)	11 (6.3)
Non-compliance	56 (15.7)	25 (14.3)
Voluntary withdrawal	273 (76.7)	136 (77.7)
Subject Participation By Randomized Treatment	1895	706[3]
Completed 60-day safety follow-up post-Dose 4[4]	1882 (99.3)	698 (98.9)
Did not complete 60-day safety follow-up post-Dose 4[4,5]	13 (0.7)	8 (1.1)
Did Not Complete 60-Day Safety Follow-up Post-Dose 4[4,5]	13 (100.0)	8 (100.0)
Adverse event	0 (0.0)	0 (0.0)
Contraindication	0 (0.0)	0 (0.0)
Lost to follow-up	3 (23.1)	0 (0.0)
Non-compliance	5 (38.5)	3 (37.5)
Voluntary withdrawal	5 (38.5)	5 (62.5)
Intent-to-Treat (ITT) Safety Population [6,7]	1862[7]	739[7]

[1]Subjects have been classified by the randomized treatment.
[2]Subjects who were terminated anytime between completing the post-Dose 3 60-day safety follow-up telephone call and receiving Dose 4. Only the primary reason for termination per subject is selected in the order listed.
[3] Subject 3253 did not complete 60-day safety follow-up post-Dose 3 but received the 4th dose.
[4] Subjects have been classified by the randomized treatment.
[5] Subjects who were terminated anytime between receipt of Dose 4 and the post-Dose 4 60-day safety follow-up telephone call. Only the primary reason for termination per subject is selected in the order listed.
[6] Subjects have been classified by the actual treatment received at Dose 4.
[7] There were treatment errors in 71 subjects: 51 subjects who were to receive Pentacel received only HCPDT, 1 subject who was to receive Pentacel received HCPDT, POLIOVAX, and ActHIB, 18 subjects who were to receive control vaccines received Pentacel, POLIOVAX, and ActHIB, and 1 subject who was to receive control vaccines received Pentacel.
Source: 49401sii.pdf, pages 80 and 83

Table 12 provides a list of adverse events leading to study withdrawal following any dose of Pentacel or Control vaccines.

Table 12. Study 494-01 Adverse events, including contraindicating events, that led to study withdrawal

Subject/ Vaccine	Adverse Event (Literal Term)	Last Dose[1]	Days since Last Dose	Duration in Days	Severity	Outcome
2214/ Pentacel	Crying	1	0	4	Severe	Information not collected
2320/ Pentacel	Benign myoclonic jerks	1	45	NR[2]	Mild	Event is continuing[3]
2447/ Pentacel	Sagittal synostosis	1	35	25	Moderate	Recovered without sequelae
2732/Pentacel	Crying >3 hours	1	0	1	Severe	Recovered without sequelae
0146/ Pentacel	Crying	2	1	7	Severe	Information not collected
364/ Pentacel	R/O seizure disorder	2	52	3	Severe	Recovered with sequelae
0178/ Pentacel	New onset seizure	3	296	1	Severe	Recovered without sequelae
497/ Pentacel	Cystic Fibrosis	3	263	-	Moderate	NR[2]
541/ Pentacel	Febrile seizure	3	99	1	Moderate	Recovered without sequelae
856/ Pentacel	Febrile seizure	3	220	1	Severe	Recovered without sequelae
858/ Pentacel	Myotonic jerking movements	3	138	2	Severe	Recovered without sequelae
1218/ Pentacel	Seizures	3	256	1	Severe	Death[4]
1336/ Pentacel	Seizure	3	149	1	Mild	Recovered without sequelae
1386/ Pentacel	Gross motor delay	3	115	-	Moderate	NR[2]
1562/ Pentacel	Holding breath/ potential seizure	3	237	1	Severe	Recovered without sequelae
1584/ Pentacel	Febrile seizure	3	106	1	Mild	Recovered without sequelae
1958/ Pentacel	Seizures	3	29	8	Severe	Recovered without sequelae
2767/ Pentacel	Crying	3	1	11	Severe	Information not collected
2962/ Pentacel	Failure to thrive	3	61	-	Mild	NR[2]
8/ Control	Pneumococcal meningitis	1	44	11	Severe	Recovered without sequelae
2613/ Control	Hives	1	1	3	Moderate	Recovered without sequelae
3449/ Control	Migraine variant seizure activity[5]	2	0	2	Severe	Recovered without sequelae
725/ Control	Nephrotic syndrome	3	NR[2,6]	NR[2,6]	NR[2,6]	NR[2,6]
955/ Control	Febrile seizure	3	290	1	Mild	Recovered without sequelae
2751/ Control	Crying	3	3	3	Severe	Information not collected

[1] The last dose is defined as the dose received on or before the date of the adverse event.
[2] Not Reported. Information not reported by the time of study termination.
[3] The outcome listed is the known outcome at the time of the database lock.
[4] This subject experienced afebrile seizure activity while hospitalized and died one day later. The cause of death was secondary to neuroblastoma
[5] This subject also had severe crying, with onset the same day as Dose 2 of study vaccines. Crying lasted for 7 days and was reported to decrease in intensity over time.
[6] The adverse event was noted as the reason for withdrawal in the case report form, but was not recorded on the adverse event page of the case report form.
Source: 49401si.pdf, page 86; 49401sii.pdf, page 81; questions1_133.pdf pages 22-25

In addition to the adverse events listed in Table 12, one subject (# 1063) in the Pentacel group withdrew at parental request approximately two months after an episode of intermittent, startle-like jerking lasting for approximately 20 minutes, followed by crying on the evening of the first dose. The event resolved without sequelae. The subject was evaluated by a physician two days

later and reported to have normal health status (source: 49401si.pdf, page 85 and response_fax09nov06.pdf, page 5). Although the event triggered the request for withdrawal, the withdrawal was coded as voluntary rather than due to an adverse event.

Summary of Concomitant Administration of Prevnar

When Study 494-01 was designed, Prevnar was not routinely administered to U.S. infants. Shortly after the study was initiated, Prevnar was licensed and recommended for use in U.S. infants. Consequently, some subjects enrolled early in Study 494-01 received Pentacel or Control vaccines without concomitant Prevnar at 2 months of age. Nearly 80% of subjects received Pentacel or Control vaccines concomitantly with Prevnar at 2, 4, and 6 months of age (Table 13).

Table 13. Study 494-01 Summary of concomitant use of Prevnar with Pentacel or Control vaccines, safety population

Received Prevnar with Pentacel or HCPDT	Pentacel	Control
	n/N (%)	n/N (%)
Dose 1	2007/2506 (80.0)	830/1032 (80.4)
Doses 1 and 2	1893/2374 (79.7)	757/945 (80.1)
Doses 1, 2 and 3	1808/2294 (78.8)	712/900 (79.1)

n=number of subjects who received concomitant Prevnar
N=number of subjects who received Pentacel or HCPDT with or without concomitant Prevnar
Source: iss.pdf, page 191

Subject Demographics

There were no notable differences between the three Pentacel lot groups with respect to age, sex, or racial distribution. Table 14 presents a summary of subject demographics at enrollment for the pooled Pentacel groups and the Control group. The mean age at administration of the fourth dose was 15.5 (range 14.1-20.8) months for the Pentacel group and 15.5 (range 14.2-19.4) months for the Control group.

Table 14. Study 494-01 Summary of subject demographics at enrollment, safety population

Demographic Characteristic	Pooled Pentacel Lots n (%)	Control n (%)
Sex	N=2506	N=1032
Male	1246 (49.7)	509 (49.3)
Female	1260 (50.3)	523 (50.7)
Age (months)		
Mean	2.1	2.1
Median	2.1	2.1
Range	(1.4, 3.3)	(1.4, 3.3)
Race		
Caucasian	1489 (59.4)	623 (60.4)
Black	273 (10.9)	111 (10.8)
Hispanic	333 (13.3)	135 (13.1)
Asian	153 (6.1)	67 (6.5)
Other	258 (10.3)	96 (9.3)

Notes: Treatment group is determined by actual treatment received at 1st vaccination.
Age (months) = (1st vaccination date - Date of birth + 1) / (365.25/12).
Source: 49401si.pdf, page 90

6.1.2.3 Safety Outcomes

Antipyretic Use

Use of antipyretics/analgesics theoretically may affect the occurrence of some local or systemic adverse events. Table 15 presents the percentage of subjects who used antipyretics within 3 days following each dose of Pentacel or Control vaccines.

Table 15. Study 494-01 Number (percentage) of subjects who received antipyretics during the period 0-3 days post-vaccination

Dose number	Pentacel (pooled lots for Doses 1-3)	Control
1	N = 2506 1114 (44.5)	N = 1032 563 (54.6)
2	N = 2374 950 (40.0)	N = 945 421 (44.6)
3	N = 2294 902 (39.3)	N = 900 391 (43.4)
4	N = 1862 616 (33.1)	N = 739 271 (36.7)

Source: 49401si.pdf, page 3273 and 49401sii.pdf, page 408

Immediate Reactions

During the 30 minute post-vaccination observation period at the study sites, one subject who received Pentacel and one subject who received Control vaccines experienced an adverse event.

Subject 3141 experienced hives on the legs within 30 minutes after the third dose of Pentacel. The event was considered mild and resolved without sequelae in two days. The Investigator considered the hives as probably related to vaccination. The subject reported no immediate reactions following the fourth dose of Pentacel.

Subject 269 experienced mild diarrhea within 30 minutes after the second dose of Control vaccines. No treatment was required and the event resolved without sequelae.

Solicited Local Reactions

Table 16 presents the frequencies of solicited local adverse events at the Pentacel and HCPDT injection sites that occurred within 0-3 days following each of doses 1-4. The frequency of local tenderness, including moderate and severe tenderness, tended to be higher following HCPDT than Pentacel. For other solicited local reactions, there were no notable differences between the two groups. In general, at both the Pentacel and HCPDT injection sites, the frequencies of redness, swelling, and tenderness were higher following the fourth dose compared with Doses 1-3 (Table 16).

There was a tendency toward higher rates of solicited local reactions for the Control group relative to the Pentacel group when reactions at any of the three Control injection sites (i.e., HCPDT, POLIOVAX, or ActHIB) were compared to the Pentacel injection site (data not shown).

In both study groups, frequencies of solicited local reactions within seven days and within three days following vaccination were similar, indicating that onset was typically within the first three days. Frequencies of each of the solicited local reactions during the period 4-7 days following Doses 1-3 of Pentacel or HCPDT were generally $\leq$1%, indicating resolution with the first three days in nearly all cases. During the period 4-7 days following the fourth dose of Pentacel or

HCPDT, redness, swelling, and tenderness were each reported in approximately 2% of subjects and increased limb circumference in approximately 9%.

For the three Pentacel subjects who reported a >40 mm increase in limb circumference post-Dose 4, the maximum reported percent increases over baseline measurement ranged from 27%-33%.

The occurrence of whole limb swelling was not solicited. No subject reported whole limb swelling as an unsolicited adverse event. For one subject, the comment section of the Case Report Form noted "swelling" of both the Pentacel and RECOMBIVAX HB injection sites. However, swelling was not reported as a solicited adverse event for this subject and no further information was provided on the characteristics of this event.

Table 16. Study 494-01: Frequencies of solicited local reactions, by severity, at the Pentacel and HCPDT injection sites occurring between 0-3 days following each dose, safety population

Event/Severity	Pentacel[1]				HCPDT			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
	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
>5mm	121 (5.3)	95 (4.4)	81 (4.1)	346 (21.4)	43 (4.6)	30 (3.5)	26 (3.3)	123 (19.5)
>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)
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)
>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)
Swelling	N=2295	N=2145	N=1987	N=1598	N=927	N=849	N=786	N=633
>5mm	111 (4.8)	69 (3.2)	43 (2.2)	187 (11.7)	47 (5.1)	25 (2.9)	14 (1.8)	72 (11.4)
>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)
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)
>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)
Tenderness[2]	N=2309	N=2155	N=2008	N=1642	N=932	N=853	N=790	N=639
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)
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)
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)
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)
Increased Limb Circumference[3]				N=1563				N=605
>5 mm	n/a	n/a	n/a	396 (25.3)	n/a	n/a	n/a	131 (21.7)
>5-<20 mm	n/a	n/a	n/a	322 (20.6)	n/a	n/a	n/a	112 (18.5)
20-40 mm	n/a	n/a	n/a	71 (4.5)	n/a	n/a	n/a	19 (3.1)
>40 mm	n/a	n/a	n/a	3 (0.2)	n/a	n/a	n/a	0 (0.0)

[1]For Doses 1-3, the three Pentacel lots are pooled.
[2]Mild = subject whimpers when site is touched; Moderate = subject cries when site is touched; Severe = subject cries when leg or arm is moved.
[3]Increase in limb 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.
n/a indicates information not collected.
Source: 49401si.pdf, pages 121-122; 49401sii.pdf, page 115

Route of Temperature Measurement

The frequency of use of different routes of temperature measurement following Doses 1, 2, and 3 of Pentacel were similar for the three Pentacel lots. Table 17 presents data on the routes of temperature measurement for the Pentacel and Control groups, by dose. Although parents were instructed to take rectal temperatures for Doses 1-3, axillary measurements were taken approximately 45% of the time. Following Dose 4 of Pentacel or Control vaccines, approximately 70% of temperature measurements were axillary, as parents were instructed, approximately 25% were rectal, and the rest were taken either orally, with tympanic thermometers, or by an unspecified route.

Table 18 presents the frequency of fever, by severity, for subjects who had a rectal temperature recorded and for subjects who had an axillary temperature recorded within three days following each dose of Pentacel or Control vaccines. Approximately 5% of subjects switched route of temperature measurement during the 0-3 day period and thus may be included in both categories, rectal and axillary. The frequency of fever $\geq$38.0°C was approximately 2.5 to 4-fold higher (depending on dose number and study group) when predominantly rectal measurements were considered compared to axillary measurements. Notable differences in fever rates for rectal versus axillary measurements were consistently observed for each severity category of fever analyzed with the exception of fever >39.5°C, which was reported in only a few (i.e., 0-10) subjects following each dose of Pentacel or Control vaccines.

Table 17. Study 494-01 Routes of temperature measurement, safety population

	Pentacel[1]				Control			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total number of days with recorded temperature	17889	16659	15559	12781	7145	6550	6017	4958
Axillary	8532 (47.7)	7444 (44.7)	6708 (43.1)	8982 (70.3)	3403 (47.6)	2970 (45.3)	2613 (43.4)	3308 (66.7)
Rectal	9108 (50.9)	8966 (53.8)	8499 (54.6)	3271 (25.6)	3644 (51.0)	3488 (53.3)	3258 (54.1)	1372 (27.7)
Tympanic	8 (0.0)	8 (0.0)	26 (0.2)	146 (1.1)	2 (0.0)	2 (0.0)	16 (0.3)	89 (1.8)
Oral	39 (0.2)	58 (0.3)	115 (0.7)	261 (2.0)	44 (0.6)	43 (0.7)	64 (1.1)	114 (2.3)
Not Recorded	202 (1.1)	183 (1.1)	211 (1.4)	121 (0.9)	52 (0.7)	47 (0.7)	66 (1.1)	75 (1.5)

[1]For Doses 1, 2, and 3, the three Pentacel lots are pooled.
Percentages are based on the total number of days with recorded temperatures in the Safety Population.
'n' is the number of temperatures taken by the specified route.
Source: 49401si.pdf, page 123; 49401sii.pdf, page 116

Table 18. Study 494-01 Number (percentage) of subjects with fever within 0-3 days following Doses 1-4 of Pentacel or Control vaccines, by route of temperature measurement (rectal or axillary), safety population

	Pentacel[1]				Control			
Route[2]/Category of fever	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
Rectal	N=1241 n (%)	N=1184 n (%)	N=1119 n (%)	N=451 n (%)	N=490 n (%)	N=458 n (%)	N=430 n (%)	N=184 n (%)
≥38.0°C	144 (11.6)	246 (20.8)	288 (25.7)	104 (23.1)	102 (20.8)	103 (22.5)	118 (27.4)	52 (28.3)
≥38.0-≤38.5°C	124 (10.0)	193 (16.3)	196(17.5)	87 (19.3)	89 (18.2)	73 (5.9)	94 (21.9)	39 (21.2)
>38.5-≤39.5°C	16 (1.3)	51(4.3)	82 (7.3)	14 (3.1)	12 (2.4)	30 (6.6)	20 (4.7)	11 (6.0)
>39.5°C	4 (0.3)	2 (0.2)	10 (0.9)	3 (0.7)	1 (0.2)	0 (0.0)	4 (0.9)	2 (1.1)
Axillary	N=1156 n (%)	N=980 n (%)	N=891 n (%)	N=1193 n (%)	N=463 n (%)	N=389 n (%)	N=342 n (%)	N=443 n (%)
≥38.0°C	42 (3.6)	56 (5.7)	85 (9.5)	70 (5.9)	23 (5.0)	28 (7.2)	37 (10.8)	29 (6.5)
≥38.0-≤38.5°C	28 (2.4)	35 (3.6)	57 (6.4)	45 (3.8)	15 (3.2)	17 (4.4)	26 (7.6)	17 (3.8)
>38.5-≤39.5°C	11 (1.0)	18 (1.8)	23 (2.6)	17 (1.4)	8 (1.7)	6 (1.5)	10 (2.9)	11 (2.5)
>39.5°C	3 (0.3)	1 (0.3)	5 (0.6)	8 (0.7)	0 (0.0)	5 (1.3)	1 (0.3)	1 (0.2)

[1]For Doses 1-3, the three lots of Pentacel are pooled.

[2]The Ns for rectal and axillary routes represent the total number of subjects for whom a temperature was recorded via the respective route within 0-3 days following vaccination. Overall, approximately 5% of subjects switched route of temperature measurement during the period 0-3 days following vaccination. Thus, some subjects may be included under both rectal and axillary.

Source: 49401si.pdf, pages 611-634 and 49401sii.pdf, Table 9.24, pages 224-229

Lot Consistency of Fever Rates

Table 19 presents results of the pre-specified secondary Pentacel lot equivalence analyses of fever rates.

Table 19. Study 494-01 Equivalence comparison of rates of fever ≥38°C across lots of Pentacel within 3 days after each dose, safety population

Fever ≥38°C within 3 days after vaccination	Pentacel			Difference in Fever Rates			Equivalence[1]
	Lot 1	Lot 2	Lot 3				
	N n (%)	N n (%)	N n (%)	Lot 2-Lot 1 (90% CI)	Lot 3-Lot 1 (90% CI)	Lot 3-Lot 2 (90% CI)	Yes/No
Dose 1	766 41 (5.4)	775 50 (6.5)	755 95 (12.6)	1.10 (-0.87, 3.07)	7.23 (4.84, 9.62)	6.13 (3.67, 8.59)	Yes
Dose 2	711 99 (13.9)	708 89 (12.6)	711 116 (16.3)	-1.35 (-4.31, 1.61)	2.39 (-0.73, 5.51)	3.74 (0.68, 6.81)	Yes
Dose 3	674 136 (20.2)	656 119 (18.1)	658 128 (19.5)	-2.04 (-5.59, 1.51)	-0.73 (-4.32, 2.87)	1.31 (-2.23, 4.86)	Yes

[1]Equivalence is achieved if the upper limit of each 90% confidence interval is <10% and the lower limit is >–10% for Lot 2-Lot 1, Lot 3-Lot 1, and Lot 3-Lot 2.
Note: 'n' is the number of subjects in the treatment group with fever.
'N' is the number of subjects with available data in the Safety Population.
Fever is based upon actual temperatures recorded with no adjustment for route of measurement.
Source: 49401si.pdf, page 111

Non-inferiority of Fever Rates

Table 20 presents the results of the pre-specified secondary non-inferiority analyses of fever rates following Pentacel vs. Control vaccines.

Table 20. Study 494-01 Rates of fever ≥38°C within 3 days after each dose, Pentacel group versus Control group, safety population

	Pentacel[1]	Control	Pentacel minus Control		Non-Inferiority[1]
Fever	N n (%)	N n (%)	%	90% CI	Yes/No
Dose 1	2296 186 (8.1)	920 127 (13.8)	-5.70	(-7.80, -3.61)	Yes
Dose 2	2130 304 (14.3)	836 131 (15.7)	-1.40	(-3.81, 1.02)	Yes
Dose 3	1988 383 (19.3)	767 158 (20.6)	-1.33	(-4.14, 1.47)	Yes
Dose 4	1630 174 (10.7)	634 83 (13.1)	-2.42	(-4.95, 0.12)	Yes

[1]For Doses 1, 2, and 3, the three Pentacel lots are pooled
[2]Non-Inferiority criteria were pre-specified as the upper limit of each 90% CI <10% for Pentacel-Control. For non-inferiority comparisons, in general, CBER currently recommends use of 95% CIs.
Notes: 'n' is the number of subjects in the treatment group with fever.
'N' is the number of subjects with available data in the Safety Population.
Fever is based upon actual temperatures recorded with no adjustment for route of measurements.

Source: 49401si.pdf, page 112; 49401sii.pdf, page 110

Observational Analyses of Solicited Systemic Adverse Events

Table 21 presents frequencies of selected solicited systemic adverse events that occurred within 0-3 days following Doses 1-4 of Pentacel or Control vaccines. In both study groups, the frequency of fever increased with successive doses from 1-3, and then decreased following dose 4 relative to dose 3. The frequency of rash tended to increase with successive doses. The frequencies of decreased activity, inconsolable crying, and fussiness tended to decrease with successive doses.

The frequencies of fever, decreased activity, inconsolable crying, fussiness, and anorexia during the period 0-7 days post-vaccination were marginally higher than frequencies reported during the period 0-3 days post-vaccination (data not shown).

Table 21. Study 494-01 Frequencies of selected systemic adverse events within 0-3 days after each dose of Pentacel or Control vaccines

Adverse Event/Severity	Pentacel[1]				Control			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fever[2]	N=2296	N=2130	N=1988	N=1630	N=920	N=836	N=767	N=634
≥38.0°C	186 (8.1)	304 (14.3)	383 (19.3)	174 (10.7)	127 (13.8)	131 (15.7)	158 (20.6)	83 (13.1)
≥38.0°C-≤38.5°C	151 (6.6)	230 (10.8)	261 (13.1)	132 (8.1)	106 (11.5)	90 (10.8)	123 (16.0)	58 (9.1)
>38.5°C-≤39.5°C	27 (1.2)	69 (3.2)	107 (5.4)	31 (1.9)	20 (2.2)	36 (4.3)	30 (3.9)	22 (3.5)
≥39.5°C	8 (0.3)	5 (0.2)	15 (0.8)	11 (0.7)	1 (0.1)	5 (0.6)	5 (0.7)	3 (0.5)
Less Active[3]	N=2330	N=2179	N=2030	N=1662	N=935	N=851	N=792	N=643
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	N=2330	N=2179	N=2030	N=1662	N=935	N=851	N=792	N=643
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)	N=2332	N=2180	N=2029	N=1662	N=935	N=851	N=792	N=643
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[4]	N=2330	N=2179	N=2028	N=1662	N=935	N=851	N=792	N=643
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)
Rash[5]	N=2330	N=2178	N=2028	N=1662	N=935	N=851	N=792	N=643
Present	34 (1.5)	36 (1.7)	52 (2.6)	61 (3.7)	16 (1.7)	17 (2.0)	26 (3.3)	18 (2.8)

[1]For doses 1-3, the three Pentacel lot groups are pooled.
[2]Fever is based upon actual temperatures recorded with no adjustment for route of measurement.
[3]Less Active: Mild = usual daily activity not affected; Moderate = interferes with or limits usual daily activity; Severe = disabling, not interested in usual daily activity.
[4]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.
[5]Rash was defined as “well-circumscribed wheals or welts with red raised irregular borders with blanched centers that may coalesce to become giant wheals”.
Notes: For each dose, each subject is counted once and is classified according to the highest recorded severity score.
'n' is the number of subjects in the treatment group with the specific reaction.
'N' is the number of subjects with available data in the Safety Population.
Source: 49401si.pdf pages 125-127; 49401sii.pdf page 118

Because there were several reports of solicited systemic adverse events or related terms that were classified as unsolicited, CBER requested summary data on fever, crying, irritability, and somnolence that were reported as unsolicited events. Within three days following any of Doses 1-4, 26 (1.0%) Pentacel subjects and 6 (0.6%) Control subjects reported fever or feeling hot or warm; 16 (0.6%) Pentacel subjects and 10 (1.0%) Control subjects reported crying, irritability, or restlessness, and 34 (1.4%) Pentacel subjects and 10 (1.0%) Control subjects reported somnolence or lethargy. Among Pentacel subjects with crying reported as unsolicited, one subject reported crying >3 hours and one subject reported unusual high pitched cry. Events graded as severe included two cases of crying and one case of irritability in Pentacel subjects, and one case each of fever, crying, irritability, and lethargy in Control subjects. Events that resulted in a medical contact (telephone call, outpatient visit, emergency room visit or hospitalization) included six cases of fever, one case of crying, and one case of somnolence in Pentacel subjects, and three cases of fever and one case of crying and irritability in Control subjects. [Source: 49401_addnl_safetyanalyses.pdf, Tables 9.65, 9.70, and 9.75]. According to the applicant, solicited events captured as unsolicited may reflect reporting solicited events during a scheduled telephone call or during a medical contact, but not in the diary card.

HHE and Hypotonia

No HHEs were reported. Five cases of hypotonia that did not meet the definition for HHE were reported—four in Pentacel subjects (N=2506) and one in a Control subject (N=1032). Of the four cases in Pentacel subjects, three occurred on the day of vaccination and were considered mild in severity. For these three cases, information on duration was not available. The other two reported cases of hypotonia, one each following Pentacel and Control vaccines, occurred >30 days post-vaccination.

Seizures

Table 22 provides a list of seizures that occurred within 30 days following any dose of Pentacel or Control vaccines. Appendix 6 provides a list of seizures that occurred anytime during the study.

Table 22. Study 494-01 Seizures and possible seizures that occurred within 30 days following any dose of Pentacel or Control vaccines

Pentacel (N=2506)						
Subject Number	Age[1] (months)	Afebrile, Febrile, or "Possible"	Literal Term	Last Dose	Days Since Last Dose	Outcome
2126	2	Afebrile	Seizure activity	1	6	Recovered without sequelae
1230	3	Afebrile	Hypoxic ischemic encephalopathy[2]	1	30	Recovered with sequelae
1958	7	Afebrile	Seizures	3	29	Recovered without sequelae[3]
0961	16	Afebrile	Seizure	4	27	Recovered without sequelae
1203	13	Febrile	Febrile seizure	4	14	Recovered without sequelae
			Possible febrile seizure[4]	4	24	Recovered without sequelae
3537	15	Febrile	Tonic-clonic febrile seizure	4	14	Recovered without sequelae
1888	4	Possible	Rule out seizure	2	20	Recovered without sequelae
0441	6	Possible	R/O seizure	3	0	Recovered without sequelae
3710	6	Possible	(Questionable seizure) Infant spasms	3	26	Recovered without sequelae
Control Vaccines (N=1032)						
Subject Number	Age[1] (months)	Afebrile, Febrile, or "Possible"	Literal Term	Last Dose	Days Since Last Dose	Outcome
3449	4	Afebrile	Migraine variant	2	0	Recovered without sequelae[5]
2501	16	Afebrile	Seizures	4	14	Recovered without sequelae
3942	2	Febrile	Febrile seizure	1	21	Recovered without sequelae
0066	15	Febrile	Possible febrile seizure[4]	4	6	Recovered without sequelae
1943	17	Febrile	Febrile seizure	4	7	Recovered without sequelae
1286	4	Possible	R/O Seizure disorder -normal exam	2	14	Recovered without sequelae

[1]Age at time of the seizure event.
[2]This subject experienced a seizure disorder secondary to anoxia and ischemic encephalopathy, as a post-operative complication of cardiac surgery.
[3]This subject continued having seizures (undetermined number) that were attributable to an intracranial lesion.
[4]This event was reported as a possible febrile seizure by the Investigator, but was categorized as a febrile seizure by the Medical Monitor.
[5]In a letter to the applicant approximately 2.5 years after the event, the Investigator indicated that the child continued to have seizures.
No seizures or possible seizures within 30 days of vaccination were reported by subjects not receiving study vaccines as randomized.
NR = information not reported
Source: 49401_addnl_safetyanalyses.pdf, pages 7-11; questions1_133.pdf pages 38-41

Incidence rates (per subjects) of seizures and possible seizures that occurred after any dose (1-4) of Pentacel or Control vaccines, by interval since vaccination, are presented in Table 23.

Table 23. Study 494-01 Incidence, **per subjects**, of seizures and possible seizures that occurred after any dose (1-4) of Pentacel or Control vaccines, safety population

Period	Control (N=1032)			Pentacel (N=2506)		
	n	%	95% CI	n	%	95% CI
Seizures (febrile and afebrile)						
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	8	0.8	(0.3, 1.5)	16	0.6	(0.4, 1.0)
0-30 Days Post Any Dose (1-4)	5	0.5	(0.2, 1.1)	6	0.2	(0.1, 0.5)
0-7 Days Post Any Dose (1-4)	3	0.3	(0.1, 0.8)	1	<0.1	(0.0, 0.2)
0-3 Days Post Any Dose (1-4)	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Afebrile Seizures						
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	3	0.3	(0.1, 0.8)	7	0.3	(0.1, 0.6)
0-30 Days Post Any Dose (1-4)	2	0.2	(0.0, 0.7)	4	0.2	(0.0, 0.7)
0-7 Days Post Any Dose (1-4)	1	0.1	(0.0, 0.5)	1	<0.1	(0.0, 0.2)
0-3 Days Post Any Dose (1-4)	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.1)
Febrile Seizures						
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	5	0.5	(0.2, 1.1)	9	0.4	(0.2, 0.7)
0-30 Days Post Any Dose (1-4)	3	0.3	(0.1, 0.8)	2	0.1	(0.0, 0.3)
0-7 Days Post Any Dose (1-4)	2	0.2	(0.0, 0.7)	0	0.0	(0.0, 0.1)
0-3 Days Post Any Dose (1-4)	0	0.0	(0.0, 0.4)	0	0.0	(0.0, 0.1)
Possible Seizures						
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	1	0.1	(0.0, 0.5)	7	0.3	(0.1, 0.6)
0-30 Days Post Any Dose (1-4)	1	0.1	(0.0, 0.5)	3	0.1	(0.0, 0.3)
0-7 Days Post Any Dose (1-4)	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
0-3 Days Post Any Dose (1-4)	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)

No seizures or possible seizures were reported by subjects not receiving study vaccines as randomized.
Source: 49401_addnl_safetyanalyses.pdf, pages 46-49; questions1_133.pdf, pages 242-245

Incidence rates (per 1000 doses) of seizures and possible seizures that occurred after any dose (1-4) of Pentacel or Control vaccines, by interval since vaccination, are presented in Table 24.

Table 24. Study 494-01 Incidence, **per 1000 doses**, of seizures and possible seizures that occurred after any dose (1-4) of Pentacel or control vaccines, safety population

	Control (Number of Doses = 3583)			Pentacel (Number of Doses = 9069)		
Period	n	Rate per 1000 doses	95% CI	n	Rate per 1000 doses	95% CI
Seizures (febrile and afebrile)						
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	8	2.23	(0.96, 4.39)	18	1.98	(1.18, 3.14)
0-30 Days Post Any Dose (1-4)	5	1.40	(0.45, 3.25)	7	0.77	(0.31, 1.59)
0-7 Days Post Any Dose (1-4)	3	0.84	(0.17, 2.44)	1	0.11	(0.00, 0.61)
Afebrile Seizures						
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	3	0.84	(0.17, 2.44)	7	0.77	(0.31, 1.59)
0-30 Days Post Any Dose (1-4)	2	0.56	(0.07, 2.01)	4	0.44	(0.12, 1.13)
0-7 Days Post Any Dose (1-4)	1	0.28	(0.01, 1.55)	1	0.11	(0.00, 0.61)
Febrile Seizures						
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	5	1.40	(0.45, 3.25)	11	1.21	(0.61, 2.17)
0-30 Days Post Any Dose (1-4)	3	0.84	(0.17, 2.44)	3	0.33	(0.07, 0.97)
0-7 Days Post Any Dose (1-4)	2	0.56	(0.07, 2.01)	0	0.00	(0.00, 0.41)
Possible Seizures						
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	1	0.28	(0.01, 1.55)	7	0.77	(0.31, 1.59)
0-30 Days Post Any Dose (1-4)	1	0.28	(0.01, 1.55)	3	0.33	(0.07, 0.97)
0-7 Days Post Any Dose (1-4)	0	0.00	(0.00, 1.03)	1	0.11	(0.00, 0.61)

No seizures or possible seizures were reported by subjects not receiving study vaccines as randomized.
Source: questions1_133.pdf, pages 246-249

Case narratives are provided below for seizures and possible seizures that occurred within 30 days following any dose of Pentacel or Control vaccines. Of the seizures that occurred within 30 days following vaccination, five were reported as serious adverse events (in Pentacel Subjects 1230, 1958 and 3537 and Control Subjects 3942 and 2501) and the case narratives contain supplemental information submitted by the Investigator. For seizures not reported as serious adverse events, the case narratives contain available pertinent information from the database, without supplemental information from the Investigator.

Case Narratives for Afebrile Seizures within 30 days Following Vaccination

Pentacel Group

Subject 2126: At age 2 months, this female infant experienced seizure activity 6 days following Dose 1 of Pentacel. The event resolved without sequelae the same day. No additional seizures were reported and the subject completed the study.

Subject 1230: Ischemic Encephalopathy: At his visit for the first dose of Pentacel, this subject was found to have a heart murmur. He was diagnosed with total anomalous pulmonary venous return and associated cardiac defects, for which he underwent surgical repair 30 days post-vaccination. Post-operatively, he had two pulmonary hypertensive crises and a cardiac arrest that

led to anoxia and hypoxic ischemic encephalopathy (Day 30 post-vaccination). Sequelae included a seizure disorder, severe neurological impairment, blindness and spastic quadriplegia.

Subject 1958: At age 7 months, this female subject developed emesis followed by fever of 101.8°F (38.8°C) and a left-sided focal seizure that spread to the right arm, 29 days following Dose 3 of Pentacel. She was admitted to the hospital. CT scan showed a right temporal or parietal bleed or calcification. Sturge-Weber syndrome or a venous malformation was initially suspected on MRI, but no intracranial vascular abnormalities were found on angiogram. The MRI findings were thought to represent old hemorrhage or calcification. Cultures (site not indicated) for herpesvirus were negative. Treatment included phenobarbital. There was no recurrence of seizures during the 7-day hospitalization, and the subject recovered without sequelae. However, she experienced another seizure >60 days (not further specified) following Dose 3 of Pentacel and withdrew from the study prior to receiving Dose 4.

Subject 0961: At age 16 months, this male subject developed gastroenteritis and experienced a seizure 27 days following Dose 4 of Pentacel. He recovered without sequelae after one day and completed the study.

Control (HCPDT + POLIOVAX + ActHIB) Group
Subject 3449: At age 4 months, this female subject, who 26 days earlier sustained an unspecified head injury, experienced migraine variant seizure activity with hemiparesis within 24 hours post-Dose 2 of Control vaccines. The event was considered severe and resulted in a medical office visit. On the day of vaccination she also developed moderate vomiting, anorexia, and decreased activity, as well as severe fussiness and crying (lasting for 7 days and decreasing in intensity). The event was considered a contraindication to further vaccination and the infant was discontinued from the study. In a letter approximately 2.5 years after the event, the Investigator indicated that the subject, who was being treated with Dilantin, continued to have seizures. The family history was notable for two siblings (same father) with unilateral seizures associated with weakness of the extremities on the same side, and an uncle with migraine hemiparesis.

Subject 2501: At age 15.8 months, this female subject sustained a blow to the head by a swing 14 days following Dose 4 of HCPDT. She had a seizure the same day, with seven subsequent seizures over the next 11 days. Diagnostic tests included a skull x-ray that showed no fracture or bony destruction, a normal CT scan of the brain (eight days after onset of seizures) and a normal EEG (a day after the last seizure was observed). She recovered without sequelae after 12 days and completed the study, without additional seizures reported.

Case Narratives for Febrile Seizures within 30 days Following Vaccination

Pentacel Group
Subject 1203: At age 13 months, this male subject experienced a febrile seizure 226 days following the third dose of Pentacel, and recovered without sequelae the same day. This subject experienced two other episodes of febrile seizure, 14 days and 24 days after the fourth dose of Pentacel. One episode was associated with a viral syndrome, and one with streptococcal pharyngitis. In each case, the subject recovered without sequelae the same day. The subject completed the study without other reports of seizures.

Subject 3537: At age 15 months, this male subject experienced a tonic-clonic febrile seizure 14 days after the fourth dose of Pentacel. The same day he was noted to have a viral exanthem and fever. He recovered without sequelae and completed the study without other seizures reported.

Control (HCPDT + POLIOVAX + ActHIB) Group
Subject 3942: At age 2 months, this female subject developed fussiness and fever of 103.6°F (39.8°C), 19 days following Dose 1 of Control vaccines and was admitted to the hospital. A urinalysis was positive for bacteria. Bacterial sepsis work-up and CSF PCR for *Herpes* and enterovirus were negative. While hospitalized, the subject developed brief stiffening episodes (21 days after vaccination) and was treated with phenobarbital. The subject recovered without sequelae and completed the study without other seizures reported.

Subject 0066: At age 15 months, this male subject experienced a possible febrile seizure six days after the fourth dose of Control vaccines. The subject had an upper respiratory infection on the day of the fourth dose that was continuing on Day 6. The parents described a 10 second episode involving arching of the body and eyes rolling back. The subject recovered quickly, without sequelae, and completed the study without additional seizures. Although the investigator reported the event as a "possible febrile seizure", the applicant categorized the event as a febrile seizure.

Subject 1943: At age 17 months, this male subject experienced a febrile seizure 7 days following Dose 4 of Control vaccines. That day he also developed a viral illness. He recovered without sequelae and completed the study.

Case Narratives for Possible Seizures within 30 days Following Vaccination

Pentacel Group
Subject 1888: At age 4 months, this female subject who had an ongoing viral infection, developed a cough and experienced a possible seizure 20 days following Dose 2 of Pentacel. The same day, she recovered without sequelae from the possible seizure. No seizure acitivity was reported following the third dose of Pentacel. She voluntarily withdrew prior to the fourth dose.

Subject 441: At age 6 months, this female subject experienced fever and seizure-like symptoms on the day of Dose 3 of Pentacel. The event resolved without sequelae. The subject voluntarily withdrew due to loss of insurance coverage prior to receiving Dose 4.

Subject 3710: At age 6 months, this female subject experienced "infantile spasms (questionable seizure)" 26 days following Dose 3 of Pentacel. She was evaluated in an Emergency Room and sent home the same day as the condition was considered stable. An EEG 16 days later was normal. The subject recovered without sequelae and completed the study without other reports of seizures or possible seizures.

Control (HCPDT + POLIOVAX + ActHIB) Group
Subject 1286: At age 4 months, this female subject was evaluated to rule out a seizure disorder 14 days following Dose 2 of Control vaccines. The examination was normal. The subject recovered without sequelae the same day and completed the study without other reports of seizures or possible seizures.

Other Neurological Events that may be Observed in the Context of Seizures
In addition to the events reported as seizures or possible seizures, one subject who received Control vaccines (N=1032) and 14 subjects who received Pentacel (N=2506) were identified by the applicant as having "Other Neurological Events". This category includes neurological events that may occur in the context of seizures, but for which the Medical Monitor deemed that a diagnosis of seizures or possible seizures was not warranted based on available information. Of

these events, six in Pentacel subjects and none in Control subjects occurred within 30 days post-vaccination (Table 25). Appendix 7 provides a listing of “Other Neurological Events” that occurred anytime during the study period.

Table 25. Study 494-01 "Other Neurological Events"[1] that occurred within 30 days following Pentacel or Control vaccines[2], safety population

Pentacel (N=2506)							
Subject Number	Literal Term	Severity	Action Taken	Last Dose	Days Since Last Dose	Outcome	Other available clinical information
0344	Shaking legs	Mild	No action taken	1	0	Recovered without sequelae	Resolution after 3 days; No neurological events reported after Doses 2 and 3; Voluntary withdrawal prior to Dose 4
0473	Staring into space	Mild	No action taken	4	0	Recovered without sequelae	Received acetaminophen for fever and fussiness on Day 0; Resolution of staring after 3 days; Completed trial without other neurological events reported.
0635	Shaking upon waking	Mild	No action taken	3	0	Recovered without sequelae	Received Pediacare® for pain on Day 0; Resolution of shaking after 4 days; Completed trial without other neurological events reported.
0934	Minor head shakes	Mild	No action taken	2	0	Recovered without sequelae	Resolution reported during a contact with parent on Day 63 (duration not specified); Completed trial without other neurological events reported.
1063	Jerking to body	Moderate	Medical office visit	1	0	Recovered without sequelae	No treatment reported; Resolution on same day; Voluntary withdrawal from trial.
1444	Breath holding spell	Mild	Medical office visit	4	12	Recovered without sequelae	No treatment reported; Resolution on same day; Completed trial without other neurological events reported.

[1]See text for definition of "Other Neurological Events".
[2] There were no events classified as "Other Neurological Events" within 30 days following Control vaccines (N=1032).
Source: 49401_addnl_safetyanalyses.pdf, pages 9-11 and pages 20-23.

Serious Adverse Events

During the study period, there was one reported death due to neuroblastoma. Subject 1218 who presented with facial weakness, rectal prolapse, and rectal and abdominal masses, was diagnosed with neuroblastoma 109 days following the third dose of Pentacel, at age 9.8 months. At presentation, he had spinal and bone marrow involvement. Following initial good response to chemotherapy, his course was complicated by *Pseudomonas aeruginosa* bacteremia and a urine culture positive for *Candida*. He developed vomiting, dehydration and fever 255 days post-vaccination, followed by seizures. Head CT showed hydrocephalus and cerebral edema. He died at age 14.8 months, while hospitalized for increased intracranial pressure.

Overall, the occurrence of any serious adverse event was similar between the two study groups. For example, within 30 days following any of Doses 1-3, 23 of 2506 (0.9%) Pentacel subjects experienced 41 serious adverse events and 11 of 1032 (1.1%) Control subjects experienced 14 serious adverse events (revised iss.pdf, page 2627). Within 30 days following dose 4, six of 1862 (0.3%) Pentacel subjects experienced 9 serious adverse events and 2 of 739 (0.3%) Control subjects experienced three serious adverse events (revised iss.pdf, page 2627). Table 26 presents serious adverse events within 30 days following any of Doses 1-4, classified according to MedDRA system organ class and preferred terms.

Table 26. Study 494-01 Incidence of serious adverse events occurring within 30 days following any of doses 1-4 of Pentacel or Control vaccines, safety population

System Organ Class Preferred Term	Control N = 1032			Pentacel N=2506		
	n	%	95% CI	N	%	95% CI
CARDIAC DISORDERS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Cardiac arrest	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
CONGENITAL AND FAMILIAL/GENETIC DISORDERS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Total anomalous pulmonary venous drainage	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
GASTROINTESTINAL DISORDERS	0	0.0	(0.0, 0.4)	3	0.1	(0.0, 0.3)
Constipation	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Gastro-oesophageal reflux disease	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Inguinal hernia NOS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Vomiting NOS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
GENERAL DISORDERS/ADMINISTRATION SITE CONDITIONS	1	0.1	(0.0, 0.5)	1	<0.1	(0.0, 0.2)
Pyrexia	1	0.1	(0.0, 0.5)	1	<0.1	(0.0, 0.2)
INFECTIONS AND INFESTATIONS	9	0.9	(0.4, 1.6)	18	0.7	(0.4, 1.1)
Bronchiolitis	6	0.6	(0.2, 1.3)	6	0.2	(0.1, 0.5)
Bronchitis NOS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Cellulitis	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Croup infectious	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Febrile convulsion	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.1)
Gastroenteritis NOS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Gastroenteritis rotavirus	0	0.0	(0.0, 0.4)	2	0.1	(0.0, 0.3)
Nasopharyngitis	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.1)
Otitis media NOS	0	0.0	(0.0, 0.4)	3	0.1	(0.0, 0.3)
Pertussis	0	0.0	(0.0, 0.4)	2	0.1	(0.0, 0.3)
Pneumonia NOS	0	0.0	(0.0, 0.4)	4	0.2	(0.0, 0.4)
Pneumonia bacterial NOS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Sepsis NOS[1]	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Viral infection NOS	2	0.2	(0.0, 0.7)	0	0.0	(0.0, 0.1)

INJURY AND POISONING	2	0.2	(0.0, 0.7)	0	0.0	(0.0, 0.1)
Accidental exposure	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.1)
Head injury	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.1)
INVESTIGATIONS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Coagulation time NOS shortened	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
METABOLISM AND NUTRITION DISORDERS	0	0.0	(0.0, 0.4)	3	0.1	(0.0, 0.3)
Dehydration	0	0.0	(0.0, 0.4)	3	0.1	(0.0, 0.3)
MUSCULOSKELETAL, CONNECTIVE TISSUE, BONE DISORDERS	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.1)
Craniosynostosis	1	0.1	(0.0, 0.5)	0	0.0	(0.0, 0.1)
NERVOUS SYSTEM DISORDERS	1	0.1	(0.0, 0.5)	3	0.1	(0.0, 0.3)
Convulsions NOS	1	0.1	(0.0, 0.5)	1	<0.1	(0.0, 0.2)
Grand mal convulsion	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Hypoxic encephalopathy	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	0.1	(0.0, 0.5)	6	0.2	(0.1, 0.5)
Asthma NOS	0	0.0	(0.0, 0.4)	2	0.1	(0.0, 0.3)
Asthma aggravated	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Bronchospasm NOS	1	0.1	(0.0, 0.5)	5	0.2	(0.1, 0.5)
SURGICAL AND MEDICAL PROCEDURES	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Lip repair	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Post-operative pain	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
VASCULAR DISORDERS	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)
Atrial thrombosis	0	0.0	(0.0, 0.4)	1	<0.1	(0.0, 0.2)

[1]Subject 1235 had *Acinetobacter* sepsis some time after 63 days post-Dose 2 of Pentacel during a prolonged hospitalization in which he required endotracheal intubation following cardiac catheterization for evaluation of congenital heart disease. Because the onset date of sepsis was unknown, in the derived database it defaulted to Day 1 of the Dose 1 visit.
NOS indicates not otherwise specified.
Notes:
One case of hearing loss requiring cochlear implants, with onset 18 days following Pentacel was incorrectly categorized by the applicant as non-serious and is not included in the table.
No adverse events in this table were reported by subjects not receiving study vaccines as randomized.
Source: 49401_addnl_safetyanalyses.pdf, pages 59-61; questions1_133.pdf pages 42-47

Clinical case narratives are presented below for selected serious adverse events of interest that occurred within 30 days following vaccination (Table 26).

Case Narratives for Selected Serious Adverse Events of Interest that Occurred within 30 Days Following Vaccination—Pentacel Group

Subject 2829 Pertussis: At age 2 months, this male subject developed an upper respiratory infection with cough, two days following the first dose of Pentacel. Symptoms worsened with cough associated with choking, color change, and apnea. He was hospitalized 14 days after the onset of symptoms. Fluorescent antibody stain was positive for pertussis. He was treated with erythromycin, discharged after four days, and recovered without sequelae. The subject had had contact with a family member with possible pertussis.

Subject 3827 Bronchiolitis, possible pertussis: At age five months, this male subject was hospitalized 18 days following the second dose of Pentacel, with a four day history of cough, difficulty breathing, grunting, and fever of 102.3°F (39.1°C). In the previous week, he had been treated with amoxicillin for nasal congestion, rhinorrhea, and eye discharge. On admission, he had expiratory wheezes, flaring and intercostal retraction. Oxygen saturation was 98%; white

blood cell count was 14.9 x 10^9/L. Chest x-ray showed peribronchial inflammatory changes. RSV and influenza swabs were negative. He experienced staccato episodes of coughing. Treatment included oxygen, intravenous fluids, nebulized albuterol, racemic epinephrine, erythromycin and ceftriaxone. The subject was discharged from the hospital 4 days later and recovered without sequelae.

Subject 1230 Cardiac Arrest, Total Anomalous Pulmonary Venous Return, Hypoxic Ischemic Encephalopathy: See case narrative in section on seizures.

Subject 1958 Afebrile seizure: See case narrative in section on seizures.

Subject 3537 Febrile seizure: See case narrative in section on seizures.

Case Narratives for Selected Serious Adverse Events of Interest that Occurred within 30 Days Following Vaccination— Control (HCPDT + POLIOVAX + ActHIB) Group
Subject 3942 Febrile seizure: See case narrative in section on seizures.

Subject 2501 Afebrile seizure: See case narrative in section on seizures.

6.1.3 Comments and Conclusions

Study Design

Although the Control DTaP vaccine, HCPDT, used in Study 494-01 is not licensed in the U.S., when the study was planned, CBER agreed that HCPDT was an appropriate Control vaccine. HCPDT was selected as the Control DTaP vaccine prior to licensure of DAPTACEL in the U.S. While HCPDT is the same as the DTaP component of Pentacel, it contains twice the amount of PT and four times the amount of FHA as DAPTACEL. Safety data on HCPDT were considered supportive for licensure of DAPTACEL in the U.S. Under the DAPTACEL BLA, CBER reviewed data on serious adverse events from the Sweden II Efficacy Trial in which approximately 20,000 infants received HCPDT, predominantly at 3, 5 and 12 months of age; a subset of approximately 2,500 subjects received HCPDT at 2, 4, and 6 months of age. The safety data from the Sweden II Efficacy Trial were also submitted to the Pentacel BLA and are presented in Section 6.7 of this review. The DAPTACEL BLA also included comparative data on more common adverse events following HCPDT or DAPTACEL from smaller studies.

In Study 494-01, Control subjects received four doses of POLIOVAX by 15-18 months of age. While this schedule is generally consistent with recommendations of the Advisory Committee on Immunization Practices (ACIP) on the spacing of IPV doses, the routinely recommended age for the fourth dose of IPV is 4-6 years[5]. See Section 8.2 for further discussion of the proposed Pentacel schedule with regard to current recommendations for use of IPV.

Data Quality

During data analysis by the applicant, the identification of errors in coding of adverse events led to an audit of the safety database, with resultant changes to the safety data. In CBER's review of the safety data in the BLA, a few additional discrepancies and errors, particularly with regard to categorization of seizures and serious adverse events were identified. These issues were resolved in the applicant's response to CBER's 5/26/06 Complete Response Letter.

With regard to solicited local and systemic adverse events, of note is that depending on dose number and event, approximately 10-15% of subjects in the ITT safety population who received the particular dose were excluded from the analyses. These exclusions reflect missing data for subjects who did not return the diary card or whose diary cards contained incomplete data. It is

possible that observed adverse event rates could be underestimated if excluded subjects had higher rates of events than included subjects. However, similar proportions of Pentacel and Control subjects were excluded from the analyses because of missing or incomplete data.

Of note was the relatively poor compliance with taking temperatures as specified in the protocol. This was more notable for Doses 1-3 for which the protocol specified that temperatures should be taken rectally. It is unclear if this resulted from insufficient instruction to the parents, parental refusal to take rectal temperatures, and/or other factors. It is possible that parental decisions about how to measure temperatures may have been influenced by perceptions about the presence or absence of fever. However, relative use of different routes of temperature measurement was similar in Pentacel and Control subjects.

Safety Results

Overall, there were no notable imbalances between Pentacel and Control subjects with regard to solicited adverse events, seizures, and overall occurrence of serious adverse events. No HHEs were reported in Pentacel or Control subjects.

On the day of vaccination, five Pentacel subjects (N=2506) and no Control subjects (N=1032) had neurological events that may be observed in the context of seizures, but which were not thought to be seizures by the Investigator and Medical Monitor; and three Pentacel subjects and no Control subjects had hypotonia not meeting the HHE definition. All but one case (graded as moderate) were considered mild. No sequelae were reported in any of these subjects.

Of note was the occurrence of protocol-specified contraindications to subsequent vaccination in four Pentacel subjects (all persistent crying >3 hours) and two Control subjects (persistent crying >3 hours in two subjects, including one who also had a seizure on the day of vaccination).

6.2 Pivotal Trial # 2

6.2.1 Applicant's Protocol # and Protocol Title

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

6.2.1.1 Objective/Rationale

Study 494-03 was conducted to assess the safety and immunogenicity of Pentacel when co-administered with a hepatitis B vaccine, a pneumococcal conjugate vaccine, a varicella vaccine, and a measles, mumps, rubella (MMR) vaccine at the recommended schedules.

6.2.1.2 Design Overview

Study 494-03 was a randomized, open-label, multi-center study designed to assess the safety and immunogenicity of Pentacel when co-administered with other recommended vaccines. All subjects (planned enrollment 1,200) were to receive Pentacel and Prevnar at 2, 4, and 6 months of age, and RECOMBIVAX HB at 2 and 6 months, or 2, 4, and 6 months of age, depending on whether the first dose of hepatitis B vaccine was received previously. At the time of recruitment, subjects were equally randomized to one of four groups for receipt of the fourth dose of Pentacel. The four groups differed with regard to age at administration of the fourth dose of Pentacel and the schedule for other vaccines that are recommended to be administered at 12-18 months of age.

6.2.1.3 Population

Inclusion and Exclusion Criteria
The inclusion and exclusion criteria were essentially the same as described in Section 6.1.1.3 for Study 494-01, with the exception that for Study 494-03 infants may have received either no previous hepatitis B vaccine or one dose of hepatitis B vaccine prior to enrollment.

Definite Contraindications to Vaccination
- Encephalopathy within 7 days following a previous vaccination
- Hypersensitivity to any vaccine component or anaphylactic reaction following a previous vaccination
- Known or suspected impairment of the immune system

Relative Contraindications (Decisions regarding continuation made on case by case basis with input from Medical Monitor)
- Rectal (or equivalent) temperature >40.5° C within 48 hours following a previous vaccination
- Seizures within 3 days following a previous vaccination
- Hypotonia and/or hyporesponsiveness within 48 hours following a previous vaccination
- Persistent crying (≥3 hours) within 3 days following a previous vaccination
- Serious adverse events possibly, probably or definitely related to the vaccine

Temporary Contraindications (Vaccination postponed, but may be rescheduled)
- Rectal temperature >100.4°F, axillary temperature >99.5°F

6.2.1.4 Products Mandated by the Protocol
Schedule of Study Vaccines
Table 27 presents the schedule of study vaccines.

Table 27. Study 494-03 Schedule of study vaccines

Group	2, 4, 6 months	12 months	15 months	16 months
1	Pentacel Prevnar RECOMBIVAX HB[1]	MMR II VARIVAX Prevnar	Pentacel	
2	Pentacel Prevnar RECOMBIVAX HB[1]	Prevnar	Pentacel MMR VARIVAX	
3	Pentacel Prevnar RECOMBIVAX HB[1]	MMR II VARIVAX	Pentacel Prevnar	
4	Pentacel Prevnar RECOMBIVAX HB[1]		MMR Varivax Prevnar	Pentacel

[1] Infants who previously received the first dose of hepatitis B vaccine did not receive RECOMBIVAX HB at 4 months of age.

Formulation of Study Vaccines
For the formulation of Pentacel, Prevnar, RECOMBIVAX HB, MMR II, and VARIVAX, see Section 6.1.1.4.

For Doses 1-3 of Pentacel, HCPDT-IPV Lot C0155AA and ActHIB Lot UA480AD (R0181) were used. For Dose 4 of Pentacel, HCPDT-IPV Lot C0790BA and ActHIB Lot UA480AE (R0181) were used.

Prevnar lots 471-212, 474-723, and 477-171 were used.

RECOMBIVAX HB lot 0581K was used.

For MMR_{II}, batch numbers MMR 1179K and MMR Diluent 1013K were used.

VARIVAX lot numbers were identified at the time of use.

Sites and Route of Vaccine Administration
The sites and route of administration of study vaccines were as follows:
Pentacel: intramuscular, left upper thigh for doses 1-3; left upper arm for dose 4
RECOMBIVAX HB: intramuscular, right lower thigh
Prevnar: intramuscular, right upper thigh for doses 1-3; right upper arm for dose 4
MMR_{II}: subcutaneous, left upper thigh
VARIVAX: subcutaneous; right upper thigh

6.2.1.5 Safety Endpoints
There were no pre-specified primary safety endpoints. Prospectively defined secondary safety endpoints with non-inferiority criteria are listed in Table 28. All other safety analyses were descriptive.

Table 28. Study 494-03 Secondary safety endpoints and non-inferiority criteria

Endpoint	Comparisons	Non-inferiority criteria
Rate of any severe adverse event with onset 0-3 days following the fourth dose of Pentacel	Group 1 vs. Group 2 Group 1 vs. Group 3	upper limit of the two-sided 90% confidence interval[1] for the ratio Group 2/Group 1 or Group 3/Group 1 <3

[1]For non-inferiority comparisons, in general, CBER currently recommends use of 95% confidence intervals.

6.2.1.6 Safety Surveillance/Monitoring
Safety monitoring was essentially as described in Section 6.1.1.6 for Study 494-01. As in Study 494-01, visits for blood sampling 28-48 days after vaccination may have served as the 30-day safety follow-up. In study 494-03, collection of blood for serology was planned for a subset of 348 subjects post-Dose 3 and for all subjects post-Dose 4 Pentacel.

6.2.1.7 Statistical Considerations Related to the Safety Evaluation
Power Calculation for Secondary Non-inferiority Safety Analyses
Assuming 243 subjects per group (after an attrition rate of ~20% through end of study) and an expected post-Dose 4 Pentacel rate of any severe reaction of 10%, the power for each of the two secondary non-inferiority safety analyses was 98% (using a one sided test at 0.05 significance level).

Analysis Population for Safety
The ITT analyses for safety included subjects who received at least one dose of vaccine, regardless of whether they adhered to the study eligibility criteria or their visits were within the protocol-specified windows.

Analyses of Fever
Considerations regarding the analyses of fever previously discussed for Study 494-01 (Section 6.1.1.7) also apply to Study 494-03.

HHE Definition
A definition for HHE was not included in the protocol. The criteria used for analyses of HHE are as described in Section 6.1.1.7 for Study 494-01.

Classification of Seizures and Related Diagnoses
Seizures and related diagnoses were classified by the applicant as described in Section 6.1.1.7 for Study 494-01.

6.2.2 Results

6.2.2.1 Site Audit Due to Non-Conformances with Good Clinical Practices
At one study site (Center 10), an audit was conducted following report of potential non-conformances with Good Clinical Practices by the Principal Investigator. The audit identified non-conformances related to subject rights, administration of investigational product, proper documentation, and product accountability. Due to the predominance of errors and omissions, the 62 subjects that had been enrolled at this site were excluded from the analyses.

6.2.2.2 Changes to the Data Resulting from Audit of Safety Database
As described for Study 494-01 (Section 6.1.2.1), because of inconsistencies in data reporting noted during data analysis, an audit of the clinical safety database was performed. A summary of changes to the database is presented in Appendices 8-10.

6.2.2.3 Populations Enrolled/Analyzed
Study Sites and Study Period
Subjects were enrolled from 11 U.S. sites. The study period from the first subject visit through the last subject contact was 7/10/00 through 12/26/02.

Subject Disposition and Follow-up
Table 29 presents a summary of subject disposition with regard to the safety evaluation, from randomization through 60 days post-Dose 3.

Table 29. Study 494-03 Summary of subject disposition for safety evaluation from randomization through 60 days post-Dose 3

Disposition	N (%)
All Randomized Subjects	1275
Randomized but excluded from all analyses (Center 10)[1]	62
All Randomized Subjects for Safety	1213
Randomized but did not receive Dose 1	6 (0.5)
Intent-to-Treat (ITT) Safety Population[2]	1207 (100.0)
Received Dose 1 of Pentacel	1207 (100.0)
Received Dose 1 and Dose 2 of Pentacel	1115 (92.4)
Received 3 doses of Pentacel	1077 (89.2)
Completed 60-Day Safety Follow-up Post-Dose 3	1061 (87.9)
Did Not Complete 60-Day Safety Follow-up Post-Dose 3[3]	146 (12.1)
Did Not Complete 60-Day Safety Follow-up Post-Dose 3[3]	146 (100.0)
Adverse event	13 (8.9)
Contraindication	0 (0.0)
Lost to follow-up	8 (5.5)
Non-compliance	28 (19.2)
Voluntary withdrawal	97 (66.4)
Other	0 (0.0)

[1]Of the 62 subjects from Center 10, 61 completed the 60-day follow-up post-Dose 3; one subject voluntarily withdrew after dose 3.
[2]Defined as all subjects enrolled in the trial who received at least one dose of Pentacel.
[3]Subjects terminated anytime between Dose 1 and the post-Dose 3 60-day safety follow-up. Percentages of sub-categories are based on the total number of subjects who did not complete the 60-day safety follow-up. Only one primary reason for termination per subject is selected in the order listed.
Source: 49403si.pdf, pages 62-63.

For subjects who completed the 60-day safety follow-up post-Dose 3, Table 30 presents a summary of subject disposition through the end of the study. Table 30 excludes subjects from Center 10. Of the 61 subjects from Center 10 who completed the post-Dose 3 follow-up, 53 received the fourth dose of Pentacel. Of these 53 subjects, 48 completed the 60-day follow-up post-Dose 4, two were non-compliant with follow-up, and three voluntarily withdrew.

Table 30. Study 494-03 Summary of subject disposition through end of study for subjects who completed the 60-day follow-up post-Dose 3

Safety Disposition	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	Groups 1-4 n (%)
Completed 60-day Safety Follow-up Post-Dose 3[1] Completed 60-day safety follow-up post-Dose 3 but terminated before Dose 4[1,2]	264 19 (7.2)	266 20 (7.5)	267 29 (10.9)	264 37 (14.0)	1061 105 (9.9)
Completed 60-day Safety Follow-up Post-Dose 3 But Terminated Before Dose 4[1,2]	19 (100.0)	20 (100.0)	29 (100.0)	37 (100.0)	105 (100.0)
Adverse event	1 (5.3)	0 (0.0)	0 (0.0)	4 (10.8)	5 (4.8)
Contraindication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	4 (21.1)	3 (15.0)	3 (10.3)	4 (10.8)	14 (13.3)
Non -compliance	1 (5.3)	0 (0.0)	6 (20.7)	8 (21.6)	15 (14.3)
Voluntary withdrawal	13 (68.4)	17 (85.0)	20 (69.0)	21 (56.8)	71 (67.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dose 4 Subject Participation by Randomized Treatment	245	247[3]	239[3]	227	958
ITT Safety Population[1,4]	246	246	240	226	958
Completed 60-Day Safety Follow-up Post-Dose 4[2]	242 (98.8)	243 (98.4)	235 (98.3)	227 (100.0)	947 (98.9)
Did not Complete 60-Day Safety Follow-up Post-Dose 4[2,3]	3 (1.2)	4 (1.6)	4 (1.7)	0 (0.0)	11 (1.1)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)	0 (0.0)
Contraindication	0 (0.0)	0 (0.0)	0 (0.0)	0 (NA)	0 (0.0)
Lost to follow-up	3 (100.0)	2 (50.0)	2 (50.0)	0 (NA)	7 (63.6)
Non-compliance	0 (0.0)	1 (25.0)	1 (25.0)	0 (NA)	2 (18.2)
Voluntary withdrawal	0 (0.0)	1 (25.0)	1 (25.0)	0 (NA)	2 (18.2)

[1]Subjects are classified by the randomized treatment.
[2]Subjects who were terminated anytime between completing the post-Dose 3 60-day safety follow-up and receiving Dose 4. Only the primary reason for termination per subject is selected in the order listed.
[3]Two subjects (one in Group 2 and one in Group 3) who had discontinued after the third dose of Pentacel received the fourth dose of Pentacel.
[4]Two subjects had a randomization error (one randomized to Group 2 received the Group 3 schedule; one randomized to Group 4 received the Group 1 schedule)
Source: 49403sii.pdf, page 78-79

Table 31 lists adverse events that led to study withdrawal following any dose of Pentacel. There were no withdrawals due to adverse events or contraindications among subjects from Site 10.

Table 31. Study 494-03 Adverse events leading to study withdrawal, safety population

Subject Number	Adverse Event (Literal Term)	Last Dose[1]	Days since Last Dose	Duration in Days	Severity	Outcome
0031	Constipation	1	38	21	Mild	Recovered without sequelae
0118	Automobile accident	1	22	2	Severe	Death
0143	Chickenpox	2	60	17	Mild	Recovered without sequelae
0186	Rhinitis	1	3	11	Mild	Recovered without sequelae
0346	Tremors, head lag (eventually diagnosed as encephalopathy)	1	8	ongoing	Severe	Event is continuing
0409	Crying, Fussiness	1	0	2	Severe	Recovered without sequelae
0473	SIDS	1	52	1	Severe	Death
0551	Afebrile seizure	2	54	1	Severe	Recovered without sequelae
0631	Fever, pallor, lethargy, fussiness, loss of appetite	1	0	NR	NR	NR
0738	Asthma	1	53	30	Mild	Recovered without sequelae
1082	Crying	1	0	7	Severe	NR
1098	Redness	1	0	2	Severe (11 cm)	NR
1228	Seizure	1	45	3	Moderate	Recovered without sequelae
0602	Seizure disorder	3	207	3	n/a	Recovered with sequelae
0325	Epilepsy	3	87	22	n/a	Recovered without sequelae
0660	Febrile seizures (2 episodes)	3	262, 284	1 (each episode)	n/a	Recovered without sequelae
0999	Broken arm	3	n/a	n/a	n/a	n/a
1107	Febrile seizure	3	187	3	n/a	Recovered without sequelae

[1] The last dose is defined as the dose received on or before the date of the adverse event.
NR = Not Reported
n/a: data not available. Each of the events of seizures in subjects 0602, 0325, 0660, and 1107 were reported as serious adverse events.
Source: 49403si.pdf, page 64; 49403sii.pdf, pages 75 and 81

Hepatitis B Vaccination Schedule

Among the 1077 subjects in the ITT Safety Population who received three doses of Pentacel, 606 (56.3%) received hepatitis B vaccine at 0, 2, and 6 months of age and 471 (43.7%) received hepatitis B vaccine at 2, 4, and 6 months of age.

Subject Demographics

Table 32 presents a summary of subject demographics at enrollment. The four Dose 4 study groups did not differ significantly with regard to race or sex. The mean ages at the fourth dose were 15.4 months in Groups 1, 2, and 3 (range overall 14.2-17.6 months), and 16.6 (range 15.8-19.1) months for Group 4.

Table 32. Study 494-03 Summary of subject demographics at enrollment, safety population

Demographic Characteristic	N=1207
Sex n (%)	
Male	601 (49.8)
Female	606 (50.2)
Age (months)	
Mean	2.2
Median	2.1
Range	(1.4, 3.0)
Race	
Caucasian	703 (58.2)
Black	103 (8.5)
Hispanic	265 (22.0)
Asian	23 (1.9)
Other	113 (9.4)

Age (months) = (1st vaccination date - Date of birth + 1) / (365.25/12).
Source: 49403si.pdf, page 65

6.2.2.4 Safety Outcomes

Antipyretic Use

Following each of the first three doses of Pentacel, approximately half of subjects received antipyretics during the period 0-3 days post-vaccination. As shown in Table 33, use of antipyretics within 3 days following the fourth dose of Pentacel was lower for subjects in Group 4 than the other groups.

Table 33. Study 494-03 Number (percentage) of subjects who received antipyretics during the period 0-3 days following the fourth dose of Pentacel

Group, N	n (%)
Group 1 N=246	102 (41.5)
Group 2 N=246	118 (48.0)
Group 3 N=240	113 (47.1)
Group 4 N=226	59 (26.1)

Source: 49403sii.pdf, page 81

Immediate Reactions

Following Doses 1-3 of Pentacel, there were no reports of adverse events occurring within 30 minutes post-vaccination. Following the fourth dose of Pentacel (administered alone in Groups 1 and 4, administered with MMR_{II} and VARIVAX in Group 2, or administered with Prevnar in Group 3), 22 (2.3%) subjects reported 32 immediate reactions within 30 minutes of vaccination: 5 subjects in Group 1; 12 subjects in Group 2; 3 subjects in Group 3; and 2 subjects in Group 4. All immediate reactions were considered mild in severity. All of the immediate reactions, except one case of nasopharyngitis, were local injection site reactions. Reactions reported included erythema, burning, induration, irritation, and limb edema. All subjects recovered without treatment or sequelae. For Subjects in Groups 2 and 3 who had immediate local reactions, the affected site (Pentacel or a concomitantly administered vaccine) was not specified.

Solicited Local Reactions

The safety profile of Pentacel with regard to solicited local reactions was generally consistent with that observed in Study 494-01 (Section 6.1.2.3).

Two subjects (<1%) included in the analyses reported a >40 mm increase in circumference of the Pentacel injected arm post-Dose 4, with maximum percent increases from baseline of 41% and 133%, respectively. Apparently inconsistent with information recorded on the diary card, the case report form for the latter subject indicated that the parent did not recall arm swelling. A higher proportion of subjects from Center 10, 6.8% (3/44), reported a >40 mm increase in arm circumference post-Dose 4 Pentacel (none reported whole limb swelling). Otherwise, the frequencies of local reactions among subjects from Center 10 appeared generally comparable to those observed among subjects from the other study sites.

The occurrence of whole limb swelling was not specifically solicited. For two subjects, the comment section of the Case Report Form noted limb swelling, but swelling was not reported as a solicited adverse event. For Subject 1037, who received Pentacel in the right upper thigh and Prevnar in the right lower thigh, the Case Report Form noted "Whole thigh swelled but she could not measure because it was not directly on the shot". For subject 1486 who received Pentacel in the left upper thigh and Prevnar in the right upper thigh, for Dose 1, the Case Report Form noted "Patients legs are swollen more than twice the normal size". Two other subjects reported mild edema of the Pentacel injected arm post-Dose 4 and mildly swollen legs post-Dose 3, respectively, as unsolicited events. (source: questions1_133.pdf, pages 152-155).

Solicited Systemic Adverse Events

The occurrence of solicited systemic adverse events among subjects from Center 10 appeared generally comparable to that observed among subjects from the other study sites.

Although parents were instructed to take rectal temperatures following Doses 1-3, approximately 45% of temperature measurements following these doses were axillary and 1.6% were either oral or by other routes. Following the fourth dose of Pentacel, approximately 72% of temperature measurements were by the axillary route, as parents were instructed, approximately 25% were taken rectally, and approximately 3% were taken orally. Routes of temperature measurement were similar across the Dose 4 study groups.

The safety profile of Pentacel with regard to solicited systemic adverse events following the first three doses was generally consistent with that observed in Study 494-01 (Section 6.1.2.3).

Table 34 presents frequencies of selected solicited systemic adverse events within 0-3 days following the fourth dose of Pentacel, by Dose 4 study group. In these analyses, rates of fever are presented, irrespective of route of measurement. The frequencies of fever and other solicited systemic adverse events following the fourth dose of Pentacel tended to be highest in Group 3 subjects who received Pentacel and Prevnar concomitantly than in subjects who received Pentacel alone or concomitantly with MMR_{II} and VARIVAX.

Table 34. Study 494-03 Frequencies of selected systemic adverse events within 0-3 days following Dose 4 of Pentacel, safety population

Event	Group 1 n (%)		Group 2 n (%)		Group 3 n (%)		Group 4 n (%)	
Fever[1]		N=232		N=232		N=225		N=193
≥38.0°C	17	(7.3)	20	(8.6)	27	(12.0)	12	(6.2)
≥38.0-≤38.5°C	10	(4.3)	13	(5.6)	15	(6.7)	6	(3.1)
>38.5-≤39.5°C	5	(2.2)	7	(3.0)	9	(4.0)	5	(2.6)
>39.5°C	2	(0.9)	0	(0.0)	3	(1.3)	1	(0.5)
Fussiness		N=234		N=233		N=226		N=195
Any	136	(58.1)	134	(57.5)	147	(65.0)	103	(52.8)
Mild (<1 hour)	80	(34.2)	81	(34.8)	77	(34.1)	61	(31.3)
Moderate (1-3 hours)	49	(20.9)	35	(15.0)	50	(22.1)	36	(18.5)
Severe (>3 hours)	7	(3.0)	18	(7.7)	20	(8.8)	6	(3.1)
Crying		N=234		N=233		N=226		N=195
Any	91	(38.9)	93	(39.9)	105	(46.5)	79	(40.5)
Mild (<1 hour)	65	(27.8)	67	(28.8)	67	(29.6)	53	(27.2)
Moderate (1-3 hours)	19	(8.1)	20	(8.6)	32	(14.2)	24	(12.3)
Severe (>3 hours)	7	(3.0)	6	(2.6)	6	(2.7)	2	(1.0)
Less activity[2]		N=234		N=233		N=226		N=195
Any	72	(30.8)	64	(27.5)	89	(39.4)	45	(23.1)
Mild	48	(20.5)	40	(17.2)	53	(23.5)	27	(13.8)
Moderate	20	(8.5)	17	(7.3)	26	(11.5)	15	(7.7)
Severe	4	(1.7)	7	(3.0)	10	(4.4)	3	(1.5)
Anorexia		N=234		N=233		N=226		N=195
Any	61	(26.1)	72	(30.9)	85	(37.6)	48	(24.6)
Mild (50% of meal)	42	(17.9)	43	(18.5)	51	(22.6)	29	(14.9)
Moderate (Refuses 1 feed)	14	(6.0)	20	(8.6)	25	(11.1)	14	(7.2)
Severe (Refuses ≥2 feeds)	5	(2.1)	9	(3.9)	9	(4.0)	5	(2.6)
Rash[3]		N=234		N=233		N=226		N=195
Present	1	(0.4)	4	(1.7)	4	(1.8)	3	(1.5)

[1]All temperature measurements included, irrespective of route; no adjustments made to any measurements.
[2]Mild = usual daily activity is not affected; Moderate = interferes with or limits usual daily activity; Severe = disabling, not interested in usual daily activity.
[3]Rash was defined as "presence of welts (large, red, swollen patches)"
Notes: Each subject is counted once, and classified according to the highest recorded severity.
Group is based on actual vaccines received at 15 months. Group 1: Received 4th Dose of Pentacel at 15 months. Group 2: Received 4th Dose of Pentacel concomitantly with MMR_{II} and VARIVAX at 15 months. Group 3: Received 4th Dose of Pentacel concomitantly with Prevnar at 15 months. Group 4: Received 4th Dose of Pentacel at 16 months.
'n' is the number of subjects with the specified reaction.
'N' is the total number of subjects with available data from the Safety Population.
Source: 49403sii.pdf, pages 116-117

Non-inferiority Analyses of Severe Solicited Events

Tables 35 and 36 present the results of the pre-specified secondary non-inferiority analyses of the occurrence of severe solicited adverse events within three days post-Dose 4 Pentacel for Group 2 (Pentacel, MMR_{II} and VARIVAX concomitantly) vs. Group 1 (Pentacel alone) and for Group 3 (Pentacel and Prevnar concomitantly) vs. Group 1, respectively.

Table 35. Study 494-03 Non-inferiority analysis of severe solicited adverse events within three days post-Dose 4 Pentacel, Group 2 vs. Group 1, safety population

Reactions	Group 1 N = 234 n (%)	Group 2 N = 233 n (%)	Group 2/Group 1 Ratio	Group 2/Group 1 90% CI	Non-inferiority[1]
At least one severe solicited local or systemic reaction	29 (12.4)	36 (15.5)	1.25	(0.85, 1.83)	Yes
At least one severe solicited local reaction	11 (4.7)	15 (6.4)	1.37	(0.73, 2.58)	Yes
At least one severe solicited systemic reaction	23 (9.8)	30 (12.9)	1.31	(0.85, 2.01)	Yes

[1] Non-Inferiority: The upper limit of the two-sided 90% CI of the Group 2 /Group 1 is <3.0. For non-inferiority comparisons, in general, CBER currently recommends use of 95% CIs.
Notes: Group is based on actual vaccines received at 15 months.
Group 1: Received 4th Dose of Pentacel at 15 months.
Group 2: Received 4th Dose of Pentacel concomitantly with MMR_{II} and VARIVAX at 15 months.
Source: 49403sii.pdf, page 100

Table 36. Study 494-03 Non-inferiority analysis of severe solicited adverse events within three days post-Dose 4 Pentacel, Group 3 vs. Group 1, safety population

Reactions	Group 1 N = 234 n (%)	Group 3 N = 226 n (%)	Group 3/Group 1 Ratio	Group 3/Group 1 90% CI	Non-inferiority[1]
At least one severe solicited local or systemic reaction	29 (12.4)	41 (18.1)	1.46	(1.01, 2.12)	Yes
At least one severe solicited local reaction	11 (4.7)	11 (4.9)	1.04	(0.52, 2.05)	Yes
At least one severe solicited systemic reaction	23 (9.8)	37 (16.4)	1.67	(1.11, 2.51)	Yes

[1] Non-Inferiority: The upper limit of the two-sided 90% CI of the Group 3 /Group 1 is <3.0. For non-inferiority comparisons, in general, CBER currently recommends use of 95% CIs.
Notes: Group is based on actual vaccines received at 15 months.
Group 1: Received 4th Dose of Pentacel at 15 months.
Group 3: Received 4th Dose of Pentacel concomitantly with Prevnar at 15 months.
Source: 49403sii.pdf, page 101

HHE and Hypotonia

No HHEs were reported by any subject, including those from Center 10. One subject (#0303) experienced truncal hypotonia at age 5.8 months, on the day of the third dose of Pentacel, Prevnar and RECOMBIVAX HB. The event was considered mild, non-serious, and did not require intervention. At 12 months of age, the subject was noted to have improving left ptosis and was assessed as developmentally normal for age.

Seizures

Table 37 provides a list of seizures that occurred within 30 days following any dose of Pentacel. Appendix 11 provides a list of seizures that occurred anytime during the study. No seizures were reported among subjects from Center 10. No events were categorized as possible seizures.

Table 37. Study 494-03 Seizures within 30 days following any dose (1-4) of Pentacel (N=1207 subjects)

Vaccine Group	Subject Number	Afebrile or Febrile or "Possible"	Literal Term	Last Dose	Days Since Last Dose	Outcome
Dose 4 Group 2	0946	Afebrile	Seizure	4	9	Recovered without sequelae
			Seizure	4	21	Recovered without sequelae
Dose 4 Group 3	0879	Afebrile	Seizure x 2	4	14	Recovered without sequelae
Dose 4 Group 3	1102	Febrile	Febrile seizure	4	13	Recovered without sequelae
Dose 4 Group 4	0385	Febrile	Febrile seizure	4	16	Recovered without sequelae

Dose 4 Group 1 received 4th Dose of Pentacel at 15 months.
Dose 4 Group 2 received 4th Dose of Pentacel concomitantly with MMR_{II} and VARIVAX at 15 months.
Dose 4 Group 3 received 4th Dose of Pentacel concomitantly with Prevnar at 15 months.
Dose 4 Group 4 received MMR_{II}, VARIVAX, and Prevnar at 15 months, and 4th Dose of Pentacel at 16 months.
Source: 49403_addnl_safetyanalyses.pdf, pages 7-8

Incidence rates (per subjects) of seizures that occurred after any dose of Pentacel, by interval since vaccination, are presented in Table 38.

Table 38. Study 494-03 Incidence, **per subjects**, of seizures that occurred after any dose (1-4) of Pentacel, safety population

Period	N=1207		
	N	%	95% CI
Seizures (febrile and afebrile)			
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	13	1.1	(0.6, 1.8)
0-30 Days Post Any Dose (1-4)	4	0.3	(0.1, 0.8)
0-7 Days Post Any Dose (1-4)	0	0.0	(0.0, 0.3)
Afebrile Seizures			
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	6	0.5	(0.2, 1.1)
0-30 Days Post Any Dose (1-4)	2	0.2	(0.0, 0.6)
0-7 Days Post Any Dose (1-4)	0	0.0	(0.0, 0.3)
Febrile Seizures			
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	8	0.7	(0.3, 1.3)
0-30 Days Post Any Dose (1-4)	2	0.2	(0.0, 0.6)
0-7 Days Post Any Dose (1-4)	0	0.0	(0.0, 0.3)

Source: 49403_addnl_safetyanalyses.pdf, pages 38-41

Incidence rates (per 1000 doses) of seizures that occurred after any dose (1-4) of Pentacel, by interval since vaccination, are presented in Table 39.

Table 39. Study 494-03 Incidence, **per 1000 doses**, of seizures that occurred after any dose (1-4) of Pentacel, safety population

Period	Pentacel (Number of Doses = 4357)		
	n	Rate per 1000 doses	95% CI
Seizures (febrile and afebrile)			
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	19	4.36	(2.63, 6.81)
0-30 Days Post Any Dose (1-4)	5	1.15	(0.37, 2.68)
0-7 Days Post Any Dose (1-4)	0	0.00	(0.00, 0.85)
Afebrile Seizures			
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	8	1.84	(0.79, 3.62)
0-30 Days Post Any Dose (1-4)	3	0.69	(0.14, 2.01)
0-7 Days Post Any Dose (1-4)	0	0.00	(0.00, 0.85)
Febrile Seizures			
Post-Dose 1 Through End of 60 Day Follow-up Post-Dose 4	11	2.52	(1.26, 4.52)
0-30 Days Post Any Dose (1-4)	2	0.46	(0.06, 1.66)
0-7 Days Post Any Dose (1-4)	0	0.00	(0.00, 0.85)

Source: 49403_addnl_safetyanalyses.pdf, pages 42-45

There were no seizures reported within 7 days following any of Doses 1-4 of Pentacel. Within 30 days following vaccination, four subjects reported five episodes of seizures. All seizures that occurred within 30 days post-vaccination were following the fourth dose of Pentacel. Of the four subjects who had a seizure(s) within 30 days following the fourth dose of Pentacel, two received Pentacel and Prevnar concomitantly, one received Pentacel, MMR_{II}, and VARIVAX concomitantly, and one received Pentacel alone. Case narratives are provided below for seizures that occurred within 30 days following vaccination.

Case Narratives for Afebrile Seizures within 30 Days Following Vaccination

Subject 0879: At age 15 months, this female subject had a seizure (stiffening with arms flexed, eyes rolled back, unresponsive) that lasted two to three minutes, 14 days following the fourth dose of Pentacel administered concomitantly with Prevnar (Group 3). During the two previous days, she had had vomiting and diarrhea. In the emergency room she appeared dehydrated and was administered intravenous fluids. Complete blood count and electrolytes were normal. On the way home, she had another seizure that lasted about 3 minutes and became unresponsive. She was admitted to the hospital. A head CT scan was normal. CSF evaluation included protein of 19 mg/dL, glucose of 44 mg/dL, one red blood cell, one white blood cell, no xanthochromia, and no organisms on Gram stain. Urine culture was negative. Treatment included phenobarbital, ceftriaxone, and intravenous fluids. She was discharged two days later, recovered without sequelae, and completed the study without further seizures.

Subject 0946: This female subject had two episodes of febrile seizures and one episode of afebrile seizures, 130, 229, and 250 days (respectively) following the third dose of Pentacel, and two afebrile seizures, 9 and 21 days (respectively) following the fourth dose administered concomitantly with MMR_{II} and VARIVAX (Group 2). Each episode is described below:

- A 5-minute febrile seizure at 10 months of age, 130 days post-vaccination, was associated with fever of 102°F, and resulted in an emergency room visit and treatment with acetaminophen and amoxicillin.

- An afebrile seizure with limpness and unresponsiveness occurred at 14 months of age, 229 days post-immunization. In the emergency room, the subject was not breathing and experienced a grand mal seizure. Treatment included intravenous and intramuscular phenobarbital and intubation. WBC count was 16.7 x 10^9/L. Basic metabolic screen, calcium, and magnesium levels, EEG, ECG, and head CT were normal.

- A 5-minute afebrile seizure, 250 days post-Dose 3, resulted in an emergency room visit and treatment with phenobarbital to continue after discharge.

- At age 15 months, 9 days following the fourth dose of Pentacel, the subject who was on phenobarbital, had 5 minutes of seizure activity. She had a normal complete blood count and basic metabolic panel. Her anticonvulsant therapy was changed to carbamazepine.

- Twenty-one days following the fourth dose of Pentacel, the subject had a 20-30 minute seizure and was admitted to the hospital. Following a right-sided tonic-clonic seizure associated with apnea, the subject was intubated. Urinalysis, complete blood count and electrolytes were unremarkable. One day later, an EEG was normal. She was noted to have otitis media. She was treated with phenobarbital, carbamazepine, and antibiotics.

In all five instances, the outcome was reported as recovered without sequelae. The subject completed the trial.

Case Narratives for Febrile Seizures within 30 days Following Vaccination
Subject 0385: At age 16 months, this male subject had a febrile seizure 16 days following the fourth dose of Pentacel (Group 4) and presented to an emergency room. He began azithromycin, recovered without sequelae and completed the study without subsequent seizures.

Subject 1102: This male subject experienced febrile seizures 265 days following the third dose of Pentacel (at 15 months of age) and 13 days following the fourth dose administered concomitantly with Prevnar (Group 3) (at 16 months of age). In both instances, he had fever >104°F and otitis media. The first seizure was manifested by unresponsiveness, shaking, and eyes rolled back for 3-5 minutes and resulted in an emergency room visit. With the second episode, he had three generalized tonic-clonic seizures, lasting less than one minute, with abrupt return to normal, and was hospitalized. In both instances, he was treated with antipyretics and antibiotics. In the second instance, he also received intravenous lorazepam. He recovered without sequelae and completed the study without subsequent seizures.

Other Neurological Events that may be Observed in the Context of Seizures
Seven subjects were considered to have "Other Neurological Events". This classification refers to neurological events that may occur in the context of seizures, but for which the Medical Monitor deemed that a diagnosis of seizures or possible seizures was not warranted. A list of "Other Neurological Events" that occurred anytime post-vaccination and within 30 days post-vaccination, are provided in Appendix 12 and Table 40, respectively. Subject 0346 developed head lag and tremors eight days following the first dose of Pentacel, and was eventually diagnosed with congenital encephalopathy (see section on serious adverse events for further details).

Table 40. Study 494-03 "Other Neurological Events"[1] that occurred within 30 days following Pentacel, safety population

Vaccine Group[2]	Subject Number	Literal Term	Severity	Action Taken	Last Dose	Days Since Last Dose	Outcome	Other clinical information from sponsor's narratives
Pentacel	0346	Head Lag	Severe	Medical Office Visit	1	8	No information reported[3]	Eventual diagnosis of congenital encephalopathy
		Tremors	Severe	Discontinuation	1	8	No information reported[3]	Eventual diagnosis of congenital encephalopathy
Dose 4 Group 4	1021	Tremors	Mild	Telephone call to physician	4	18	Recovered without sequelae	--
Dose 4 Group 2	1030	Breath holding spells	Mild	No action taken	4	6	Recovered without sequelae	--
Pentacel	1330	Trembling Trembling Trembling	Mild Mild Moderate	No action taken No action taken Medical office visit	1 2 2	0 0 7	Recovered without sequelae for all 3 episodes	Resolution the same day for first 2 episodes and within 3 days for third episode. 2nd and 3rd episodes accompanied by fever. Subject discontinued from study at request of parent.

[1]See text for definition of "Other Neurological Events"
[2]For "Other Neurological Events" that occurred after Dose 1 or 2, vaccine group is listed as Pentacel. For events that occurred after Dose 4, the Dose 4 stud group is listed.
[3]No stop date was recorded at the time of study termination.
For Doses 1, 2, and 3, all subjects received Pentacel and Prevnar at 2, 4, and 6 months and RECOMBIVAX HB at 0, 2, and 6 months or 2, 4, and 6 months.
Dose 4 Group 1 received 4th Dose of Pentacel at 15 months.
Dose 4 Group 2 received 4th Dose of Pentacel concomitantly with MMRII and VARIVAX at 15 months.
Dose 4 Group 3 received 4th Dose of Pentacel concomitantly with Prevnar at 15 months.
Dose 4 Group 4 received MMRII, VARIVAX, and Prevnar at 15 months, and 4th Dose of Pentacel at 16 months.
Source: 49403_addnl_safetyanalyses.pdf, pages 8-9

Serious Adverse Events

During the study period, there were two reported deaths:

- Subject 0118 was a 2-month-old female who died due to head trauma with intraventricular hemorrhage following an automobile accident. The accident occurred 22 days following the first dose of Pentacel, and the subject died one day later.

- Subject 0473, a male subject, died at age 4 months of SIDS (per medical examiner report), 52 days following the first dose of Pentacel. The subject was born at 38 weeks gestation and had an Apgar score of 9. Neonatal hearing screen showed decreased hearing in the left ear. Physical examination was normal, with responsiveness to sound. It was not known whether a repeat hearing test was performed.

Within 30 days following any of Doses 1-3 of Pentacel, 25 of 1207 (2.1%) subjects experienced 38 serious adverse events (source: revised iss.pdf, page 2627). Within 30 days following Dose 4 of Pentacel, 8 of 958 (0.8%) subjects experienced 11 serious adverse events (source: revised iss.pdf, page 2627). Among the 62 subjects from Center 10 excluded from the analyses, one had a serious adverse event-- RSV bronchiolitis 32 days following the first dose of Pentacel.

Table 41 presents serious adverse events classified according to MedDRA system organ class and preferred terms that occurred within 30 days following any of Doses 1-4.

Table 41 Study 494-03 Incidence of serious adverse events occurring within 30 days following any of Doses 1-4 of Pentacel, safety population

System Organ Class	N=1207		
Preferred Term	n	%	95% CI
GASTROINTESTINAL DISORDERS	3	0.2	(0.1, 0.7)
Constipation	1	0.1	(0.0, 0.5)
Gastro-oesophageal reflux disease	2	0.2	(0.0, 0.6)
Intussusception	1	0.1	(0.0, 0.5)
INFECTIONS AND INFESTATIONS	24	2.0	(1.3, 2.9)
Bronchiolitis	10	0.8	(0.4, 1.5)
Cellulitis	1	0.1	(0.0, 0.5)
Febrile convulsion	1	0.1	(0.0, 0.5)
Gastroenteritis NOS	1	0.1	(0.0, 0.5)
Gastroenteritis rotavirus	2	0.2	(0.0, 0.6)
Mastoiditis NOS	1	0.1	(0.0, 0.5)
Otitis media NOS	3	0.2	(0.1, 0.7)
Pneumonia NOS	3	0.2	(0.1, 0.7)
Pneumonia respiratory syncytial viral	1	0.1	(0.0, 0.5)
Pyelonephritis NOS	1	0.1	(0.0, 0.5)
Upper respiratory tract infection NOS	1	0.1	(0.0, 0.5)
Viral infection NOS	2	0.2	(0.0, 0.6)
Viral rash NOS	1	0.1	(0.0, 0.5)
INJURY AND POISONING	2	0.2	(0.0, 0.6)
Foreign body trauma	1	0.1	(0.0, 0.5)
Road traffic accident	1	0.1	(0.0, 0.5)
METABOLISM AND NUTRITION DISORDERS	4	0.3	(0.1, 0.8)
Dehydration	4	0.3	(0.1, 0.8)
NERVOUS SYSTEM DISORDERS	5	0.4	(0.1, 1.0)
Convulsions NOS	2	0.2	(0.0, 0.6)
Developmental coordination disorder NOS	1	0.1	(0.0, 0.5)
Hydrocephalus NOS	1	0.1	(0.0, 0.5)
Meningitis aseptic	1	0.1	(0.0, 0.5)
Tremor NEC	1	0.1	(0.0, 0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4	0.3	(0.1, 0.8)
Apnoea	2	0.2	(0.0, 0.6)
Bronchospasm NOS	1	0.1	(0.0, 0.5)
Respiratory distress	1	0.1	(0.0, 0.5)

NOS indicates not otherwise specified.
NEC indicates not elsewhere classified.
Source: 49403_addnl_safetyanalyses.pdf, pages 49-50

Clinical case narratives are presented below for selected serious adverse events from Table 41.

Case Narratives for Selected Serious Adverse Events of Interest that Occurred within 30 Days Following Vaccination

Subject 0112 Mastoiditis: At age 4 months, this male subject developed post-auricular swelling and fever of 39.4°C, 12 days following the second dose of Pentacel, and was admitted to the hospital. The WBC count was 17.7 $x10^9$/L. Blood cultures were negative. CSF protein and glucose were normal. CSF cultures and Gram stain were negative. A CT scan of the head showed right mastoiditis with soft tissue swelling and possible bony destruction. The subject was treated with antibiotics, discharged after two days and recovered without sequelae.

Subject 0497 Pyelonephritis: At age 16 months, following five days of rhinorrhea, cough, emesis, decreased oral intake and urine output, this female subject developed fever of 39.4°C, 11 days following the fourth dose of Pentacel (administered concomitantly with MMR_{II} and VARIVAX) and was admitted to the hospital. Urinalysis revealed WBCs too numerous to count. WBC count was 17.2 x 10^9/L (30% lymphocytes, 22% polys, 32% bands). BUN was 14 mg/dL. Creatinine was 0.5 mg/dL. Urine culture grew *E. coli*. Blood culture was negative. Renal ultrasound was normal. The subject was treated with intravenous fluids and antibiotics, discharged after two days, and recovered without sequelae.

Subject 1213 Hydrocephalus: At age 7 months, 12 days following the third dose of Pentacel, this subject was evaluated for excessive head growth and a full fontanel. Head ultrasound and brain MRI revealed hydrocephalus, choroid plexus enlargement, and a left middle cranial fossa arachnoid cyst. The subject underwent occipital venticuloperitoneal shunt insertion. The CSF was noted to be clear, with high opening pressure, glucose of 41 mg/dL and total protein of 7.3 mg/dL. The subject was discharged three days later, and recovered with sequelae.

Subject 0346 Head Lag, Tremors, Encephalopathy: At age 1 month, this subject developed an inability to hold his head up, loss of visual following, and shaking or jitteriness in the legs, eight days following the first dose of Pentacel. No neurological problems were noted at a clinic visit six days later. Eighteen days after the onset of symptoms, a neurologist noted several café au lait spots, absence of visual fixation and mild head lag. EEG was normal. MRI showed left frontal horn enlargement and left frontal atrophy. One month later, an eye exam showed no evidence of primary eye disease and improved visual following. Three months later, the subject appeared to be developing subtle left hemiparesis. The subject was diagnosed as having congenital encephalopathy. Treatment included physical and occupational therapy. The event was reported as continuing. The subject discontinued from the trial.

Subject 0451 Aseptic Meningitis: At age 2 months, this female subject developed fever of 102-103°F (38.9-39.4°C), increasing irritability and lethargy, five days following the first dose of Pentacel, and was admitted to the hospital. On exam, she was lethargic, hypotonic and irritable. WBC count was 16.8 x 10^9/L. Urinalysis was negative. CSF showed glucose of 43, protein of 47, with 15 RBCs and 115 WBCs, 40% lymphocytes, 23% segs and 23% bands. CSF culture was negative. The subject was treated with intravenous antibiotics, discharged two days later, and recovered without sequelae.

Subject 0738 Apnea: At age 2 months, this male subject developed gastroesophageal reflux on the same day as the first dose of Pentacel. Six days post-vaccination, he experienced 30 seconds of apnea and was hospitalized. A cardiorespirogram was normal with no further episodes of apnea. A gastrografin enema, an ECG and an EEG were normal. A pH probe was positive for gastroesophageal reflux disease. He was treated with albuterol, ranitidine HCl and metoclopramide HCl, discharged three days later, and recovered without sequelae.

Subject 1294 Apnea and Bronchiolitis: At age 2 months, following three days of cough, fever, difficulty breathing and poor oral intake, this male subject had three apneic spells, 18 days after the first dose of Pentacel and was admitted to the hospital. RSV testing was negative. Chest x-ray showed hyperinflation. Complete blood count was normal. He was treated with albuterol, supplemental oxygen, and intravenous fluids. He was discharged five days later and recovered without sequelae.

Subject 0946 Afebrile Seizure: See case narrative in section on seizures.

Subject 0879 Afebrile Seizure: See case narrative in section on seizures.

Subject 1102 Febrile Seizures: See case narrative in section on seizures.

Other Unsolicited Adverse Events of Note
There was one case of pertussis, not considered a serious adverse event, reported in a 5.7 month old male infant. Within approximately one month following the second dose of Pentacel the infant developed an upper respiratory tract infection, conjunctivitis, pneumonia, and bronchiolitis, for which he received antibiotics and albuterol. Thirty-nine days following vaccination, he was diagnosed with pertussis based on clinical symptoms of a 2-week history of cough, night-time wheezing and reddening of the face, without relief from albuterol. Neither culture nor PCR for pertussis were performed. There was no history of exposure to pertussis. The subject was treated empirically with oral erythromycin and sulfisoxazole and recovered in 17 days.

6.2.3 Comments and Conclusions
Study Design
This study contributes approximately 1,000 subjects to the overall safety database for Pentacel. A limitation of the study design is the lack of a control group that received licensed vaccines.

Data Quality
Data quality issues previously discussed for Study 494-01 (Section 6.1.3) including audits of already analyzed safety data and changes to the safety database, identification of data discrepancies and apparent errors in coding of seizures and serious adverse events in CBER's initial review (resolved in applicant's response to CBER's 5/26/06 Complete Response Letter), missing or incomplete data on solicited adverse events in up to 20% (Study 494-03) of subjects, and relatively poor compliance with the protocol recommended route of temperature measurement, also apply to Study 494-03. In addition, one study site was audited because of non-conformance with Good Clinical Practices and subjects from this site (N=62) were excluded from the analyses.

Safety Results
There were no safety concerns identified regarding administration of the fourth dose of Pentacel concomitantly with MMR_{II} and VARIVAX or with Prevnar relative to Pentacel alone.

Adverse events of interest that will be discussed further in the Overview of Safety Across Trials (Section 7) include two withdrawals due to severe crying with onset on the day of vaccination and lasting 2 and 7 days, respectively, one case of hypotonia that did not fulfill criteria for HHE on the same day as receipt of Pentacel, and one case of congenital encephalopathy with onset of symptoms eight days following Pentacel.

6.3 Pivotal Trial # 3

6.3.1 Applicant's Protocol # and Protocol Title
Study 5A9908: Safety and Immunogenicity Study of Pentacel When Administered as a 4th Dose at 15 to 18 Months of Age

6.3.1.1 Objective/Rationale
Study 5A9908 was conducted to assess the safety and immunogenicity of Pentacel given to toddlers at ages ranging from 15 to 18 months.

6.3.1.2 Design Overview

Study 5A9908 was a randomized, open-label, multi-center study designed to assess the safety and immunogenicity of Pentacel when administered as a fourth consecutive dose to toddlers ranging in age from 15 to 18 months. Planned enrollment was 1800 subjects who had been immunized with 3 doses of Pentacel by age 8 months in Canada. Subjects were recruited at 12 months of age from seven study centers in Canada, and were randomized equally to receive Pentacel at either 15, 16, 17, or 18 months of age. All subjects were to be assessed for safety. Serum samples for evaluation of immunogenicity were obtained before and 1 month (28 to 48 days) after vaccination from a subset of subjects (760 planned) from 3 study sites.

6.3.1.3 Population

Inclusion Criteria

- Toddlers 12 months (≥12 but <13) of age in good health on the basis of medical history who were immunized with three doses of Pentacel by 8 months of age, as verified with the participant's physician or public health record
- Parent/guardian able to read, write, and understand French or English
- Informed consent from parent or legal guardian
- Able to attend the scheduled visits and to comply with study procedures

Exclusion Criteria

- Clinically significant findings on review of systems
- Known or suspected hypersensitivity to any component of the study vaccines
- Known or suspected impairment of immunologic function or receipt of immunosuppressive therapy or immunoglobulin since birth
- Known HIV-positive
- Personal or immediate family history of congenital immune deficiency
- History of developmental delay or neurological disorders, including seizures
- History of chronic underlying medical, congenital, or developmental disorder, or major neonatal surgical condition
- Participation in any other experimental drug or vaccine trial
- History of clinically diagnosed or laboratory confirmed pertussis
- Any condition, which in the opinion of the investigator, would interfere with evaluation of the vaccine or pose a health risk to the subject
- Already received a fourth dose of diphtheria, pertussis, tetanus, Hib conjugate or poliovirus vaccine

Definite Contraindications to Vaccination

- Encephalopathy within 7 days following a previous vaccination
- Hypersensitivity to any vaccine component or anaphylactic reaction following a previous vaccination
- Known or suspected impairment of the immune system

Relative Contraindications (Decisions regarding continuation made on case by case basis with input from Medical Monitor)

- Hypotonia and/or hyporesponsiveness within 48 hours following a previous vaccination
- Serious adverse events possibly, probably or definitely related to the vaccine

Temporary Contraindications (Vaccination postponed, but may be rescheduled)

- Rectal temperature ≥38.0°C

6.3.1.4 Products Mandated by the Protocol

Schedule of Study Vaccines

Pentacel was administered at 15, 16, 17 or 18 months of age, depending on study group.

VARIVAX$_{II}$ and the first dose of MMR$_{II}$ was offered at ≥12 months but <13 months (unless already received). A second dose of MMR$_{II}$ was offered to participants residing in health regions where this dose is routinely given at 18 months of age. However, VARIVAX$_{II}$ and MMR$_{II}$ could not be given <60 days prior to or within 60 days following vaccination with Pentacel.

Formulation of Study Vaccines

For the formulation of Pentacel, see Section 1.2.3. HCPDT-IPV Lot C0154B and ActHIB lot P1332 were used to formulate Pentacel.

MMR$_{II}$ and VARIVAX$_{II}$, manufactured by Merck and Co., Inc., and licensed and purchased in Canada were used. For the formulation of MMR$_{II}$, see Section 6.1.1.4. When reconstituted and stored at room temperature for 30 minutes, the formulation of VARIVAX$_{II}$ is the same as that of U.S.-licensed VARIVAX. Whereas VARIVAX$_{II}$ may be stored at 2-8°C for as long as 90 days prior to administration (or in a freezer at -15°C), U.S. licensed VARIVAX may only be stored at refrigerator temperature for ≤72 continuous hours prior to reconstitution. Lot numbers of MMR$_{II}$ and VARIVAX$_{II}$ and diluents were identified at time of use.

Sites and Route of Vaccine Administration

The sites and routes of administration of vaccines were as follows:
Pentacel: intramuscular, left deltoid
MMR$_{II}$: subcutaneous, deltoid
VARIVAX$_{II}$: subcutaneous, deltoid
If MMR$_{II}$ and VARIVAX$_{II}$ were given concomitantly, they were to be administered in opposite limbs.

6.3.1.5 Safety Endpoints

There were no pre-specified primary safety endpoints. Secondary comparative analyses of rates of fever ≥38.0°C within 0-3 days post-vaccination were conducted between two combined age groups: fourth dose of Pentacel at 15 or 16 months and fourth dose of Pentacel at 17 or 18 months. Equivalence was demonstrated if the two-sided 90% confidence interval for the difference in fever rate between the two combined age groups was >-10% and <10%. All other analyses of safety were descriptive.

6.3.1.6 Safety Surveillance/Monitoring

Safety monitoring was essentially as described in Section 6.1.1.6 for Study 494-01. The protocol did not specify a recommended route of temperature measurement. The final study report indicates that parents measured the longest diameter of injection site redness and swelling using a ruler, but the revised Integrated Summary of Safety submitted to the BLA 9/7/06 indicates that the measurements were performed using a template with graduated circumferences in millimeters.

6.3.1.7 Statistical Considerations Related to the Safety Evaluation

Power for Equivalence Analyses of Fever Rates

With a sample size of 710 per combined age group (15 and 16 months, and 17 and 18 months), using α=0.05, the power was more than 99% to evaluate the hypothesis that fever rates are equivalent between the two combined groups, given an expected fever rate of 21.5% (based on historical studies of Pentacel) and a 10% equivalence margin.

Analysis Population for Safety
The ITT analyses for safety included all subjects who received the fourth dose of Pentacel.

HHE Definition
The definition of HHE used for the analyses of Studies 494-01 and 494-03 (see Section 6.1.1.7) was pre-specified in the protocol for Study 5A9908.

Classification of Seizures and Related Diagnoses
Seizures and related diagnoses were classified by the applicant as described in Section 6.1.1.7.

6.3.2 Results

6.3.2.1 Changes to the Data Resulting from Audit of Safety Database
As described for Study 494-01 (Section 6.1.2.1), because of inconsistencies in data reporting identified by the applicant during data analysis, an audit of the clinical safety database was performed. A summary of database changes resulting from the audit is presented in Appendix 13.

6.3.2.2 Populations Enrolled/Analyzed
Subjects were recruited and enrolled from seven Canadian sites. The study period from enrollment of the first subject through the last subject visit was 8/15/00 through 10/21/01. Rates of participation among eligible subjects who were contacted through recruitment efforts ranged from approximately 15% to 58% across the seven sites.

Subject Disposition and Follow-up
Table 42 presents a summary of subject disposition with regard to the safety evaluation, from randomization through 60 days post-vaccination.

Table 42. Study 5A9908 Summary of subject disposition for safety evaluation from randomization through 60 days post-vaccination

	15 Months N (%)	16 Months n (%)	17 Months n (%)	18 Month n (%)	All n (%)
All Randomized Subjects for Safety	468	466	465	470	1869
Randomized but did not receive Dose 4	21 (4.5)	21 (4.5)	16 (3.4)	29 (6.2)	87 (4.7)
Intent-to-Treat (ITT) Safety Population[1]	445 (100.0)	449 (100.0)	450 (100.0)	438 (100.0)	1782 (100.0)
Completed 60-day safety follow-up post Dose 4	442 (99.3)	448 (99.8)	449 (99.8)	434 (99.1)	1773 (99.5)
Did not complete 60-day safety follow-up post Dose 4[2]	3 (0.7)	1 (0.2)	1 (0.2)	4 (0.9)	9 (0.5)
Did not complete 60-day safety follow-up post Dose 4[2]	3 (100.0)	1 (100.0)	1 (100.0)	4 (100.0)	9 (100.0)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation by investigator	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	2 (50.0)	2 (22.2)
Voluntary withdrawal	3 (100.0)	1 (100.0)	1 (100.0)	1 (25.0)	6 (66.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (11.1)

[1]ITT Safety Population includes all enrolled subjects who received a dose of Pentacel. Treatment age group was determined by actual age at vaccination. Some subjects were vaccinated at an age other than that to which they were allocated due to missed and rescheduled appointments or study site errors (i.e., 15 Months lost 2, 16 Months gained 4, 17 Months gained 1, and 18 Months lost 3).
[2]Subjects terminated anytime between receipt of Dose 4 and the 60-day safety follow-up telephone call. Percentages are based on the number of subjects who did not complete the safety follow-up. Only the primary reason for termination per subject was selected in the order listed.
Source: 5a9908.pdf, page 63

Subject Demographics

At the time of vaccination with the fourth dose of Pentacel, subjects ranged in age from 14.5 to 19.6 months. The mean ages for each group were 15.4 months, 16.4 months, 17.4 months, and 18.3 months, respectively, with an overall mean of 16.9 months. Among the 1782 subjects overall, 921 (51.7%) were female; 1532 (86.0%) were Caucasian, 34 (1.9%) were Black, 15 (0.8%) were Hispanic, 77 (4.3%) were Asian, 35 (2.0%) were East Indian, 9 (0.5%) were Native Indian, and 80 (4.5%) were of other racial/ethnic groups. The four age groups were similar with respect to sex and racial distribution.

6.3.2.3 Safety Outcomes

Antipyretic Use

Within 3 days following vaccination, 36.9% of subjects, overall, used an antipyretic. Rates of use did not differ across the study groups.

Immediate Reactions

Nine subjects reported 10 immediate reactions within 30 minutes following Pentacel administration. Four subjects had reactions classified as mild (injection site bruising [n=2], injection site redness [n=1], and red flat spots [n=1]), 3 as moderate (hives [n=1], tremor with mottled skin [n=1], and 85 mm injection site redness [n=1]), and 2 as severe (injection site redness [n=2]). All subjects who had immediate reactions recovered without sequelae. The subject who experienced hives within 30 minutes following Pentacel was treated with diphenhydramine for one day, with resolution. Other adverse events reported by this subject included injection site swelling, redness and tenderness, anorexia, fever, fussiness and decreased activity.

Solicited Local Reactions

Although comparisons across studies are difficult to interpret, the frequencies of solicited redness and swelling in Study 5A9908 appeared somewhat higher than observed following the fourth dose of Pentacel in other pivotal studies. This apparent difference may reflect differences in methods for measuring local redness and swelling (see Sections 6.1.1.6 and 6.3.1.6).

Although formal statistical testing was not performed, the frequencies of solicited local adverse events of any of the severity grades appeared similar across the four age groups in Study 5A9908. Table 43 presents the frequencies of solicited local adverse events within 0-3 days following Pentacel for the four groups combined. The data on redness and swelling in Table 43 are from a revised Integrated Summary of Safety submitted to the BLA on 9/7/06, rather than from the final study report. The revised Integrated Summary of Safety corrected a programming error that affected the results for local redness and swelling. The final study report in the BLA is incorrect with regard to rates of local redness and local swelling >5 mm and >5-<25 mm.

Table 43. Study 5A9908: Frequencies of solicited local reactions, by severity, within 0-3 days following the fourth dose of Pentacel, pooled study groups, safety population

Reaction	n (%)
Redness	N = 1735
>5 mm	603 (34.8)
>5-<25 mm	158 (9.1)
25-50 mm	373 (21.5)
>50 mm	72 (4.1)
Swelling	N = 1729
>5 mm	357 (20.6)
>5-<25 mm	131 (7.6)
25-50 mm	187 (10.8)
>50 mm	39 (2.3)
Increase in Limb Circumference[1]	N = 1714
>5 mm	647 (37.7)
>5 mm-<20 mm	499 (29.1)
20-40 mm	130 (7.6)
>40 mm	18 (1.1)
Tenderness[2]	N = 1740
Any	586 (33.7)
Mild	444 (25.5)
Moderate	92 (5.3)
Severe	50 (2.9)

[1]Increase in limb 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.
[2]Tenderness: Mild = subject whimpers when site is touched, no crying; Moderate = subject cries when site is touched; Severe = subject cries when leg or arm is moved.
Source: 5a9908.pdf, page 78 and iss.pdf (revised) Table 9.30

Among the 18 subjects with >40 mm increase in limb circumference within 0-3 days post-vaccination, the maximum percentage increase over the baseline measurement ranged from 23% to 35% for 16 subjects, was 47% for one subject and was 111% for one subject. Swelling of the entire injected limb was not solicited, and was not reported as an unsolicited adverse event in any subject.

Nearly all solicited local reactions had an onset within the first three days following vaccination. Available data indicate that most cases of local redness, swelling, and tenderness had resolved by Day 7 following vaccination. During the period 4-7 days following vaccination, redness, swelling, and tenderness were reported in 7.2%, 5.4%, and 1.6% of subjects, respectively. During the period 4-7 days post-vaccination, increased limb circumference of any severity was reported in 18.1% of subjects, and of moderate or severe severity in 1.7% of subjects.

Other Local Adverse Events

In addition to the solicited local adverse events presented previously, injection site reactions within 0-3 days following vaccination that were reported as unsolicited events included: 9 subjects (0.5%) with injection site bruising, 6 subjects (0.3%) with injection site erythema, 2 subjects (0.1%) with injection site induration, and 1 subject (0.1%) each with injection site dermatitis, unspecified injection site reaction, and edema lower limb (source 5a9908.pdf, Table 9.31). Of these events, three cases of injection site erythema were graded as severe. None of these events required medical attention. According to the applicant, solicited events captured as unsolicited may reflect reporting solicited events during a scheduled telephone call or medical visit, but not in the diary card.

Route of Temperature Measurement

Temperature measurements were most frequently taken axillary (71.3% [8756/12287 recordings]), with 14.2% (1746/12287) taken rectally, and 3.5% (436/12287) tympanic. For 11.0% (1349/12287) of temperature measurements, the route was not recorded. There were no notable differences between the four study groups with respect to routes of temperature measurement. The frequency of fever was substantially higher among subjects who had rectal vs. axillary measurements. For example, for the four study groups combined, the frequency of fever $\geq$38.0°C and >39.5°C within three days after vaccination was 67.6% and 3.6%, respectively, for subjects with at least one rectal measurement recorded, compared with 7.3% and 0.3%, respectively, for subjects with an axillary measurement recorded. In these comparisons, there may be some overlap between the rectal and axillary categories as some subjects may have used different routes of temperature measurements on different days during the post-vaccination monitoring period.

Comparison of Fever Rates by Age Group

The rates of fever $\geq$38.0°C within 0-3 days post-vaccination for the 15 and 16 month group combined [16.2% (141/870)] and for the 17 and 18 month group combined [18.8% (160/851)] [difference 15 and 16 month minus 17 and 18 month = -2.59; 90% confidence interval for difference (-5.61, 0.42)] met the predefined equivalence criterion.

Observational Analyses of Solicited Systemic Adverse Events

Although comparisons across studies may not be valid and are difficult to interpret, rates of fever appeared to be somewhat higher in Study 5A9908 compared with Dose 4 Pentacel in Studies 494-01 and 494-03. Otherwise, there were no apparent notable increases in the frequencies of solicited systemic adverse events in Study 5A9908 relative to those observed in Studies 494-01 and 494-03.

HHE and Hypotonia

No cases of HHE or hypotonia were reported.

Seizures

A list of seizures that occurred within 30 days following the fourth dose of Pentacel and anytime during the study is provided in Table 44 and Appendix 14, respectively.

Table 44. Study 5A9908 Seizures that occurred within 30 days following Pentacel, safety population (N=1782)

Subject Number	Afebrile, Febrile, or "Possible"	Literal Term	Days Since Vaccine	Outcome
2182	Afebrile	Seizure	9	Recovered without sequelae
1082	Febrile	Febrile seizure	2	Recovered without sequelae
1334	Febrile	Febrile seizure	4	Recovered without sequelae
1231	Febrile	Febrile convulsion	20	Recovered without sequelae
1258	Febrile	Febrile convulsion	26	Recovered without sequelae
5170	Febrile	Possible atypical febrile seizure	27	Recovered without sequelae

Source: 5a9908_addnl_safetyanalyses.pdf, page 6

Incidence rates of seizures, per subjects, after the fourth dose of Pentacel, by interval since vaccination, are presented in Table 45.

Table 45. Study 5A9908 Incidence, **per subjects**, of seizures following the fourth dose of Pentacel, pooled study groups, safety population

Period	N=1782		
	n	%	95% CI
Seizures (febrile and afebrile)			
0-60 Days Post-Dose 4	8	0.4	(0.2, 0.9)
0-30 Days Post Dose 4	6	0.3	(0.1, 0.7)
0-7 Days Post Dose 4	2	0.1	(0.0, 0.4)
Afebrile Seizures			
0-60 Days Post-Dose 4	1	0.1	(0.0, 0.3)
0-30 Days Post Dose 4	1	0.1	(0.0, 0.3)
0-7 Days Post Dose 4	0	0.0	(0.0, 0.2)
Febrile Seizures			
0-60 Days Post-Dose 4	7	0.4	(0.2, 0.8)
0-30 Days Post Dose 4	5	0.3	(0.1, 0.7)
0-7 Days Post Dose 4	2	0.1	(0.0, 0.4)

Source: 5a9908_addnl_safetyanalyses.pdf, pages 26-29

The incidence rates, per 1000 doses, of seizures are presented in Table 46.

Table 46. Study 5A9908 Incidence, **per 1000 doses**, of seizures following the fourth dose of Pentacel, pooled study groups, safety population

Period	Pentacel (Number of Doses = 1782)		
	n	Rate per 1000 doses	95% CI
Seizures (febrile and afebrile)			
0-60 Days Post-Dose 4	8	4.49	(1.94, 8.85)
0-30 Days Post Dose 4	6	3.37	(1.24, 7.33)
0-7 Days Post Dose 4	2	1.12	(0.14, 4.05)
Afebrile Seizures			
0-60 Days Post-Dose 4	1	0.56	(0.01, 3.13)
0-30 Days Post Dose 4	1	0.56	(0.01, 3.13)
0-7 Days Post Dose 4	0	0.00	(0.00, 2.07)
Febrile Seizures			
0-60 Days Post-Dose 4	7	3.93	(1.58, 8.09)
0-30 Days Post Dose 4	5	2.81	(0.91, 6.55)
0-7 Days Post Dose 4	2	1.12	(0.14, 4.05)

Source: 5a9908_addnl_safetyanalyses.pdf, pages 30-33

Case narratives are provided below for seizures that occurred within 30 days following vaccination. For one of these events which was reported as a serious adverse event (Subject 5170), the case narrative contains supplemental information from the Investigator. For seizures not reported as serious adverse events, the case narratives contain available pertinent information from the database, without supplemental information from the Investigator.

Case Narratives for Afebrile Seizures within 30 Days Following Vaccination

Subject 2182: At age 15 months, this male subject experienced a seizure 9 days following the fourth dose of Pentacel. "Unspecified viremia" also was noted. He presented to an emergency room, recovered without sequelae the same day, and completed the study without other seizures reported.

Case Narratives for Febrile Seizures within 30 days Following Vaccination

Subject 1082: At age 15 months, this male subject experienced a febrile seizure 2 days following the fourth dose of Pentacel, and was also diagnosed with streptococcal pharyngitis. Treatment included acetaminophen and clarithromycin. He presented to an emergency room and recovered from the seizure the same day, without sequelae. He voluntarily withdrew from the study.

Subject 1231: At age 15 months, this female subject experienced a febrile seizure 20 days following the fourth dose of Pentacel. She presented to an emergency room. No treatment was reported. The subject recovered without sequelae the same day and completed the study without other seizures reported.

Subject 1258: At age 16 months, this female subject experienced a febrile seizure 26 days following the fourth dose of Pentacel. She presented to an emergency room. No treatment was reported. The subject recovered without sequelae the same day and completed the study without other seizures reported.

Subject 1334: At age 17 months, this female subject experienced a febrile seizure 4 days following the fourth dose of Pentacel. She had a concurrent upper respiratory infection. She presented to an emergency room, was treated with paracetamol, and recovered from the seizure the same day, without sequelae. She completed the study without other seizures reported.

Subject 5170: At age 19 months, this female subject developed vomiting of one day duration, 27 days following the fourth dose of Pentacel. Two days later, she experienced episodes of difficulty breathing with eyes rolling back and loss of consciousness, and was taken to an emergency room. Blood and urine tests were normal. Treatment included dimenhydrinate. Although fever was not documented, the emergency room diagnosis was "possible atypical febrile seizure". EEG two weeks later was normal. The subject recovered without sequelae and completed the study without other seizures reported. Past medical history included a febrile seizure approximately six months earlier.

Other Neurological Events that may be Observed in the Context of Seizures

One event was categorized by the applicant as an "Other Neurological Event". This category includes neurological events that may occur in the context of seizures, but for which the Medical Monitor deemed that a diagnosis of seizures or possible seizures was not warranted.

Subject 2188, at age 17 months, developed tremor and mottled skin within 30 minutes following the fourth dose of Pentacel. The events were considered moderate in severity. Concurrent symptoms/diagnoses included diarrhea, loss of appetite, and an upper respiratory tract infection. The tremor resolved without sequelae the same day and the subject completed the study without other neurological events reported.

Serious Adverse Events

No deaths occurred during the study. Within 30 days following the fourth dose of Pentacel, 19 of 1782 (1.1%) subjects experienced 30 serious adverse events (revised iss.pdf, page 2627). Table 47 presents serious adverse events classified according to MedDRA system organ class and preferred terms that occurred within 30 days following vaccination.

Table 47. Study 5A9908 Incidence of serious adverse events occurring during the period 0-30 days following the fourth dose of Pentacel, pooled study groups, safety population

System Organ Class	N=1782		
Preferred Term	n	%	95% CI
GASTROINTESTINAL DISORDERS	2	0.1	(0.0, 0.4)
Diarrhoea NOS	1	0.1	(0.0, 0.3)
Vomiting NOS	1	0.1	(0.0, 0.3)
GENERAL DISORDERS/ADMINISTRATION SITE CONDITIONS	2	0.1	(0.0, 0.4)
Pyrexia	2	0.1	(0.0, 0.4)
INFECTIONS AND INFESTATIONS	17	1.0	(0.6, 1.5)
Bronchopneumonia NOS	1	0.1	(0.0, 0.3)
Cellulitis orbital	1	0.1	(0.0, 0.3)
Croup infectious	1	0.1	(0.0, 0.3)
Ear infection NOS	2	0.1	(0.0, 0.4)
Febrile convulsion	1	0.1	(0.0, 0.3)
Gastroenteritis NOS	4	0.2	(0.1, 0.6)
Influenza	2	0.1	(0.0, 0.4)
Kidney infection NOS	1	0.1	(0.0, 0.3)
Pneumonia NOS	3	0.2	(0.0, 0.5)
Respiratory tract infection NOS	1	0.1	(0.0, 0.3)
Viral infection NOS	2	0.1	(0.0, 0.4)
INJURY AND POISONING	1	0.1	(0.0, 0.3)
Burns NOS	1	0.1	(0.0, 0.3)
METABOLISM AND NUTRITION DISORDERS	4	0.2	(0.1, 0.6)
Dehydration	4	0.2	(0.1, 0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	0.1	(0.0, 0.4)
Asthma NOS	2	0.1	(0.0, 0.4)

NOS indicates not otherwise specified
Source: 5a9908.pdf, page 36

Clinical case narratives are presented below for selected serious adverse events from Table 47.

Case Narratives for Selected Serious Adverse Events that Occurred within 30 days Following Vaccination

Subject 2248 Orbital cellulitis: At age 18 months, this male subject developed right orbital cellulitis following an insect bite 14 days post-vaccination, was hospitalized and treated with intravenous antibiotics. He was discharged on oral antibiotics two days later, recovered and continued in the trial.

Subject 7159 Kidney infection: At age 16 months, this subject was hospitalized for persistent fever with onset 12 days post-vaccination. Urinalysis showed >100 white blood cells and >100 red blood cells per high-power field. Urine culture was positive for *E. coli*. He was treated with intravenous antibiotics, and on Day 4 was discharged on oral antibiotics. He recovered and continued in the trial.

Subject 5170 Febrile seizure: See case narrative in section on seizures.

Subject 5097 Fever: At age 15 months, this male subject developed fever and cough 21 days post-vaccination. The next day, he was hospitalized for fever and difficulty breathing. He was diagnosed with croup and discharged one day later. He recovered and continued in the trial.

Subject 3030 Fever: At age 16 months, this subject developed cough 16 days post-vaccination. Two days later, he developed fever, shortness of breath, grunting respirations, and lethargy, and was subsequently hospitalized. He was enrolled in an aerosol-bronchiolitis blinded study with a licensed product. Additional treatment included oxygen, Ventolin and Tylenol. He fully recovered and continued in the trial.

6.3.3 Comments and Conclusions

Study Design

This study, which was primarily designed to evaluate the safety of a fourth dose of Pentacel administered at different ages, contributes to the overall safety database for Pentacel by providing post-Dose 4 safety data on approximately 1,700 subjects. Limitations of the study worth noting are the lack of a control group that received licensed vaccines, other recommended vaccines (MMR_{II}, VARIVAX and Prevnar) were not administered concomitantly with Pentacel, and the potential for self-selection bias. If subjects who experienced adverse events after previous doses of Pentacel were less likely to participate, and if the occurrence of post-Dose 4 adverse events is positively correlated with adverse events following previous doses, then the true rate of adverse events may be underestimated.

Data Quality

As previously discussed for Study 494-01 (Section 6.1.2.1), because of data inconsistencies and errors identified by the applicant during analyses, an audit was conducted of already analyzed safety data and changes made to the safety database. Questions regarding the coding of serious adverse events that were conveyed in the 5/26/06 Complete Response Letter were adequately addressed by the applicant.

As noted in Section 6.3.2.3, a programming error that affected analyses of some local reactions was identified by the applicant during the process of preparing responses to CBER's 5/26/06 Complete Response Letter. Corrected analyses were submitted to the BLA.

Safety Results

Of some note was one case of hives that occurred within 30 minutes following Pentacel. The event resolved following treatment with Benadryl. Interpretation of the data from Study 5A9908 is limited by the lack of a control group. Rates of some solicited local reactions and fever appeared to be somewhat higher in Study 5A9908 relative to post-Dose 4 Pentacel data from other pivotal studies. However, comparisons across studies are difficult to interpret. Overall, the data from Study 5A9908 did not raise any notable safety concerns.

6.4 Pivotal Trial #4

6.4.1 Applicants Protocol # and Protocol Title

Study P3T06: Safety, immunogenicity and lot comparability of DAPTACEL (Aventis Pasteur classic five-component pertussis vaccine in combination with diphtheria and tetanus toxoids adsorbed) when administered with other recommended vaccines at 2, 4, 6 and 15-16 months of age.

6.4.1.1 Objective/Rationale

Originally, this study was planned primarily to evaluate DAPTACEL lot consistency and the immune responses to DAPTACEL administered concomitantly with other recommended vaccines. During the course of the study, the protocol was amended to include primary non-inferiority analyses of the immunogenicity of Pentacel relative to DAPTACEL + ActHIB + IPOL.

6.4.1.2 Design Overview

Study P3T06 was a multicenter study in which subjects were randomized at recruitment. For each study site, randomization was provided in blocks of 12 (3 subjects for each of 3 DAPTACEL lots and 3 subjects to receive Pentacel). Subjects who received a particular lot of DAPTACEL for the first three doses were randomized to one of three DAPTACEL groups for the fourth dose. The fourth dose DAPTACEL groups all received a single lot of DAPTACEL. They differed with regard to concomitantly administered vaccines. Pentacel subjects were enrolled to receive four consecutive doses of Pentacel. Safety and immunogenicity comparisons between lots of DAPTACEL were assessed in a blinded manner. Comparisons between DAPTACEL and Pentacel were open-label. The planned duration of the study, per subject, was 21-23 months.

6.4.1.3 Population

Inclusion and exclusion criteria were essentially the same as those for Study 494-01 (Section 6.1.1.3).

Temporary Contraindication to Vaccination

- Rectal temperature >38.5°C (101.3°F)

Relative Contraindications (decision to continue in trial made on a case by case basis)

- Rectal temperature >39.5°C (>103.1°F) or equivalent (axillary of ~102.0°F) within 48 hours following a previous vaccination
- Seizure within 3 days following a previous vaccination
- HHE within 48 hours of a previous vaccination
- Serious adverse events related to the vaccine (possible, probable, or definite)

Definite Contraindications

- Encephalopathy within 7 days of a previous vaccination
- Severe hypersensitivity to any component of the vaccine such as an anaphylactic reaction following a previous vaccination
- Known or suspected impairment of the immune system

6.4.1.4 Products Mandated by the Protocol

Study Vaccines—Schedule of Administration

Tables 48 and 49 present the schedule of study vaccines. The protocol-specified interval between doses 1 and 2 of DAPTACEL or Pentacel was 60 days +/- 10 days. The protocol-specified interval between doses 2 and 3 of DAPTACEL or Pentacel was 60-90 days.

Table 48. Study P3T06: Schedule of vaccine administration through six months of age

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

* All subjects received hepatitis B vaccine at 0, 2, and 6 months; the first dose (manufacturer not specified) was administered prior to enrollment in the study; the second and third doses were with RECOMBIVAX HB, administered during the study.

Table 49. Study P3T06: Schedule of vaccine administration from 12-17 months of age

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

Study Vaccines—Formulation and Lot Numbers: All study vaccines except for Pentacel are licensed in the U.S. For the formulation of Pentacel, see section 1.2.3. For the formulation of ActHIB, Prevnar, RECOMBIVAX HB, MMR_{II}, and VARIVAX, see Section 6.1.1.4.

The composition of DAPTACEL (DTaP manufactured by Sanofi Pasteur Limited) per 0.5 ml dose is as follows:

Active Ingredients:
10 µg detoxified PT
5 µg FHA
5 µg FIM (types 2 & 3)
3 µg PRN
15 LF Diphtheria toxoid
5 LF Tetanus toxoid
Adjuvant: 0.33 mg aluminum
Excipient: 0.6% 2-phenoxyethanol

The composition of IPOL (poliovirus vaccine, inactivated, manufactured by Sanofi Pasteur Inc.) per 0.5 ml dose is as follows:

Active Ingredients:
40 D antigen units of poliovirus Type 1 (Mahoney)
8 D antigen units of poliovirus Type 2 (MEF-1)
32 D antigen units of poliovirus Type 3 (Saukett)
Preservatives: 0.5% 2-phenoxyethanol and a maximum of 0.02% formaldehyde
Residual calf serum protein: <1 ppm
Other ingredients that may be present:
neomycin <5 ng
streptomycin <200 ng
polymyxin B <25 ng

The following vaccine lot numbers were specified:
Pentacel Doses 1-3: HCPDT-IPV Lot C0790BA and ActHIB Lot UA596AB

Pentacel Dose 4: HCPDT-IPV Lot C1362A and ActHIB Lot UA685AA
DAPTACEL Doses 1-3: C0239A (lot 1), C0314A (lot 2), and C0191A (lot 3)
DAPTACEL Dose 4: C0950AA
IPOL: T1189-2
ActHIB Doses 1-3: UA596AB
ActHIB Dose 4: UA685AA

For Prevnar, RECOMBIVAX HB, MMR_{II} and VARIVAX, lots available at the study sites were used.

Study Vaccines: Route and Site of Administration

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

Doses 1-3 of Control vaccines and other vaccines (Study Groups 1-3)
DAPTACEL – Left upper thigh
ActHIB – Left lower thigh
IPOL – Left arm
Prevnar – Right lower thigh
RECOMBIVAX HB – Right upper thigh

Doses 1-3 of Pentacel and other vaccines (Study Group 4)
Pentacel – Left upper thigh
Prevnar – Right lower thigh
RECOMBIVAX HB – Right upper thigh

Dose 4 of Control vaccines and other vaccines (Study Groups 1-3):
Group 1:

12 months:	MMR_{II} and VARIVAX – sites not specified
15 to 16 months:	DAPTACEL – Left deltoid
	ActHIB – Right deltoid

Group2:

15 to 16 months:	DAPTACEL – Left deltoid
	ActHIB – Right deltoid
	MMR_{II} – Left upper thigh
	VARIVAX – Right upper thigh
	Prevnar - Left lower thigh

Group 3:

15 to 16 months:	ActHIB – Right deltoid
	MMR_{II} – Left upper thigh
	VARIVAX – Right upper thigh
	Prevnar - Left lower thigh
16 to 17 months:	DAPTACEL – Left deltoid

Dose 4 of Pentacel and other vaccines (Study Group 4):

12 months:	MMR_{II}, VARIVAX, and Prevnar – sites not specified
15 to 16 months:	Pentacel– Left deltoid

6.4.1.5 Safety Endpoints

There were no primary or secondary safety endpoints. All analyses of safety were descriptive, without pre-specified evaluation criteria.

6.4.1.6 Safety Surveillance/Monitoring

Overview of Safety Monitoring Procedures

Safety monitoring was essentially as described in Section 6.1.1.6 for Study 494-01, with notable differences described herein. Compared with Study 494-01, differences in safety monitoring in Study P3T06 included telephone contact at Day 2 or 3 following vaccination rather than at Day 4, instruction to take temperatures rectally rather than axillary post-Dose 4, additional information collected during Day 2 or 3 and Day 8 telephone interviews to further characterize reported rashes, more active monitoring for HHEs, and a longer follow-up period through 6 months after Dose 4 of Pentacel or Control vaccines.

In Study P3T06, for Days 0 and 1 following Doses 1-3 of Pentacel or Control vaccines, the diary card included questions about generalized decrease or loss of muscle tone, extreme paleness of skin or cyanosis, and decreased level of consciousness, awareness, or responsiveness. If such symptoms occurred, parents/guardians were to contact the study site. If the study site determined that the symptoms met the protocol-specified criteria for HHE (same definition used for analysis in Study 494-01; see Section 6.1.1.7), the subject was to be further evaluated in the clinic.

In Study P3T06, a telephone call or review of computerized records (if available) was conducted at or after Day 180 post-Dose 4 Pentacel or Control vaccines, to inquire about serious adverse events, chronic events, or events of possible autoimmune origin that may have occurred since the previous contact (Day 60 post-Dose 4). During the telephone interviews, the following questions were asked:

1. Has your child been admitted to a hospital?
2. Has your child experienced a life-threatening episode that required attendance to the emergency room or a physician's office?
3. Does your child have a medical condition that requires repeated visits to the health care provider?
4. Has your child been diagnosed by a physician as having:
   a. Low blood count or low platelet count
   b. Swelling or redness of the joints
   c. Bronchial asthma
   d. Diabetes Mellitus
   e. Autism

6.4.1.7 Statistical Considerations Related to the Safety Evaluation

Sample Size

The planned sample size was 2,000 subjects randomized equally to one of three lots of DAPTACEL or one lot of Pentacel. An attrition rate of 15% to the end of post-Dose 3 follow-up and an additional 15% to the end of the study was assumed. The sample size was determined by immunogenicity endpoints.

Analysis Population for Safety

The ITT safety population included any subject who received a DAPTACEL or Pentacel dose. Analyses at each dose were based on the actual treatment received. Analyses of safety outcomes across doses were based on randomized group.

Classification of Seizures and Related Diagnoses
Seizures and related diagnoses were classified by the applicant as described in Section 6.1.1.7 for Study 494-01.

Dose 4 Comparative Safety Analyses
For post-Dose 4 comparative safety analyses, the group that received MMR_{II} and VARIVAX at 12 months of age and DAPTACEL and ActHIB at 15-16 months of age (Dose 4, Group 1) served as the control group for the fourth dose of Pentacel administered at 15-16 months of age.

6.4.2 Results

6.4.2.1 Site Audit Due to Non-Conformance with Good Clinical Practices
One clinical site audit due to non-conformance with Good Clinical Practices was conducted. Findings included study procedures conducted prior to consent, investigational product accountability issues, and cold chain issues. The applicant reported that corrective actions were implemented.

6.4.2.2 Changes to the Data Resulting from Audit of Safety Database
As described for Study 494-01 (Section 6.1.2.1), because of inconsistencies in data reporting noted by the applicant during data analysis, an audit of the safety database was performed. A summary of resultant changes to the database is presented in Appendices 15 and 16.

6.4.2.3 Populations Enrolled/Analyzed
Subjects were enrolled from 31 U.S. sites. The study period from the first subject visit to the last subject contact was 5/4/01 through 1/21/04.

Subject Disposition and Follow-up
Table 50 presents a summary of subject disposition with regard to the safety evaluation, from randomization through 60 days post-Dose 3. Among subjects who were randomized to receive DAPTACEL, two had parental consent withdrawn before Dose 1 and one received Pentacel for the first dose.

Table 50. Study P3T06: Summary of subject disposition for safety evaluation, from randomization through 60 days post-Dose 3

Safety and Immunogenicity Disposition	Control (DAPTACEL pooled lots) n (%)	Pentacel n (%)
All Randomized Subjects	1457	484
ITT Safety Population[1]	1454 (100.0)	485 (100.0)
Received Dose 1 of DAPTACEL or Pentacel[1]	1454 (100.0)	485 (100.0)
Received Dose 1 and Dose 2 of DAPTACEL or Pentacel[2]	1400 (96.3)	469 (96.7)
Received All 3 doses of DAPTACEL or Pentacel[3]	1376 (94.6)	461 (95.1)
Completed 60-day Safety Follow-up post-Dose 3[4]	1350 (92.8)	452 (93.4)
Did Not Complete 60-day Safety Follow-up[4,5]	105 (7.2)	32 (6.6)
Did Not Complete 60-day Safety Follow-up[4,5]	105 (100.0)	32 (100.0)
Adverse event	5 (4.8)	1 (3.1)
Contraindication	0 (0.0)	0 (0.0)
Lost to follow-up	18 (17.1)	9 (28.1)
Non-compliance	21 (20.0)	9 (28.1)
Voluntary withdrawal	60 (57.1)	13 (40.6)
Other	1 (1.0)	0 (0.0)

[1] Subjects classified by the actual treatment received at Dose 1.
[2] Subjects classified by the actual treatment received at Dose 2.
[3] Subjects classified by the actual treatment received at Dose 3.
[4] Subjects have been classified by the randomized treatment.
[5] Subjects terminated anytime between receipt of Dose 1 and the post-Dose 3 60-day safety follow-up telephone call; Only the primary reason for termination per subject is selected in the order listed.
Source: p3t06si.pdf, pages 79-80

Among subjects who completed the 60-day safety follow-up post-Dose 3, 7.4% (100/1350) of Control subjects and 4.9% (22/452) of Pentacel subjects did not receive the fourth dose of vaccines. Table 51 presents the reasons for termination for these subjects.

Table 51. Study P3T06: Reasons for termination after the 60-day follow-up post-Dose 3 and before dose 4 of Pentacel or Control vaccines

Safety Disposition	Control (DAPTACEL pooled lots) n (%)	Pentacel n (%)
Completed 60-day follow-up post-Dose 3	1350	452
Completed 60-day follow-up post-Dose 3 but terminated before Dose 4	100 (7.4)	22 (4.9)
Completed 60-day follow-up post-Dose 3 but terminated before Dose 4[1]	100 (100.0)	22 (100.0)
Adverse event	6 (6.0)	0 (0.0)
Contraindication	1 (1.0)	0 (0.0)
Lost to follow-up	25 (25.0)	7 (31.8)
Non-compliance	27 (27.0)	3 (13.6)
Voluntary withdrawal	41 (41.0)	12 (54.5)

[1] Only the primary reason per subject is selected in the order listed.
Source: p3t06sii.pdf, page 84

Table 52 presents subject disposition from the fourth dose of Pentacel or Control vaccines through the end of the study.

Table 52. Study P3T06: Summary of subject disposition for safety evaluation, from dose 4 Pentacel or Control vaccines through the end of the study

Subject Disposition	Control				Pentacel
	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Total n (%)	Group 4 n (%)
Subject Participation by Randomized Treatment	419	418	413	1250	430
ITT Safety Population[1]	418[2]	420[2]	411[2]	1249[2]	431[2]
Completed 180-Day Safety Follow-up Post-Dose 4[3]	406 (96.9)	407 (97.4)	404 (97.8)	1217 (97.4)	416 (96.7)
Did not Complete 180-Day Safety Follow-up Post-Dose 4[3,4]	13 (3.1)	11 (2.6)	9 (2.2)	33 (2.6)	14 (3.3)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Contraindication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	7 (53.8)	6 (54.5)	9 (100.0)	22 (66.7)	8 (57.1)
Non-compliance	3 (23.1)	1 (9.1)	0 (0.0)	4 (12.1)	2 (14.3)
Voluntary withdrawal	3 (23.1)	4 (36.4)	0 (0.0)	7 (21.2)	3 (21.4)

[1] Subjects are grouped per actual treatment received
[2] Eight subjects who were randomized to one of the DAPTACEL groups, received vaccines for another DAPTACEL group; 4 subjects who were randomized to receive DAPTACEL, received Pentacel; 3 subjects who were randomized to receive Pentacel, received DAPTACEL.
[3] Percentages are based on total number of subjects at Dose 4 by Randomization.
[4] Only the primary reason per subject is selected in the order listed.
Group 1: Received the 4th doses of DAPTACEL and ActHIB at 15-16 months of age; Group 2: Received the 4th doses of DAPTACEL and ActHIB concomitantly with Prevnar, MMR_{II}, and VARIVAX at 15-16 months of age; Group 3: Received the 4th Dose of ActHIB concomitantly with Prevnar, MMR_{II} and VARIVAX at 15-16 months of age and the 4th dose of DAPTACEL one month later; Group 4: Received the 4th Dose of Pentacel at 15-16 months of age.
Source: p3t06 Stage II.pdf, page 86

Table 53 presents a listing of withdrawals due to adverse events anytime during the study. There were two withdrawals due to adverse events, including one death, among subjects who received Pentacel. There were 11 withdrawals due to adverse events among subjects who received Control vaccines.

Table 53. Study P3T06 Study withdrawals due to adverse events

Pentacel (N=484)	
Subject #	Adverse event(s) that led to withdrawal
0347	"Unspecified health issues" listed as reason for termination. Subject had mild gastroesophageal reflux same day as Dose 1 Pentacel and mild gastroenteritis 16 days post-Dose 1.
0493	Asphyxiation and death 8 days post-Dose 4 Pentacel
Control (N=1455)	
Subject #	Adverse event(s) that led to withdrawal
0076	Gastroenteritis, methemoglobinemia, dehydration, metabolic acidosis, malnutrition, aortic valve stenosis with onset 22-32 days post-Dose 1
1362	Severe seizure with apnea same day as dose 1
1296	Cerebral palsy diagnosed 128 days post-Dose 3
1825	Ependymoma 54 days post-Dose 3 (subject subsequently died)
2230	Allergic reaction (non-anaphylactic) within 30 minutes post-Dose 3
2293	Mitochondrial disorder with myopathy diagnosed 260 days post-Dose 3
0472	Chickenpox 64 days post-Dose 1
1633	Chickenpox
1326	Chickenpox at 12 month visit
0885	Croup and otitis media 38 days post-Dose 1
2388	Severe failure to thrive and severe bronchiolitis12 and 48 days, respectively, post-Dose 1

Source: P3T06 stage I.pdf, pages 78-79 and P3T06 Stage II.pdf, pages 83 and 85

Table 54 presents a summary of subject demographics at the time of enrollment.

Table 54. Study P3T06 Summary of subject demographics at enrollment, safety population

Demographic Characteristic	Control (Pooled DAPTACEL Lots)	Pentacel
	1454	485
Sex	n (%)	n (%)
Male	703 (48.3)	243 (50.1)
Female	751 (51.7)	242 (49.9)
Age (months)		
Mean	2.2	2.1
Range	(1.3, 3.5)	(1.4, 3.0)
Race	n (%)	n (%)
Caucasian	1123 (77.2)	375 (77.3)
Black	91 (6.3)	34 (7.0)
Hispanic	95 (6.5)	33 (6.8)
Asian	13 (0.9)	5 (1.0)
Other	132 (9.1)	38 (7.8)

Group is defined by actual vaccine received at first dose.
Source: p3t06si.pdf, page 82

For Control subjects in Dose 4 Group 1 that served as the comparison group for Dose 4 of Pentacel, the mean age at receipt of the fourth dose of DAPTACEL and ActHIB was 15.6 (range 15.0-19.5) months. For the Pentacel group, the mean age at receipt of the fourth dose was 15.6 (range 14.7-18.3) months.

6.4.2.4 Safety Outcomes

There were no notable differences in safety outcomes across the three DAPTACEL lot groups for Doses 1-3. Therefore, in this review, safety data for Control subjects for Doses 1-3 are pooled across the three DAPTACEL lot groups.

As explained in Section 6.4.1.7, for fourth dose safety comparisons, Control subjects from Dose 4 Group 1 (MMR_{II} and VARIVAX at 12 months of age; DAPTACEL and ActHIB at 15-16 months of age) served as the comparator for the fourth dose of Pentacel. Therefore, in this review, safety data following the fourth dose of Control vaccines will be presented only for this group, unless otherwise noted. The fourth dose safety data for the other DAPTACEL groups were reviewed under DAPTACEL Supplement STN #103666/5071.

Antipyretic Use

Within 3 days after receipt of each of the first three doses of Pentacel or Control vaccines, antipyretics were used by approximately half of subjects: 44-47% of Pentacel subjects and 45-49% of Control subjects (source: p3t06si.pdf, page 151). Within 3 days following the fourth dose of Pentacel, antipyretics were used by 33.6% of subjects. Within 3 days following the fourth dose of Control vaccines, antipyretics were used by 31.1% of subjects in Dose 4 Group 1 (DAPTACEL + ActHIB at 15-16 months of age).

Immediate Reactions

During the immediate 30 minute post-vaccination period, two subjects had an adverse event following Pentacel (both injection site erythema post-Dose 4) and 12 subjects had an adverse event following Control vaccines (nine with local injection site reactions, one with crying and irritability, and two with allergic reactions). The allergic reactions are described below.

Subject 2230 At age 6.3 months, this male subject developed a generalized raised, red rash of moderate severity, within 30 minutes post-Dose 3 of Control vaccines (DAPTACEL + ActHIB + IPOL administered concomitantly with Prevnar and RECOMBIVAX HB). He was treated with diphenhydramine for 3-4 days and recovered without sequelae by Day 4. Because of this event, the Investigator discontinued the subject from the study prior to Dose 4.

Subject 0707 At age 16.3 months, this female subject experienced urticaria within 30 minutes following the fourth dose of Control vaccines. There were no concomitantly administered vaccines. The event was moderate in severity. The subject was seen in an emergency room, treated with diphenhydramine and cetirizine and recovered without sequelae the same day.

Rashes

Information on rashes was solicited to capture allergic reactions to vaccination. Table 54 presents the frequency of rash and the frequency of rash all over the body within 3 days following each dose of Pentacel or Control vaccines.

Table 54. Study P3T06 Frequency of rash and frequency of generalized rash within 3 days following each dose of Pentacel or Control vaccines, safety population

	Pentacel[1]				Control: (Doses 1-3 DAPTACEL pooled lots; Dose 4 Group 1)[2]			
	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=468	N=452	N=441	N=398	N=1407	N=1360	N=1312	N=381
Rash present	20 (4.3)	26 (5.8)	24 (5.4)	28 (7.0)	48 (3.4)	78 (5.7)	88 (6.7)	39 (10.2)
All over body	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.8)	6 (0.4)	8 (0.6)	10 (0.8)	2 (0.5)

[1]Subjects received Pentacel and Prevnar at 2, 4, and 6 months of age. RECOMBIVAX HB was also administered at 2 and 6 months of age. Subjects received the fourth dose of Pentacel at 15-16 months of age.
[2]Subjects received DAPTACEL, IPOL, ActHIB, and Prevnar at 2, 4 and 6 months of age. RECOMBIVAX HB was also administered at 2 and 6 months of age. Dose 4 Group 1 received the 4th doses of DAPTACEL and ActHIB at 15-16 months of age.
'n' is the number of subjects in the treatment group with the specific reaction.
'N' is the number of subjects with available data per treatment group who received the indicated dose.
Source: p3t06si.pdf, pages 130-131 and 690-693; p3t06sii.pdf, pages 121-122 and 308 ; questions1_133.pdf, pages 283-284.

Solicited Local Reactions

Table 55 presents the frequencies of solicited local adverse events at the injection sites of Pentacel, DAPTACEL, and of the Control vaccines combined (highest severity measurement of all Control sites) within 0-3 days following vaccination.

For both Pentacel and DAPTACEL, the frequency of injection site tenderness, redness and swelling of any intensity tended to be higher following Dose 4 than following Doses 1-3 (Table 55). The rates of redness and swelling >25 mm and >50 mm also tended to be higher following Dose 4 than previous doses. Increase in arm circumference was monitored only after the fourth dose of study vaccines. Approximately one-third of subjects reported increased circumference of the Pentacel or DAPTACEL injected arm after the fourth dose, with <1% reporting an increase >40 mm.

Among subjects with redness >50 mm at the Pentacel or DAPTACEL injection site within 3 days post-vaccination, the maximum reported area of redness was 85 mm for Pentacel subjects and 100 mm for DAPTACEL subjects.

Among subjects with swelling >50 mm at the Pentacel or DAPTACEL injection site within 3 days post-vaccination, the maximum reported area of swelling was 80 mm for Pentacel subjects and 150 mm for DAPTACEL subjects.

Two subjects reported a >40 mm increase in the circumference of the Pentacel injected arm within 3 days post-Dose 4. For these subjects, the maximum reported increase was 50 mm and 60 mm, respectively, representing 29% and 43% increases, respectively, over the baseline measurements. Three Control subjects in Dose 4 Group 1 reported a >40 mm increase in the circumference of the DAPTACEL injected arm within 3 days post-Dose 4. For one of these subjects, the calculated maximum increase of 151 mm is thought to be erroneous due to an apparent error in the recorded baseline measurement of 10 mm. Therefore, the data on increase in arm circumference in this subject is not interpretable. For the other two subjects, the maximum reported increase was 47 mm and 52 mm, respectively, representing 29% and 33% increases, respectively, over the baseline measurements.

As in the other pivotal studies, information on whole limb swelling was not specifically solicited. While there were some unsolicited reports (3 Pentacel subjects and 6 Control subjects) of limb swelling or enlargement following Pentacel or DAPTACEL or other concomitantly administered vaccines, in each case the event was graded as mild or moderate in severity. In four instances in which the event was reported following the fourth dose and in which limb circumference data were available, the maximum reported increase in circumference ranged from 8 mm to 25 mm.

Table 55. Study P3T06: Frequency of solicited local reactions by severity occurring within 0-3 days following each dose of Pentacel or Control vaccines: Pentacel injection site, DAPTACEL injection site, and any Control injection site, safety population

	Pentacel Injection Site				DAPTACEL Injection Site Doses 1-3: Lots 1 – 3 Pooled Dose 4: Group 1[2]				Any Control Injection Site[1] Doses 1-3: DAPTACEL, ActHIB , IPOL (Groups 1 - 3 Pooled) Dose 4: DAPTACEL, ActHIB (Group 1)[2]			
Reactions	Dose 1 n(%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4 n (%)	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4 n (%)	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4 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)
Increased Limb Circumference	n/a			N=387	n/a			N=376	n/a			N=376
>5 mm				130 (33.6)				115(30.6)				141 (37.5)
>5 - <20 mm				112 (28.9)				89 (23.7)				106 (28.2)
20 – 40 mm				16 (4.1)				23 (6.1)				31 (8.2)
>40 mm				2 (0.5)				3 (0.8)				4 (1.1)

[1]For the control injection sites, the highest severity/measurement of all injection sites is reported for each subject.
[2]Dose 4 Group 1 received the fourth doses of DAPTACEL and ActHIB at 15-16 months of age
[3]Mild: subject whimpers when site is touched; Moderate: subject cries when site is touched; Severe: subject cries when leg or arm is moved.
n/a indicates data not collected
Source: p3t06si.pdf, page 114, p3t06sii.pdf, pages 113, 116, and 183

For both Pentacel and DAPTACEL, following each of Doses 1-4, the frequencies of each of the solicited local adverse events within 3 days and within 7 days following vaccination were nearly the same, indicating that the onset of these events typically was within the first three days following vaccination. For both Pentacel and DAPTACEL, during the period 4-7 days post-vaccination for Doses 1-3, the frequency of any redness, swelling, and tenderness was generally <2%, indicating that these events usually resolved within the first three days following vaccination. For both Pentacel and DAPTACEL, during the period 4-7 days following the fourth dose, the frequency of any redness, swelling, and tenderness was generally ≤4%. During the period 4-7 days post-Dose 4, 14.4% of Pentacel subjects and 12.9% of DAPTACEL subjects still reported increased upper arm circumference.

Other Local Adverse Events Reported as Unsolicited

In addition to the solicited local adverse events presented previously, 21 (4.3%) subjects who received Pentacel and 88 (6.0%) subjects who received Control vaccines (pooled groups for all four doses) reported an injection site reaction(s) coded as unsolicited within 3 days following any of Doses 1-4. Some of these events included solicited events, although the injection site involved (i.e., Pentacel or DAPTACEL or other vaccines) was not always noted. Some of the events were not specifically solicited (e.g., bruising). One event, injection site pain following the first dose of Pentacel, was graded as severe. Seven subjects in the pooled Control groups and three subjects in the Pentacel group had an injection site reaction coded as unsolicited that resulted in a medical contact. These events included injection site erythema, injection site induration, injection site edema, and upper limb edema. [Source: p3t06_addnl_safetyanalyses.pdf]. According to the applicant, solicited events captured as unsolicited may reflect reporting solicited events during a scheduled telephone call or visit, but not in the diary card.

Solicited Systemic Reactions

Although parents were instructed to measure temperatures rectally, nearly half of temperature measurements were axillary following Doses 1-3 of Pentacel or Control vaccines, and approximately two-thirds were axillary following the fourth dose of study vaccines (Table 56).

Table 56. Study P3T06: Frequencies by which temperatures were measured by the indicated routes following Pentacel or Control vaccines, safety population

	Pentacel[1]				Control: DAPTACEL (pooled lots for Doses 1-3; Dose 4 Group 1)[2]			
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 1	Dose 2	Dose 3	Dose 4
Route	%	%	%	%	%	%	%	%
Total N	3684	3564	3450	3112	10976	10641	10303	2999
Axillary	48.2	45.7	44.8	63.0	47.0	44.5	43.8	61.0
Rectal	51.0	53.1	54.1	34.4	52.3	54.6	54.4	36.6
Oral	0.8	1.2	1.2	2.2	0.6	0.8	1.6	1.8
Not Recorded	0.0	0.1	0.0	0.4	0.1	0.1	0.2	0.5

[1]Subjects received Pentacel and Prevnar at 2, 4, and 6 months of age, and RECOMBIVAX HB at 2 and 6 months of age. Subjects received the fourth dose of Pentacel at 15-16 months of age.
[2]Subjects received DAPTACEL, IPOL, ActHIB and Prevnar at 2, 4 and 6 months of age. RECOMBIVAX HB was also administered at 2 and 6 months of age. Dose 4 Group 1 received the 4th doses of DAPTACEL and ActHIB at 15-16 months of age.
Notes: Percentages are based on the total number of days with recorded temperatures.
'N' is the number of temperatures taken per treatment group for which subjects received the indicated dose
Source: P3T06 stageI.pdf, page 116 and P3T06stageII.pdf, page 117

Table 57 presents the frequency of fever within three days following each dose of Pentacel or Control vaccines, by route of temperature measurement, axillary or rectal, and severity. Overall, at each dose, approximately 5% of subjects switched route of temperature measurement during the 0-3 day period, and therefore may be included under both axillary and rectal measurements. Nevertheless, following each dose, rates of fever were notably higher among subjects who had at least one rectal temperature measurement compared to those who had at least one axillary measurement. This difference was not apparent for fever >39.5°C, although few subjects reported this level of fever.

Table 57. Study P3T06: Frequency of fever within 0-3 days following each dose of Pentacel or Control vaccines, by route of temperature measurement (axillary or rectal), safety population

Fever	Pentacel[1]				Control: (DAPTACEL pooled lots for Doses 1-3; Dose 4 Group 1)[2]			
	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4 n (%)	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4 N (%)
Axillary measurements	N=233	N=220	N=198	N=257	N=684	N=626	N=595	N=241
≥38.0°C	5 (2.1)	5 (2.3)	17 (8.6)	15 (5.8)	25 (3.7)	56 (8.9)	55 (9.2)	7 (2.9)
38.0-38.5°C	3 (1.3)	3 (1.4)	13 (6.6)	7 (2.7)	21 (3.1)	39 (6.2)	30 (5.0)	4 (1.7)
>38.5-39.5°C	1 (0.4)	2 (0.9)	3 (1.5)	7 (2.7)	3 (0.4)	17 (2.7)	22 (3.7)	3 (1.2)
>39.5°C	1 (0.4)	0 (0.0)	1 (0.5)	1 (0.4)	1 (0.1)	0 (0.0)	3 (0.5)	0 (0.0)
rectal measurements	N=247	N=252	N=243	N=147	N=760	N=761	N=740	N=147
≥38.0°C	22 (8.9)	44 (17.5)	53 (21.8)	36 (24.5)	104 (13.7)	162 (21.3)	149 (20.1)	26 (17.7)
38.0-38.5°C	18 (7.3)	35 (13.9)	38 (15.6)	24 (16.3)	86 (11.3)	121 (15.9)	109 (14.7)	17 (11.6)
>38.5-39.5°C	3 (1.2)	9 (3.6)	13 (5.3)	12 (8.2)	18 (2.4)	36 (4.7)	39 (5.3)	6 (4.1)
>39.5°C	1 (0.4)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	5 (0.7)	1 (0.1)	3 (2.0)

[1]Subjects received Pentacel and Prevnar at 2, 4, and 6 months of age, and RECOMBIVAX HB at 2 and 6 months of age. Subjects received the fourth dose of Pentacel at 15-16 months of age.
[2]Subjects received DAPTACEL, IPOL, ActHIB, and Prevnar at 2, 4 and 6 months of age. RECOMBIVAX HB was also administered at 2 and 6 months of age. Dose 4 Group 1 received the 4th doses of DAPTACEL and ActHIB at 15-16 months of age.
Source: p3t06si.pdf, pages 499-522; p3t06sii.pdf, pages 257-260

Table 58 presents analyses of solicited systemic adverse events, including fever, within 0-3 days following each dose of Pentacel or Control vaccines. Analyses of fever were based on actual temperatures recorded with no adjustments to the measurement for route.

For the Pentacel group, the frequency of fever increased with consecutive doses from Dose 1 to Dose 3, without further increase post-Dose 4. For the Control group, the frequency of fever increased from Dose 1 to Dose 2, and was similar following Doses 2 and 3. The frequency of fever following the fourth dose of Control vaccines was similar to that observed following the first dose. For both Pentacel and Control vaccines, the frequencies of decreased activity, inconsolable crying and fussiness were highest post-Dose 1, with a notable decrease by Dose 4. The frequency of anorexia was generally similar across doses.

The frequency of any fever post-Dose 4 was 13.4% among Pentacel subjects and 8.7% among subjects who received DAPTACEL + ActHIB concomitantly (Dose 4 Group 1). However, for each category of fever severity, the 95% confidence intervals for the fever rates were overlapping between the two study groups (data not shown in table). The frequencies of other solicited systemic adverse events were not notably higher among subjects who received Pentacel relative to those who received Control vaccines.

Table 58. Study P3T06 Frequencies of selected solicited systemic adverse events within 0-3 days after Pentacel or Control vaccines, safety population

	Pentacel[1]				Control (DAPTACEL pooled lots for Doses 1-3; Dose 4 Group 1)[2]			
Event	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4 n (%)	Dose 1 n (%)	Dose 2 n (%)	Dose 3 n (%)	Dose 4 n (%)
Fever[3]	N=466	N=451	N=435	N=389	N=1390	N=1346	N=1301	N=379
≥38.0°C	27 (5.8)	49 (10.9)	71 (16.3)	52 (13.4)	129 (9.3)	217 (16.1)	205 (15.8)	33 (8.7)
38.0-38.5°C	21 (4.5)	38 (8.4)	52 (12.0)	32 (8.2)	107 (7.7)	159 (11.8)	139 (10.7)	21 (5.5)
>38.5-39.5°C	4 (0.9)	11 (2.4)	16 (3.7)	19 (4.9)	21 (1.5)	53 (3.9)	62 (4.8)	9 (2.4)
>39.5°C	2 (0.4)	0 (0.0)	3 (0.7)	1 (0.3)	1 (0.1)	5 (0.4)	4 (0.3)	3 (0.8)
Less Active[4]	N=467	N=452	N=440	N=398	N=1406	N=1360	N=1312	N=381
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	N=467	N=452	N=440	N=398	N=1406	N=1360	N=1312	N=381
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)	N=467	N=452	N=440	N=398	N=1406	N=1360	N=1312	N=381
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[5]	N=467	N=452	N=441	N=398	N=1406	N=1360	N=1312	N=381
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]Subjects received Pentacel and Prevnar at 2, 4, and 6 months of age. RECOMBIVAX HB was also administered at 2 and 6 months of age. Subjects received the fourth dose of Pentacel at 15-16 months of age.
[2]Subjects received DAPTACEL, IPOL, ActHIB, and Prevnar at 2, 4 and 6 months of age. RECOMBIVAX HB was also administered at 2 and 6 months of age. Dose 4 Group 1 received the 4th doses of DAPTACEL and ActHIB at 15-16 months of age.
[3]Fever is based upon actual temperatures recorded with no adjustments to the measurement for route.
[4]Less Active: Mild: usual daily activity is not affected; Moderate: interferes with or limits usual daily activity; Severe: disabling, not interested in usual daily activity.
[5]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.
Notes: Each subject is counted once and is classified according to the highest recorded severity score.
'n' is the number of subjects in the treatment group with the specific reaction.
'N' is the number of subjects with available data per treatment group who received the indicated dose.
Source: P3T06 stageI.pdf, pages 126-127 and p3t06sii.pdf, page 119

Table 59 presents a summary of the frequencies of selected systemic adverse events during the periods 0-3, 4-7, and 0-7 days post-vaccination for Pentacel or Control vaccines, Doses 1-3 combined and Dose 4. For these events, the pattern of temporal relationship to vaccination was similar for Pentacel and Control vaccines. In general, the frequencies of solicited systemic adverse events during Days 0-7 following vaccination tended to be somewhat higher than the frequencies within Days 0-3 post-vaccination, indicating onset beyond Day 3 in some subjects. The frequencies of adverse events during Days 4-7 post-vaccination relative to Days 0-3 post-vaccination suggest that except for fever post-Dose 4, the majority of events had resolved by Day 3. Nevertheless, a substantial proportion of subjects reported each of the systemic adverse events listed in Table 59 beyond Day 3 post-vaccination. The contribution of background occurrence (i.e., in the absence of vaccination) of these events on the observed frequencies is not known.

Table 59. Study P3T06: Frequencies of selected solicited systemic reactions of any intensity reported during 0-3 days, 4-7 days, and 0-7 days after each dose of Pentacel or Control vaccines, safety population

Event	Period	Pentacel[1]		Control[2]	
		Doses 1-3 N=472	Dose 4 N=389-398	Doses 1-3 Pooled lots N=1424-1429	Dose 4 Group 1 N=377-381
		%	%	%	%
Fever	Day 0-3	25.2	13.4	30.1	8.7
	Day 4-7	9.1	7.7	9.1	6.4
	Day 0-7	29.2	18.2	33.4	12.9
Less Active	Day 0-3	66.3	24.1	67.8	24.1
	Day 4-7	15.3	8.3	17.3	8.7
	Day 0-7	68.2	26.1	69.5	28.6
Crying	Day 0-3	82.0	35.9	79.6	36.2
	Day 4-7	29.0	9.3	32.3	11.0
	Day 0-7	83.5	38.9	82.1	39.4
Fussiness	Day 0-3	93.4	53.5	91.7	53.8
	Day 4-7	41.9	16.6	41.9	17.3
	Day 0-7	93.9	57.0	92.7	57.0
Anorexia	Day 0-3	44.7	23.4	46.8	24.9
	Day 4-7	17.6	12.3	16.7	12.6
	Day 0-7	49.2	26.4	49.9	30.7

[1]Subjects received Pentacel and Prevnar at 2, 4, and 6 months of age. RECOMBIVAX HB was administered at 2 and 6 months of age. Subjects received the fourth dose of Pentacel at 15-16 months of age.
[2]Subjects received DAPTACEL, IPOL, ActHIB, and Prevnar at 2, 4 and 6 months of age. RECOMBIVAX HB was administered at 2 and 6 months of age. Dose 4 Group 1 received the 4th doses of DAPTACEL and ActHIB at 15-16 months of age.
Notes: 'n' is the number of subjects in the treatment group with the specific reaction.
'N' is the number of subjects with available data per treatment group who received the indicated dose.
Source: P3T06 Stage I.pdf, pages 614-638 and P3T06 Stage II.pdf, pages 264-288

Because there were several reports of solicited systemic adverse events or related terms that were classified as unsolicited, the applicant was asked to provide a summary of fever, crying, irritability, and somnolence that were reported as unsolicited. Within three days following any of Doses 1-4, 13 (2.7%) Pentacel subjects and 49 (3.4%) Control subjects (pooled groups for all doses) reported fever; 15 (3.1%) Pentacel subjects and 30 (2.1%) Control subjects (pooled groups for all doses) reported crying, irritability, or restlessness; and no Pentacel subjects and 4 (0.3%) Control subjects (pooled groups for all doses) reported somnolence or lethargy. Severe events included two cases of fever and one case of irritability following Control vaccines, and one case

each of fever and irritability following Pentacel. Events that resulted in a medical contact (telephone call, outpatient or emergency room visit, or hospitalization) included four cases of fever and three cases of irritability in Control subjects. [Source: p3t06_addnl_safetyanalyses.pdf, Tables 9.65, 9.70, and 9.75]. According to the applicant, solicited events captured as unsolicited may reflect reporting events during a scheduled telephone call or visit, but not in the diary card.

HHE, Hypotonia, and Hyporesponsiveness

No events that met the protocol criteria for HHE were reported. Two control subjects experienced symptoms of HHE that did not fully meet the criteria for HHE.

Four days after the first dose of Control vaccines, Subject 0293 experienced hypotonia described as very slight decrease in muscle tone and not holding head well. Medical attention was not sought. The event resolved after one day, without sequelae. The investigator considered the event to be mild in severity.

Sixteen days after the second dose of Control vaccines, Subject 0132 experienced crying as in pain, lethargy, unresponsiveness, shallow breathing, cold arms and hands, and cyanosis. There was no limpness, rigidity, jerking, or tremors. She was admitted to the hospital. EEG and EKG were normal. A nasopharyngeal swab was positive for influenza A. The subject was treated with amantadine and discharged two days later on an apnea monitor. No apnea was reported. The subject recovered without sequelae.

Seizures

Within 30 days following any dose of Pentacel, no subject (N=484) reported seizures. Table 60 provides a list of subjects with seizures within 30 days following Control vaccines (pooled DAPTACEL lots for Doses 1-3 and Dose 4 Group 1 only). One subject (Subject 0051) in Dose 4 Group 3 (not included in Table 60) experienced a febrile seizure 20 days after the fourth dose of DAPTACEL. Appendix 17 provides a list of seizures that occurred anytime following Pentacel or DAPTACEL (pooled lots for Doses 1-3; Dose 4 Group 1 only).

Table 60. Study P3T06: Seizures that occurred within 30 days following any dose of Pentacel[1] or Control vaccines (pooled DAPTACEL lot groups for Doses 1-3; Dose 4 Group 1)

Control vaccines (DAPTACEL pooled lots for Doses 1-3, N=1,455; Dose 4 Group 1, N=418)					
Subject Number	Afebrile or Febrile or Possible	Literal Term	Last Dose	Days Since Last Dose	Outcome
1362	Afebrile	Seizure with apnea	1	0	Recovered without sequelae
1931	Afebrile	Seizure	1	22	Recovered without sequelae
1833	Febrile	Febrile convulsion	3	30	Recovered without sequelae

[1]No subject who received Pentacel (N=485) had a seizure within 30 days post-vaccination.
No seizures within 30 days of vaccination occurred in a subject who did not receive study vaccines as randomized.
Source: p3t06_addnl_safetyanalyses.pdf, Table 1 page 16 (7 of 273)

Table 61 presents the incidence, per subjects, of seizures within 30 days and 7 days following any of Doses 1-3 of Pentacel or Control vaccines.

Table 61. Study P3T06: Incidence, **per subjects**, of seizures that occurred following Doses 1-3 of Pentacel or Control vaccines, by interval since vaccination, safety population

Period	Pentacel N = 484			Control (pooled DAPTACEL lots) N = 1455		
	n	%	95% CI	N	%	95% CI
Seizures (febrile and afebrile)						
0-30 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 0.8)	3	0.2	(0.0, 0.6)
0-7 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Afebrile Seizures						
0-30 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 0.8)	2	0.1	(0.0, 0.5)
0-7 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Febrile Seizures						
0-30 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
0-7 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 0.8)	0	0.0	(0.0, 0.3)

Source: p3t06_addnl_safetyanalyses.pdf, Table 1 page 16 (7 of 273); questions1_133.pdf, pages 303-305.

Table 62 presents the incidence rates (per 1000 doses) of seizures within 30 days and 7 days following any of Doses 1-3 of Pentacel or Control vaccines.

Table 62. Study P3T06: Incidence, **per 1000 doses,** of seizures that occurred following any of Doses 1-3 of Pentacel or Control vaccines, safety population

Period	Pentacel (Number of Doses = 1415)			Control (pooled DAPTACEL lots) (Number of Doses = 4230)		
	n	Rate per 1000 doses	95% CI	n	Rate per 1000 doses	95% CI
Seizures (febrile and afebrile)						
0-30 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 2.60)	3	0.71	(0.15, 2.07)
0-7 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 2.60)	1	0.24	(0.01, 1.32)
Afebrile Seizures						
0-30 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 2.60)	2	0.47	(0.06, 1.71)
0-7 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 2.60)	1	0.24	(0.01, 1.32)
Febrile Seizures						
0-30 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 2.60)	1	0.24	(0.01, 1.32)
0-7 Days Post-vaccination (Doses 1-3 combined)	0	0.0	(0.0, 2.60)	0	0.00	(0.00, 0.87)

Source: questions1_133.pdf, pages 306-308.

Case narratives are provided below for seizures that occurred within 30 days following vaccination. For Subject 1362, the event was considered serious and the case narrative contains information submitted by the Investigator. The other narratives include available information from the database without supplemental information from the Investigator.

Case Narratives for Seizures within 30 days Following Vaccination

Subject 1362 This one-month old female developed left leg tenderness nine hours following the first dose of Control vaccines, for which she received acetaminophen. Twelve hours post-vaccination, she had a 15-second episode of whole-body twitching and staring, accompanied by 5 seconds of apnea. Subsequently, she was deeply asleep/unresponsive for a period variably reported as 10-45 minutes. In the emergency room, she was afebrile, awake, crying and consolable. Diagnostic studies including CBC, SMA-7, EKG, urinalysis, and cultures of urine and blood were negative. She was observed for 15 hours and discharged with an apnea monitor. One week later, waking and sleep EEGs were normal. An esophagram showed no significant gastroesophageal reflux. The subject recovered without sequelae.

Subject 1931 This 2-month old female experienced a seizure 22 days after the first dose of Control vaccines. She presented to an emergency room, recovered without sequelae after one day, and completed the study without additional seizures reported.

Subject 1833 At age 7 months, this female experienced a febrile convulsion 30 days after the third dose of Control vaccines. The event resulted in a medical office visit. The subject recovered without sequelae after one day and completed the study without additional seizures reported.

Subject 0051 This 17-month old male experienced a febrile seizure 20 days after the fourth dose of DAPTACEL (Dose 4 Group 3). He presented to an emergency room. The same day, he was diagnosed with a respiratory viral infection, and a day later with otitis media. He recovered without sequelae from the seizure the same day.

Other Neurological Events that may be Observed in the Context of Seizures
Seven subjects who received Control vaccines (N=1,455) and no subjects who received Pentacel (N=484) had "Other Neurological Events". This category includes neurological events that may occur in the context of seizures, but for which the Medical Monitor deemed that a diagnosis of seizures or possible seizures was not warranted. These events are summarized in Table 63.

Table 63. Study P3T06 subjects with "Other Neurological Events" following any dose of Pentacel[1] or Control vaccines, safety population

Subject Number	Preferred Term	Literal Term	Severity	Action Taken	Last Dose	Days Since Last Dose
Control (DAPTACEL pooled lots for Doses 1-3; Dose 4 Group 1)						
0432	Breath holding	Breath holding spells	Moderate	Medical office visit	1	73
0740	Staring	Staring spells	Mild	Medical office visit	3	216
0916	Neuromuscular disorder NOS	Shaking episode (probable disinhibition)	Moderate	Telephone call to physician	2	26
1235	Breath holding	Breath holding episode	Mild	Medical office visit	1	55
1330	Tremor NEC	Shaking spell	Mild	Emergency room visit	3	43
2110	Tremor NEC	Leg tremors	Mild	Medical office visit	2	0
2387	Myoclonic seizure	Clonic activity	Mild	Medical office visit	2	56

[1]No subject who received Pentacel had an event classified as "Other Neurological Event".
Source: Source: p3t06_addnl_safetyanalyses.pdf, Table 1 page 17 (8 of 273)

Additional available information is provided below for the two events in Table 63 that occurred within 30 days post-vaccination.

Case Narratives for "Other Neurological Events" within 30 Days Post-Vaccination

Subject 0916: At age 5 months, this male subject experienced a shaking episode ("probable disinhibition") 26 days after the second dose of Control vaccines. He also had a possible seizure 35 days later. The event was considered moderate in severity and resulted in a telephone call to the physician. The subject recovered without sequelae the same day and completed the study. Other than the events noted above, no other seizure-like events were reported.

Subject 2110: At age 4 months, this male subject experienced leg tremors the same day as the second dose of Control vaccines. At the time of the event, he was being treated with albuterol for bronchiolitis. The event resolved without sequelae. The subject completed the study without other neurological events reported.

Serious Adverse Events

There were two deaths during the study, one due to aspiration in a subject with ependymoma 222 days following Control vaccines, and one due to suffocation 8 days following Pentacel. Case narratives for serious adverse events of interest, including deaths, will be provided later in this section.

Overall, the incidence of any serious adverse event was similar following Pentacel or Control vaccines. Within 30 days following any of Doses 1-3, a total of 50/1455 (3.4%) Control subjects (DAPTACEL pooled lots) experienced 61 serious adverse events and 19/484 (3.9%) Pentacel subjects experienced 24 serious adverse events. Within 30 days post-Dose 4, 4/418 (1.0%) Control subjects in Dose 4 Group 1 experienced six serious adverse events and 5/431 (1.2%) Pentacel subjects experienced five serious adverse events.

Table 64 presents serious adverse events classified according to MedDRA system organ class and preferred terms that occurred within 30 days following any of Doses 1-3 of Pentacel or DAPTACEL (pooled lots).

Table 64. Study P3T06 Serious adverse events within 30 days following any of Doses 1-3[1] of Pentacel or Control vaccines (DAPTACEL pooled lots), safety population

System Organ Class Preferred Term	Pentacel N=484			Control N=1455		
	n	%	95% CI	n	%	95% CI
BLOOD AND LYMPHATIC SYSTEM	2	0.4	(0.1, 1.5)	1	0.1	(0.0, 0.4)
Idiopathic thrombocytopenic purpura	1	0.2	(0.0, 1.1)	0	0.0	(0.0, 0.3)
Lymphadenitis NOS	1	0.2	(0.0, 1.1)	0	0.0	(0.0, 0.3)
Methaemoglobinaemia NOS	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
GASTROINTESTINAL	1	0.2	(0.0, 1.1)	4	0.3	(0.1, 0.7)
Constipation	1	0.2	(0.0, 1.1)	0	0.0	(0.0, 0.3)
Diarrhoea NOS	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Diarrhoea haemorrhagic	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Gastro-oesophageal reflux disease	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Pyloric stenosis NOS	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
INFECTIONS AND INFESTATIONS	15	3.1	(1.7, 5.1)	41	2.8	(2.0, 3.8)
Bronchiolitis	4	0.8	(0.2, 2.1)	28	1.9	(1.3, 2.8)
Croup infectious	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Gastroenteritis NOS	2	0.4	(0.1, 1.5)	3	0.2	(0.0, 0.6)
Gastroenteritis rotavirus	1	0.2	(0.0, 1.1)	0	0.0	(0.0, 0.3)
Gastroenteritis viral NOS	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Influenza	1	0.2	(0.0, 1.1)	0	0.0	(0.0, 0.3)
Meningitis NOS	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Meningitis viral NEC	1	0.2	(0.0, 1.1)	1	0.1	(0.0, 0.4)
Nasopharyngitis	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Otitis media chronic NOS	2	0.4	(0.1, 1.5)	2	0.1	(0.0, 0.5)
Pertussis	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Pneumonia NOS	2	0.4	(0.1, 1.5)	2	0.1	(0.0, 0.5)
Pneumonia haemophilus	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Pneumonia respiratory syncytial viral	2	0.4	(0.1, 1.5)	0	0.0	(0.0, 0.3)
Septicaemia haemophilus	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Urinary tract infection NOS	1	0.2	(0.0, 1.1)	1	0.1	(0.0, 0.4)
INJURY AND POISONING	0	0.0	(0.0, 0.8)	2	0.1	(0.0, 0.5)
Mouth injury	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Skull fracture NOS	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Subdural haematoma	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
METABOLISM AND NUTRITION	3	0.6	(0.1, 1.8)	2	0.1	(0.0, 0.5)
Dehydration	3	0.6	(0.1, 1.8)	1	0.1	(0.0, 0.4)
Failure to thrive	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Metabolic acidosis NOS	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
NERVOUS SYSTEM	0	0.0	(0.0, 0.8)	2	0.1	(0.0, 0.5)
Coma NEC[2]	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Seizure anoxic	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
PSYCHIATRIC	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Irritability	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
RESPIRATORY, THORACIC, MEDIASTINAL	1	0.2	(0.0, 1.1)	2	0.1	(0.0, 0.5)
Asthma NOS	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
Pneumonia aspiration	1	0.2	(0.0, 1.1)	0	0.0	(0.0, 0.3)
Status asthmaticus	0	0.0	(0.0, 0.8)	1	0.1	(0.0, 0.4)
SURGICAL AND MEDICAL PROCEDURES	1	0.2	(0.0, 1.1)	1	0.1	(0.0, 0.4)
Lip repair	1	0.2	(0.0, 1.1)	1	0.1	(0.0, 0.4)

[1] Subjects are grouped as per randomization. No events in this table were in subjects not receiving study vaccine according to randomization.
[2]This event was reported as unresponsiveness (see case narrative in section on HHEs), and was classified by the sponsor as "Coma NEC"
Each subject is counted once per System Organ Name or Preferred Term.
Source: questions1_133.pdf, Table 52 (pages 312-314)

Table 65 presents serious adverse events classified according to MedDRA system organ class and preferred terms that occurred within 30 days following Dose 4 of Pentacel or Control vaccines (Dose 4 Group 1).

Table 65. Study P3T06 Serious adverse events within 30 days following Dose 4 of Pentacel or Control vaccines (Dose 4 Group 1), safety population

System Organ Class Preferred Term	Pentacel N=431			Control (Dose 4 Group 1) N=418		
	n	%	95% CI	n	%	95% CI
INFECTIONS AND INFESTATIONS	3	0.7	(0.1, 2.0)	3	0.7	(0.1, 2.1)
Croup infectious	1	0.2	(0.0, 1.3)	0	0.0	(0.0, 0.9)
Gastroenteritis NOS	1	0.2	(0.0, 1.3)	1	0.2	(0.0, 1.3)
Gastroenteritis rotavirus	0	0.0	(0.0, 0.9)	1	0.2	(0.0, 1.3)
Gastroenteritis viral NOS	1	0.2	(0.0, 1.3)	0	0.0	(0.0, 0.9)
Upper respiratory tract infection NOS	0	0.0	(0.0, 0.9)	1	0.2	(0.0, 1.3)
INJURY AND POISONING	1	0.2	(0.0, 1.3)	0	0.0	(0.0, 0.9)
Asphyxiation	1	0.2	(0.0, 1.3)	0	0.0	(0.0, 0.9)
METABOLISM AND NUTRITION	0	0.0	(0.0, 0.9)	2	0.5	(0.1, 1.7)
Dehydration	0	0.0	(0.0, 0.9)	2	0.5	(0.1, 1.7)
RESPIRATORY, THORACIC, MEDIASTINAL	1	0.2	(0.0, 1.3)	1	0.2	(0.0, 1.3)
Asthma NOS	1	0.2	(0.0, 1.3)	0	0.0	(0.0, 0.9)
Pneumonitis NOS	0	0.0	(0.0, 0.9)	1	0.2	(0.0, 1.3)

No events in this table were in subjects not receiving study vaccine according to randomization.
Each subject is counted once per System Organ Name or Preferred Term.
Source: questions1_133.pdf, Table 53, page 315

Clinical case narratives are presented below for the two deaths and for selected serious adverse events from Tables 64 and 65. A narrative is also provided for a case of pertussis syndrome that was not a serious adverse event.

Case Narratives for Selected Serious Adverse Events of Interest—Control Subjects (Pooled DAPTACEL Lots for Doses 1-3 and Dose 4 Group 1)

Subject 1825 Ependymoma, Aspiration, Death This 8-month old female developed vomiting and lethargy 54 days following the third dose of Control vaccines. She was hospitalized and diagnosed with metastatic ependymoma. She had a 4 x 4 cm posterior fossa mass extending to the level of T2, with marked hydrocephalus. She underwent ventriculostomy and experimental chemotherapy, and was hospitalized several times due to complications. She died 222 days post-vaccination, secondary to aspiration.

Subject 0382 Meningitis At age 2 months, this female subject developed fever, vomiting and irritability, 12 days following the first dose of Control vaccines, and was hospitalized. Her WBC count was 14 x 10^9/L (43% segs; 44% polys). Following unsuccessful attempts to obtain CSF, she was treated with antibiotics. CSF obtained one day later, with 4,000 WBC and 4,000 RBC, was thought to be consistent with meningitis. CSF culture was negative, thought to reflect partial

treatment with antibiotics. Blood and urine cultures were negative. The subject recovered without sequelae.

Subject 1541 Viral Meningitis At age 1 month, this male subject developed fever of 101ºF the same day as the first dose of Control vaccines. Subsequently, he developed fever of 103ºF, diarrhea, emesis, decreased oral intake, congestion and irritability and was admitted to the hospital four days post-vaccination. CSF showed WBCs of 51 x 10^9/L (50% segs, 5% lymphocytes, 42% monos and 3% eosinophils), RBC was 1, protein 54, glucose 40. Cultures of CSF, blood and urine were negative. Treatment included ceftriaxone and intravenous fluids. He recovered without sequelae.

Subject 1891 H. influenzae Pneumonia and Sepsis At age 2 months, this female subject developed fever, cough, congestion and cyanosis five days following the first dose of Control vaccines. Chest x-ray showed hyperaeration. Blood and sputum cultures grew *H. influenzae*. Although no typing information was provided in the initial submission of the BLA, in response to an item in the 5/26/06 Complete Response Letter, the applicant reported that the *H. influenzae* isolate was non-typeable. The subject was intubated for nine days and received cefotaxime and lorazepam. Nineteen days post-vaccination, she was hospitalized again and diagnosed with reactive airways disease. Her WBC count was 21.9 x 10^9/L (66% neutrophils). Chest x-ray showed a left upper lobe infiltrate. Sputum culture grew *H. influenzae* type b. Blood cultures and RSV ELISA were negative. Treatment included supplemental oxygen, intravenous fluids, ipratropium bromide, albuterol and antibiotics. She had two subsequent hospitalizations 68 and 94 days post-vaccination for persistent cough/wheezing and diagnostic studies, respectively. Reflux studies and pulmonary function tests showed gastroesophageal reflux induced wheezing. She recovered without sequelae and continued in the trial.

Subject 1362 Seizure with Apnea See case narrative in section on seizures.

Subject 1915 Irritability At age 5 months, 12 days following the second dose of Control vaccines, this male subject developed irritability, inconsolable crying, otitis media, vomiting, and diarrhea. He was hospitalized two days later. Urinalysis, CBC, and chest x-ray were normal. A barium swallow showed gastroesophageal reflux. He was discharged one day later, and recovered without sequelae.

Subject 0132 Episode of Unresponsiveness See case narrative in section on HHE.

Subject 0509 Febrile Illness At age 7 months, this male subject was hospitalized due to fever and cough which began 19 days following the third dose of Control vaccines. On admission, his rectal temperature was 101.3ºF. His WBC count was 24.2 x 10^9/L (24% neutrophils; 70% lymphocytes). Chest x-ray showed air trapping. “Testing for RSV” and blood culture were negative. Urine culture grew "probable contaminants”. He was treated with antibiotics, discharged three days later, and recovered without sequelae.

Subject 0070 Pertussis At age 3 months, this male subject developed severe cough with cyanosis and vomiting, 30 days following the first dose of Control vaccines. He was hospitalized for one day, diagnosed with pertussis (basis for diagnosis not specified), treated with erythromycin and recovered without sequelae.

Subject 0487 Pertussis Syndrome (non-serious) At age 2.7 months, this male subject experienced pertussis syndrome 22 days following the first dose of Control vaccines. The event was mild in severity and resulted in a medical office visit. No cultures or PCR for pertussis were obtained.

Treatment included six days of azithromycin, beginning 11 days after onset. Symptoms of pertussis syndrome lasted 23 days. On the 23rd day, the subject developed an upper respiratory tract infection and otitis media. Subsequent adverse events included protracted bronchitis with onset on the day of Dose 3 of Control vaccines.

Case Narratives for Selected Serious Adverse Events of Interest—Pentacel

Subject ----p Suffocation, Death At age 15 months, this male subject was found dead, face down in his bedding (a box covered by plexiglass), eight days following the fourth dose of Pentacel. Bedding and pill vials (not further specified) were retained by law enforcement. Based on the Medical Examiner's report, significant findings included petechiae involving the right periorbital area, upper chest, and thoracic organs. The cause of death was listed as asphyxia due to suffocation. Results of post-mortem histology, toxicology, and chemistry analyses and radiology were not provided. It was reported that there was no trauma, congenital defects or obvious infection. Past medical history included multiple upper respiratory infections and bronchiolitis.

Subject 1946 Idiopathic Thrombocytopenic Purpura, Viral Meningitis At age 2 months, this female subject developed nasal congestion, fever, lethargy, irritability and rash, 23 days following the first dose of Pentacel, and was admitted to the hospital. Petechiae were noted on exam. The platelet count was 4.0 x 10^9/L and WBC count was 14.9 x 10^9/L (42% neutrophils; 525% lymphocytes). Bone marrow aspirate showed increased megakaryocytes, consistent with immune destruction of platelets. CSF obtained 24 hours after initiation of antibiotics showed no WBCs or organisms. Blood, urine and CSF cultures were negative. She was discharged after three days, following treatment with intravenous immunoglobulin, and recovered without sequelae.

Chronic Conditions and Events of Possible Autoimmune Origin

The final safety follow-up on or after Day 180 following the fourth dose of Pentacel or Control vaccines was conducted to capture serious adverse events, chronic conditions and events of possible autoimmune origin that occurred since the previous contact (Day 60 post-Dose 4). Table 66 presents events that were considered chronic by the Investigator or based on a duration $\geq$30 days (cut-off not pre-specified in protocol). Table 67 presents events that were considered to have a possible autoimmune origin.

Table 66. Study P3T06 Chronic adverse events occurring 61 to 180 days post-Dose 4 Pentacel or Control vaccines (Dose 4 Group 1)

Subject	Vaccine Group[1]	Preferred Term	Latency[2] (Days)	Duration (Days)	Outcome
1818	Pentacel	Cellulitis	73	43	Recovered without sequelae
1900	Pentacel	Congenital Aortic Valve Incompetence	169	30	Recovered without sequelae
		Cardiac Failure Congestive	169	30	Recovered without sequelae
1173	Control	Otitis Media Chronic NOS	108	> 30	Event is continuing[3]
1829	Control	Oral Candidiasis	171	Not Reported	Recovered without sequelae
2127	Control	Failure to thrive	78	>30	Event is continuing[3]

[1]Data are presented for Pentacel subjects and Control subjects in Dose 4 Group 1. Subjects completing the 180 day follow-up included 416 Pentacel subjects and 406 Control subjects in Dose 4 Group 1.
[2]Days to onset after Dose 4.
[3]Reported as ongoing at study termination.
NOS indicates not otherwise specified
Source: questions1_133.pdf, page 140

Table 67. Study P3T06 Adverse events of possible autoimmune origin occurring 61 to 180 days post-Dose 4 Pentacel or Control vaccines (Dose 4 Group 1)

Subject	Vaccine Group[1]	Preferred Term	Latency[2] (Days)	Duration (Days)	Severity	Outcome
0540	Pentacel	Serum Sickness	70	1	Severe	Recovered without sequelae
0834	Pentacel	Asthma NOS	119	12	Severe	Recovered without sequelae
1817	Pentacel	Leucopenia NOS	151	Not Reported	Mild	Event is continuing[3]
		Thrombocytopenia	151	Not Reported	Mild	Event is continuing[3]
1900	Pentacel	Asthma Aggravated	169	30	Moderate	Recovered without sequelae
0233	DAPTACEL	Bronchospasm NOS	127	17	Severe	Recovered without sequelae

[1]Data are presented for Pentacel subjects and Control subjects in Dose 4 Group 1. Subjects completing the 180 day follow-up included 416 Pentacel subjects and 406 Control subjects in Dose 4 Group 1.
[2]Days to onset after Dose 4.
[3]Reported as ongoing at study termination.
NOS indicates not otherwise specified
Source: questions1_133.pdf, page 141

Case narratives are presented below for Subjects 0540 (serum sickness) and 1817 (leucopenia and thrombocytopenia) included in Table 67.

Subject 0540 Serum Sickness Reaction
This 18 month old male subject was treated with ceftriaxone for fever associated with a WBC count of 38 x 10^9/L. Two days later, he presented to an emergency room with fever and rash, and was given cefdinir. Two days later (70 days post-Dose 4 Pentacel), he was hospitalized with an urticarial rash and swollen, painful joints. He was diagnosed with serum sickness secondary to

ceftriaxone. Treatment included intravenous fluids, ibuprofen, acetaminophen and prednisolone. He was discharged the same day and recovered without sequelae.

Leukopenia and Thrombocytopenia
This 20-month-old female experienced "mild" leukopenia and thrombocytopenia 151 days following the fourth dose of Pentacel. She was evaluated in an outpatient clinic. No treatment was reported. The events were listed as continuing at the end of the study.

6.4.3 Comments and Conclusions

Study Design
Study P3T06 provides safety data on Pentacel relative to all U.S. licensed separately administered vaccines (DAPTACEL + ActHIB + IPOL). The randomization ratio was 3:1 for Control vaccines to Pentacel, as the study originally was planned primarily to evaluate DAPTACEL lot consistency and concomitant administration of the fourth dose of DAPTACEL with other recommended vaccines. For evaluating the safety of the first three doses of Pentacel relative to Control vaccines, the three DAPTACEL lot groups were pooled. For evaluating the safety of the fourth dose of Pentacel, one of the Dose 4 DAPTACEL study groups (DAPTACEL + ActHIB at 15-16 months) served as the control.

In contrast to Study 494-01, in which Control subjects received four doses of IPV by 15-18 months of age, in Study P3T06, Control subjects received three doses of IPV at 2, 4, and 6 months of age; a fourth dose was not given at 15-18 months of age. The IPV schedule used in Control subjects in Study P3T06 is consistent with routinely recommended ages for administration of IPV in U.S. infants and children (i.e., 2, 4, and 6-18 months, and 4-6 years).

Data Quality
Data quality issues previously discussed for Study 494-01 (Section 6.1.3) including audits of already analyzed safety data and changes to the safety database, identification of data discrepancies and apparent errors in coding of serious adverse events in CBER's initial review (adequately addressed by applicant), exclusion of subjects from analyses of solicited adverse events (10% for dose 4 analyses in Study P3T06), and poor compliance with taking rectal temperatures as specified in the protocol, also apply to Study P3T06. In addition, one site audit was conducted due to non-conformance with Good Clinical Practices (study procedures prior to informed consent, product accountability issues, and cold chain issues). According to the applicant, corrective actions at this site were successfully implemented.

Safety Results
There were no notable differences between Pentacel and Control vaccines with regard to solicited local and systemic adverse events.

There were no cases of HHE or hypotonia following Pentacel and no seizures within 30 days following Pentacel. Overall, the rate of any serious adverse event was similar in Pentacel and Control subjects. However, the sample size for Study P3T06 is inadequate to draw conclusions about the occurrence of HHE, seizures, and particular serious adverse events following Pentacel relative to Control vaccines.

There were two deaths reported in study participants: a 15-month old child died as a result of suffocation 8 days following Pentacel; and a subject with ependymoma died secondary to aspiration 222 days following DAPTACEL.

6.5 Historical Pentacel Studies

Table 68 presents a summary of eight historical studies that provided the basis for Pentacel licensure in Canada. None of these studies was conducted under U.S. IND and none included a control group that received a U.S. licensed DTaP vaccine or HCPDT. Six of the studies were conducted in Canada, one in Mexico, and one in Israel. Information on race/ethnicity of study subjects was not provided. Overall, across the eight studies, approximately 2,500 subjects were enrolled to receive Pentacel. In three studies, a total of 996 subjects previously vaccinated with three doses of whole cell DTP vaccine received a single dose of Pentacel between 16-20 months of age. In the other studies, a total of 1,694 subjects were enrolled as infants to receive either three or four consecutive doses of Pentacel.

In general, in these studies, information was collected on serious adverse events that occurred through at least 30 days post-vaccination. Serious adverse events that occurred within 30 days following any dose of Pentacel are summarized in Table 68. There was one death reported following Pentacel—a case of SIDS 40-44 days post-Dose 2 in a 23-week old infant in Study 5A9703. Across all studies, there were five febrile seizures and three afebrile seizures within 30 days following Pentacel and 2 reports of HHEs on the same day as Pentacel that were considered serious. In all studies except for PNF35, seizures and HHEs not considered serious were not coded or analyzed. In Study PNF35, information was provided on all occurrences of seizures and HHEs, whether or not considered serious. In this study, there were no cases of HHE and one afebrile seizure (reported as serious) that occurred 7 days following Pentacel. Other serious adverse events within 30 days following Pentacel are summarized in Table 68.

Table 68. Summary of serious adverse events from historical non-IND studies of Pentacel

Protocol Number	Country	Study Period	Population Enrolled	No. Ss in Pentacel Group (ITT)	Pentacel Schedule	Concomitant Vaccines	Monitoring for Serious Adverse Events[1]	Serious Adverse Events within 30 days Following Pentacel
PERTB9402	Canada	1/95-5/95	Children 18-19 mo., previously vx'd w/ DTwP, Hib conjugate vx, and IPV or OPV	33	1 dose at 18-19 mo.	None	-Phone call at 24 and 72 hrs. post-vx -Parental reports through 1 mo. post-vx	None
PERTB9501	Canada	3/95-9/95	Children 18-19 mo., previously vx'd w/ DTwP, Hib vx, and IPV or OPV	295	1 dose at 18-19 mo.	None	-Phone call at 24 and 72 hrs. post-vx -Parental reports through 1 mo. post-vx -Not systematically captured in database	2 febrile seizures (Day 7 and Day 16, respectively), 2 circumcisions, 1 each of lung infection, ear infection, hospitalization (unknown reason/outcome)
PERTB9502	Canada	3/95-3/97	Infants, 2 mo.	335	2, 4, 6, 18-19 mo.	none	-Phone call at 24 and 72 hrs. post-vaccination -Parental reports through 1 mo. post-vx	1 each of febrile seizure (Day 0), afebrile seizure (Day 2), asthma, craniopharyngioma, parapertussis, myringotomy, adenoidectomy
PERTB9505	Canada	1/96-5/96	Children 16-20 mo., previously vx'd w/ DTwP, Hib conjugate vx, and IPV or OPV	668	1 dose at 16-20 mo.	none	-Phone call at 24 h, 72 h, 7-8 d, and 30 d post-vaccination -Parental reports through 1 mo. post-vaccination	4 pneumonia, 1 each of febrile seizure (Day 24) otitis media, myringotomy, pertussis, asthma
PERTB9506	Canada	1/96-10/96	Infants, 2 mo.	661	2, 4, 6 mo.	none	-Phone call at 24 and 72 hrs. post-vx and 30 d post-Dose 3 -Query prior to Doses 2 and 3	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	1/96-7/98	Infants, 2 mo.	118	2, 4, 6, and 18 mo.	none	-Phone call at 24 and 72 hrs. post-vx -Query prior to Doses 2 and 3, and 30 days post-Doses 3 and 4	3 bronchiolitis, 1 each of allergic reaction (Day 12), gastroesophageal reflux w/ apnea and cyanosis, urinary tract infection/rule out sepsis, otitis media

							-Parental reports anytime during the study	
5A9703	Mexico	1/97-4/99	Infants, 2 mo.	110	2, 4, 6, and 18 mo.	none	-Phone calls or personal contact at ~48 hrs. post-vx -Queries at each dose, and 30 days post-Doses 3 and 4 -Parental reports anytime during the study	"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	Infants, 2 mo.	470 (Group 1: 235 Group 2: 235)	2, 4, and 12 mo.; (DTaP/PRP-T[2] at 6 mo.)	Group 1: PnC[3] at 2, 4, 6, 12 mo. and OPV at 4, 6, 12 mo. Group 2: OPV at 4, 6, 12 mo.	-Interviews at each visit -Parental reports through 30 days following last dose	Group 1: 2 bronchiolitis; 2 gastroenteritis; 1 each: herpangia, pneumonia, pneumonitis, otitis media, pyrexia (Day 0), gastroesophageal reflux disease, inguinal hernia, animal bite, skull fracture, arthritis, convulsions (Day 7), irritability (Day 0) Group 2: 4 bronchiolitis; 1 each: pneumonia, otitis media, hypocalcemia, asthma aggravated, respiratory distress, stridor, wheezing

[1]For Studies PERTB9402, PERTB9501, PERTB9502, PERTB9595, and PERTB9506, a serious adverse event was defined as one which results in 1) death; 2) permanent or substantial disability; 3) inpatient hospitalization; 4) prolongation of existing inpatient hospitalization; 5) cancer; 6) or is the result of an overdose; 7) or is life threatening. For Study PERTB9601, a serious adverse event was defined as one which resulted in: 1) death; 2) life threatening; 3) permanent or substantial disability; 4) requires or prolongs inpatient hospitalization; 5) necessitates surgical or medical intervention to preclude permanent impairment of a body function or permanent damage to a body structure; 6) neurological reactions (acute or sub acute encephalitis/encephalomyelitis/encephalopathy; collapse and/or unexplained loss of consciousness (HHE) within 72 hours of receipt of the study vaccine; convulsions; infantile spasms); 7) Reye's syndrome; 8) general allergic reactions or anaphylactic reactions; 9) invasive bacterial infections (e.g. sepsis or meningitis); 10) onset of chronic disease; 11) vaccine failure; 12) Cancer; 13) Overdose. For Studies 5A9703 and PNF35, a serious adverse event was defined as one which: 1) resulted in death; 2) was life-threatening; 3) resulted in persistent or substantial disability/incapacity; 4) required inpatient hospitalization; 5) prolonged existing inpatient hospitalization; 6) resulted in a congenital anomaly/birth defect

[2]DTaP/PRP-T not licensed in the U.S.

[3]11-valent pneumococcal polysaccharide conjugate vaccine 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.

6.6 Sweden I Efficacy Trial

The Pentacel BLA includes the Technical Report from the Sweden I Efficacy Trial, the pivotal pertussis efficacy study for DAPTACEL, which was conducted in Sweden from March 1992 through January 1995. This report is authored by the investigators from the Swedish Institute of Infectious Disease Control. In this trial, the safety and efficacy of DAPTACEL, another DTaP vaccine manufactured by GlaxoSmithKline (not U.S. licensed), and a whole cell DTP vaccine manufactured Sanofi Pasteur Inc. (no longer licensed in the U.S) were evaluated. A total of 2,587 infants were randomized to receive DAPTACEL, which was administered at 2, 4, and 6 months of age. Most infants received a non-U.S. licensed IPV concomitantly with DAPTACEL at 4 and 6 months of age, either alone or as a combination of Hib conjugate vaccine-IPV (not U.S. licensed). The safety data from the Sweden I Efficacy Trial were reviewed by CBER under the DAPTACEL BLA (STN 103666), and will not be presented in this review.

6.7 Sweden II Efficacy Trial

The Pentacel BLA includes the Technical Report from the Sweden II Efficacy Trial, authored by the investigators from the Swedish Institute of Infectious Disease Control. Safety data from the Sweden II Efficacy Trial were reviewed by CBER under the DAPTACEL BLA (STN 103666). An overview of the study design and a summary of data on serious adverse events from this trial will be presented here. These data provide relevant background information on the safety of HCPDT, the non-U.S. licensed DTaP component of Pentacel that was used as the Control DTaP vaccine in Study 494-01.

In the Sweden II Efficacy Trial, the safety and efficacy of three DTaP vaccines (none U.S.-licensed) were compared to a British whole-cell DTP vaccine (Medeva). The three DTaP vaccines were HCPDT, a three-component (PT, FHA, and pertactin) DTaP vaccine manufactured by Chiron (DTPa3), and a two-component (PT and FHA) DTaP vaccine manufactured by GlaxoSmithKline (DTPa2). The trial was conducted in Sweden during the period September 1993 through October 1996.

A total of 82,892 infants were enrolled. Of these, 20,747 subjects were randomized to receive HCPDT. In the majority of these infants (approximately 18,000), HCPDT was administered at 3, 5, and 12 months of age, concomitantly with ActHIB and a non-U.S. licensed IPV. It was recommended that IPV and ActHIB be mixed in the same syringe. Approximately 2,500 subjects received HCPDT at 2, 4, and 6 months of age, concomitantly with admixed IPV and ActHIB at 2 and 4 months.

Subjects were monitored for serious adverse events and events that would contraindicate subsequent doses until 6 months after Dose 3 or until 8 months of age if they had only received one or two doses of study vaccine.

Serious adverse events were defined as:

- Sudden death
- Severe neurological reactions:
  - Acute conditions with either major alterations in consciousness or unresponsiveness, or seizures of greater than 30 minutes duration, or infantile spasms
  - Collapse or unexplained loss of consciousness (including HHE), within 48 hours of vaccination; (HHE prospectively defined as a condition in which a child had loss of muscle tone and a diminished or absent response to stimulation)
- Systemic allergic reactions within 48 hours of vaccination
- Invasive bacterial infections

- Other life-threatening events

Contraindicating events were:
- Severe neurological symptoms within 72 hours of a trial dose
- Rectal fever 40.5°C or more within 24 hours of a trial dose
- Systemic allergic reaction within 48 hours of a trial dose
- Shock-like reaction within 48 hours of a trial dose (including HHE)
- Seizures, with or without fever

Monitoring procedures included reporting by study personnel for up to two months following the last vaccination; active surveillance of hospitalizations involving death, anaphylactic shock, encephalitis/encephalopathy, infantile spasms, invasive bacterial infections, HHE, or loss of consciousness; parental interviews at the time of Doses 2 and 3 and when the subjects were 18 months of age.

For the pre-planned analysis of safety, follow-up ended on 8/4/95. The hospital surveillance data were not part of the pre-planned safety analyses. Table 69 provides the results of the pre-planned analysis of serious adverse events and contraindicating events that occurred after any of Doses 1-3 and within 6 months following the last dose of trial vaccines.

Table 69. Sweden II Efficacy Trial, Serious adverse events and contraindicating events after any of Doses 1-3, through six months following the last dose and before August 4, 2005

Event	HCPDT N= 20,745 n (%)	DTPa-2 N=20,692 n (%)	DTPa-3 N=20,725 n (%)	Whole cell DTP N=20,716 n (%)
Death	4 (0.02)	8 (0.04)	10 (0.05)	8 (0.04)
Acute severe neurological event >30 minutes duration	1[1]	1	4	6
Infantile spasms	2	2	3	5
HHE within 48 hours	29 (0.14)	22 (0.11)	16 (0.08)	34 (0.16)
General allergic reaction	0	0	0	0
Invasive bacterial infection	9 (0.04)	4 (0.02)	2 (0.01)	6 (0.03)
Other life threatening event[2]	2	2	1	2
Severe neurological symptoms within 72 hours	0	0	0	0
Temperature >40.5°C within 24 hours	7 (0.03)	15 (0.07)	15 (0.07)	37 (0.18)
Convulsions, including suspected	18 (0.09)	26 (0.13)	33 (0.16)	37 (0.18)

[1]This event, intermittent febrile seizures (temperature 40.0°C) for approximately one hour occurred 184 days following the second dose of HCPDT
[2]Other life threatening events included four "Apparent Life Threatening Episodes", one cerebral infarction, one cardiac arrhythmia, and one post-traumatic epidural hematoma
note: acute severe neurological event and infantile spasms were mutually exclusive categories
Source: DAPTACEL BLA Clinical Review, pages 70-71, swedenii.pdf, pages 58-59, and swedenii_a.pdf, page 50

There were no statistically significant differences between the groups with regard to rates of each of the serious adverse events (death, acute severe neurological event >30 minutes duration, infantile spasms, HHE, general allergic reaction, invasive bacterial infection, other life threatening event). Fever >40.5°C occurred significantly less frequently in the HCPDT group relative to the whole cell DTP group [Relative Risk = 0.19; 95% confidence interval (0.08, 0.42)].

Convulsions and suspected convulsions occurred significantly less frequently in the HCPDT group relative to the whole cell DTP group [Relative Risk = 0.31; 95% confidence interval (0.10, 0.94)]. Among subjects who reported seizures following HCPDT, four had seizures within 48 hours post-vaccination for a rate of 0.02% of subjects.

The DAPTACEL BLA clinical review noted a relatively high rate of HHEs following HCPDT (as well as the other DTaP study vaccines) in the Sweden II Efficacy Trial compared with historical data for DTaP vaccines. The incidence of HHE among subjects who received HCPDT was 14/10,000, similar to that observed for the whole-cell DTP group (16/10,000). Of the 29 cases of HHE in HCPDT recipients, 20 were after the first dose, eight after the second dose, and one after the third dose. All occurred within 24 hours post-vaccination. Twenty of the 29 cases in the HCPDT group resolved in 60 minutes; two cases lasted >2 hours. All children in the HCDPT group with reported HHE recovered without sequelae. The rate of HHE in HCPDT recipients in the Sweden II Efficacy Trial, per doses administered was 29/61,220 doses (0.047%).

There were two reported cases of suspected encephalitis in study participants. One occurred 190 days following the third dose of HCPDT and after 8/4/05 (not included in Table 69) and one occurred 98 days following the first dose of DTPa3. The separate surveillance for hospitalized cases of encephalitis (not part of pre-planned safety analyses) that occurred from 11/11/93 through 8/4/95 in children born between 6/1/93 and 5/31/94, identified one case of suspected encephalitis among study participants (N=82,892) (not stated whether this was the case in a DTPa3 recipient that was also included in pre-planned analysis) and three cases among 17,607 eligible children who did not participate in the Sweden II Efficacy Trial, corresponding to rates of 1/100,000 for study participants and 17/100,000 for non-participants. Of note is that the three non-participants with suspected encephalitis had culture-confirmed pertussis.

Through October 1996 (end of efficacy follow-up), there were 10 deaths in the HCPDT group, including two cases of SIDS (one 28 days post-Dose 1 in an infant born at 34 weeks gestation; one 49 days post-Dose 2) and one sudden death with no abnormal findings on autopsy (175 days post-Dose 3). Other causes of death in subjects who had received HCPDT were one case each of accidental strangulation, skull fracture and brain injury, drowning, intestinal dysplasia, metastatic ependymoma, congenital heart disease, and Pompe's disease.

7. Overview of Safety Across Studies

7.1 Safety Database – Number of Subjects and Extent of Exposure

Table 6 in Section 5.2 enumerates subjects from the four pivotal safety studies of Pentacel. Across the four 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 (1,032 HCPDT + POLIOVAX + ActHIB and 1,454 DAPTACEL + IPOL + ActHIB)[*]. Across U.S. Studies 494-01, 494-03 and P3T06, a total of 4,198 infants received at least the first dose of Pentacel, including 3,251 who received four consecutive doses. In addition, 1,782 toddlers who had received three doses of Pentacel as part of routine immunization in Canada received a fourth dose of Pentacel in Study 5A9908.

For each of the four studies, Table 70 provides the number of doses of Pentacel or Control vaccines administered. In total, 17,021 doses of Pentacel were administered.

[*] For Studies 494-01 and P3T06, the number of subjects who received Pentacel or Control vaccines are based on the vaccines received at the first dose.

Table 70. Pivotal Pentacel safety studies: Summary of vaccine exposure, safety population

	494-01		494-03	P3T06		5A9908
	Pentacel	HCPDT + POLIOVAX + ActHIB	Pentacel	Pentacel	DAPTACEL + IPOL[1] + ActHIB	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[2]	NA
Dose 4 only	NA	NA	NA	NA	NA	1782

[1]For the fourth dose, Control subjects received DAPTACEL + ActHIB; a fourth dose of IPOL was not administered in the study.
[2]Dose 4 Group 1 only
NA indicates not applicable
Source: iss.pdf, page 191

Table 71 provides a summary of subjects who completed the 60 day follow-up post-Dose 3 and the 60- or 180 day follow-up post-Dose 4.

Table 71. Numbers of subjects with specified safety follow-up, pivotal safety studies of Pentacel

	494-01		494-03	P3T06		5A9908
	Pentacel	HCPDT	Pentacel	Pentacel	DAPTACEL	Pentacel
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Received at least one dose of Pentacel or Control vaccines[1]	2506	1032	1207	485	1454	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[2,3,4]	1882 (75.1)	698 (67.6)	947 (78.5)	416 (85.8)	1217[5] (83.7)	1773 (99.5)

[1]For Studies 494-01 and P3T06, subjects are classified by actual treatment received at Dose 1.
[2]Percentages are based on the number of subjects who received at least one dose of Pentacel or Control vaccines.
[3]Follow-up post-Dose 4 was 60 days in Studies 494-01, 494-03, and 5A9908, and 180 days in Study P3T06.
[4]Subjects are classified by randomized treatment. Treatment errors: In Study 494-01, for Dose 4, 52 subjects randomized to receive Pentacel received Control vaccines and 19 subjects randomized to receive Control vaccines received Pentacel. In Study P3T06, 4 subjects randomized to the Control group received Pentacel, and 2 subjects randomized to Pentacel received Control vaccines. In Study 5A9908, 87 subjects randomized at 12 months of age did not receive the scheduled dose of Pentacel at 15 to 18 months of age.
[5]Includes Control subjects from the three Dose 4 Control groups.
NA indicates not applicable.
Source: iss.pdf (revised), pages 53-58 and p3T06sii.pdf, page 86

Table 72 provides an overall summary of demographics for subjects who received Pentacel in the three pivotal safety studies conducted in the U.S. and in the Canadian fourth dose study (Study 5A9908). Although not shown in the table, in the two controlled studies, Studies 494-01 and P3T06, the demographic characteristics of Pentacel and Control subjects were similar.

Table 72. Pivotal safety studies: Demographics of subjects who received Pentacel, safety population

	Studies 494-01, 494-03, and P3T06 combined	Study 5A9908
	N = 4198	N = 1782
Mean age at first dose (months)	2.1	N/A
Sex n (%)		
Male	2090 (49.8)	861 (48.3)
Female	2108 (50.2)	921 (51.7)
Race/Ethnicity n (%)		
Caucasian	2567 (61.1)	1532 (86.0)
Black	410 (9.8)	34 (1.9)
Hispanic	631 (15.0)	15 (0.8)
Asian	181 (4.3)	77 (4.3)
East Indian[1]	N/A	35 (2.0)
Native Indian[1]	N/A	9 (0.5)
Other	409 (9.7)	80 (4.5)

[1]East Indian and Native Indian categories applied only to Study 5A9908.
N/A indicates not applicable
Source: Iss.pdf, page 60; 5a9908.pdf page 64

7.2 Safety Assessment Methods

In general, the methods for safety monitoring were similar across the pivotal safety studies of Pentacel, with a 60-day follow-up period following the last dose of study vaccines in three of the studies, and a 6-month follow-up period following the last dose of vaccines in Study P3T06. Subsequent sections of this review will include Pentacel data pooled across the four safety studies for some relatively low frequency adverse events of interest (e.g., deaths, encephalopathy, HHEs and seizures).

The majority of the safety analyses were observational, without formal statistical comparisons. In three of the studies, secondary non-inferiority or equivalence analyses for pre-specified safety outcomes were conducted. Analyses of adverse events across doses were performed according to randomized group assignment at enrollment.

7.3 Significant/Potentially Significant Events

7.3.1 Deaths

A total of five deaths occurred during the four pivotal safety studies, four of them in subjects who had received Pentacel (N=5,979) and one in a subject who had received DAPTACEL + IPOL + ActHIB (N=1,455). There were no deaths among Control subjects who received HCPDT + POLIOVAX + ActHIB (N=1,032). Causes of death among Pentacel subjects were asphyxia due to suffocation, head trauma, SIDS, and neuroblastoma (8, 23, 52, and 256 days post-vaccination, respectively). One subject with metastatic ependymoma died secondary to aspiration 222 days following receipt of DAPTACEL + IPOL + ActHIB.

Among the 2,690 subjects who received at least one dose of Pentacel in the non-pivotal historical studies, there was one death due to SIDS 40-44 days post-vaccination.

Over a 9-year period during which approximately 13.5 million doses of Pentacel were distributed in other countries (primarily Canada), there were 14 deaths following Pentacel identified through post-marketing spontaneous reports or in the literature. These deaths included five cases of SIDS,

four other deaths due to unknown cause, two deaths due to invasive Hib disease (both post-Dose 1), one death due to Group B streptococcal sepsis, one due to an unspecified congenital anomaly, and one death following convulsions. The deaths identified in the post-marketing setting were described in further detail in Section 5.1.2.1.

7.3.2 Other Significant/Potentially Significant Events

Anaphylaxis/Life-Threatening Immediate Reactions

Across the pivotal safety studies, there were no life-threatening immediate reactions (e.g., anaphylaxis, angioedema, bronchospasm) reported among Pentacel (N=5,979) or Control subjects [DAPTACEL + IPOL + ActHIB (N=1455); HCPDT + POLIOVAX + ActHIB (N=1032)].

In the post-marketing safety survey, Study M5A08, among approximately 3,000 subjects who were queried about adverse events following the fourth dose of Pentacel, there was one report of an allergic episode characterized by swelling around the nose, lips, and cheeks and heavy breathing within hours after vaccination. The reaction was reported as life-threatening, but without progression to anaphylaxis. The subject recovered following treatment with Benadryl.

Encephalopathy

Encephalopathy is a recognized complication of classical pertussis, and is thought to be due to cerebral hypoxia resulting from severe paroxysms of coughing. Among 28,998 persons of all ages with pertussis reported to the Centers for Disease Control and Prevention during 2001-2003, 33 cases of encephalopathy were reported (0.1%).[6] Among 18,500 infants with pertussis reported in the U.S. during 1990-1999 for whom information was available, 0.3% had encephalopathy reported as a complication.[7] Historically, whole-cell DTP vaccines have been associated with acute encephalopathy, with an estimated risk of 0-10.5 episodes per million doses[8].

In the pivotal safety studies, two cases of encephalopathy were reported in subjects who received Pentacel (N=5,979); none were reported in subjects who received Control vaccines [DAPTACEL + IPOL + ActHIB (N=1455); HCPDT + POLIOVAX + ActHIB (N=1032)]. One infant developed hypoxic encephalopathy 30 days following Pentacel secondary to cardiac arrest following surgical repair of congenital heart defects. The other case was in an infant who had onset of neurological symptoms eight days following the first dose of Pentacel, and who was found to have structural cerebral abnormalities on MRI and was subsequently diagnosed with "congenital encephalopathy".

While the size of the pivotal studies safety database for Pentacel is not adequate to reliably evaluate the occurrence of such a rare event, post-marketing data also provide some information on the occurrence of encephalopathy following Pentacel. In the post-marketing setting, during a period when approximately 13.5 million doses of Pentacel were distributed outside the U.S. (92% of them in Canada), five cases of encephalopathy were identified. One case, identified in Study M5A08, occurred 10 days post-vaccination in association with atypical Kawasaki syndrome. The other four cases were identified through spontaneous post-marketing reports or from literature sources. Two cases that occurred one and seven days post-vaccination, respectively, were thought to be due to influenza A virus, which was isolated from nasopharyngeal aspirates. Another case occurred five days post-vaccination in association with bloody diarrhea. One case occurred 24 days post-vaccination in association with pneumonia and hepatosplenomegaly.

The BLA also cited a publication on encephalopathy from IMPACT, a nationwide Canadian hospital-based program that conducts active surveillance for selected post-vaccination adverse events. As previously reviewed in Section 5.1.2.3, any risk of encephalopathy or encephalitis

attributable to vaccination in the population under surveillance by IMPACT was estimated as <1 per 3.5 million administered doses of acellular pertussis vaccine (i.e., Pentacel for Doses 1-4 and Sanofi Pasteur's DTaP-IPV for Dose 5).

Finally, data on HCPDT may be considered supportive in the evaluation of the safety of Pentacel. In the Sweden II Efficacy Trial, among approximately 20,000 subjects who received approximately 60,000 doses of HCPDT, one case of suspected encephalitis 190 days post-vaccination was identified. In the Sweden II Efficacy Trial, there were no reported cases of encephalitis or encephalopathy within seven days following HCPDT.

Seizures

There were no notable differences in rates of seizures across the pivotal safety studies. Tables 73 and 74 summarize the rates of seizures (febrile, afebrile, and possible), per subjects (Table 73) or per 1,000 doses (Table 74), within 30 days and within seven days after any of Doses 1-3 and after Dose 4 of Pentacel or Control Vaccines in the pivotal studies. For rates of seizures following any of Doses 1-3 of Pentacel, subjects or doses are pooled across Studies 494-01, 494-03 and P3T06. For rates of seizures following Dose 4 of Pentacel, subjects or doses are pooled across Studies 494-01, 494-03, P3T06, and 5A9908. Seizures within 3 days post-vaccination were reported for two subjects who received Pentacel (one febrile seizure and one possible seizure) and one subject each who received HCPDT (afebrile seizure) and DAPTACEL (afebrile seizure).

Table 73. Pivotal safety studies: Incidence of seizures, **per subjects**, within 30 days and within 7 days after any of Doses 1-3 and after Dose 4, Pentacel and Control vaccines, safety population

	Control						Pooled Pentacel[4] Doses 1-3 (any): N=4197 Dose 4: N=5033		
	HCPDT + POLIOVAX + ActHIB[1] Doses 1-3 (any): N=1032 Dose 4: N=739			DAPTACEL + IPOL + ActHIB[2] Doses 1-3 (any): N=1455 Dose 4: N=418[3]					
	n	%	95% CI	N	%	95% CI	N	%	95% CI
Febrile Seizure									
0-30 Days									
Post Dose 1-3	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	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	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	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	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	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 group from Study 494-01.
[2]DAPTACEL + IPOL + ActHIB groups from Study P3T06.
[3]Dose 4 Group 1: Subjects who received DAPTACEL + ActHIB at 15-16 months of age.
[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.
N=number of subjects
Subjects are classified by randomized treatment for Post Dose 1-3 (any).
Source: iss.pdf revised, Tables 9.119-9.121

Table 74. Pivotal safety studies: Incidence of seizures, **per 1000 doses**, within 30 days and within 7 days after any of Doses 1-3 and after Dose 4, Pentacel and Control vaccines, safety population

	Control						Pooled Pentacel[4] Doses 1-3 (any): N=11988 Dose 4: N=5033		
	HCPDT + POLIOVAX + ActHIB[1] Doses 1-3 (any): N=2877 Dose 4: N=739			DAPTACEL+ IPOL + ActHIB[2] Doses 1-3 (any): N=4230 Dose 4: N=418[3]					
	n	%	95% CI	N	%	95% CI	N	%	95% CI
Febrile Seizure									
0-30 Days									
Post Dose 1-3	1	0.3	(0.0, 1.9)	1	0.2	(0.0, 1.3)	0	0.0	(0.0, 0.3)
Post-Dose 4	2	2.7	(0.3, 9.7)	0	0.0	(0.0, 8.8)	9	1.8	(0.8, 3.4)
0-7 Days									
Post Dose 1-3	0	0.0	(0.0, 1.3)	0	0.0	(0.0, 0.9)	0	0.0	(0.0, 0.3)
Post-Dose 4	2	2.7	(0.3, 9.7)	0	0.0	(0.0, 8.8)	2	0.4	(0.0, 1.4)
Afebrile Seizure									
0-30 Days									
Post Dose 1-3	1	0.3	(0.0, 1.9)	2	0.5	(0.1, 1.7)	3	0.3	(0.1, 0.7)
Post-Dose 4	1	1.4	(0.0, 7.5)	0	0.0	(0.0, 8.8)	4	0.8	(0.2, 2.0)
0-7 Days									
Post Dose 1-3	1	0.3	(0.0, 1.9)	1	0.2	(0.0, 1.3)	1	0.1	(0.0, 0.5)
Post-Dose 4	0	0.0	(0.0, 5.0)	0	0.0	(0.0, 8.8)	0	0.0	(0.0, 0.7)
Possible Seizure[5]									
0-30 Days									
Post Dose 1-3	1	0.3	(0.0, 1.9)	0	0.0	(0.0, 0.9)	3	0.3	(0.1, 0.7)
Post-Dose 4	0	0.0	(0.0, 5.0)	0	0.0	(0.0, 8.8)	0	0.0	(0.0, 0.7)
0-7 Days									
Post Dose 1-3	0	0.0	(0.0, 1.3)	0	0.0	(0.0, 0.9)	1	0.1	(0.0, 0.5)
Post-Dose 4	0	0.0	(0.0, 5.0)	0	0.0	(0.0, 8.8)	0	0.0	(0.0, 0.7)

[1]HCPDT + POLIOVAX + ActHIB group from Study 494-01.
[2]DAPTACEL + IPOL + ActHIB groups from Study P3T06.
[3]Dose 4 Group 1: Subjects who received DAPTACEL + ActHIB at 15-16 months of age.
[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.
N=number of doses
Subjects are classified by randomized treatment for Post Dose 1-3 (any).
Source: response_fax09nov06.pdf, pages 11-13

As reviewed in Section 5.1.2.3, IMPACT data from Canada suggested a decreased risk for febrile seizures with the introduction of Pentacel in Canada in place of whole cell DTP vaccines.

Data on seizures following HCPDT in the Sweden II Efficacy Trial were reviewed in Section 6.7. Among approximately 20,000 infants who received HCPDT, usually at 3, 5 and 12 months of age, four subjects (0.02%) reported seizures within 48 after vaccination.

HHE

In one of the pivotal studies, Study P3T06, the diary cards included questions pertaining to HHE. In the other pivotal safety studies, a question about the occurrence of seizures, fainting, or change in mental status was asked during the post-vaccination phone calls, but otherwise symptoms of HHE were not specifically solicited.

Across the four pivotal safety studies, no cases of HHE (as defined in Section 5.1.2.1) were reported in either Pentacel (N=5,979) or Control subjects [DAPTACEL + IPOL + ActHIB (N=1455); HCPDT + POLIOVAX + ActHIB (N=1032)]. One subject who received DAPTACEL + IPOL + ActHIB had symptoms that met the definition for HHE except that the episode occurred 16 days post-vaccination.

Across the pivotal safety studies, within seven days following any of Doses 1-4 of Pentacel or Control vaccines, four Pentacel subjects (N=5,979) and one DAPTACEL + IPOL + ActHIB subject (N=1,455) experienced hypotonia not meeting the HHE definition. Each case was considered mild in severity. All four cases following Pentacel occurred on the day of vaccination (one post-Dose 1 and three post-Dose 3). The case following DAPTACEL + IPOL + ActHIB occurred four days post-Dose 1.

In considering comparisons across studies, it should be noted that reported rates of HHEs could be affected by several factors, including HHE definitions, safety monitoring procedures, vaccination schedule, and concomitantly administered vaccines. As noted in Section 6.7, in the Sweden II Efficacy Trial, using a definition of loss of muscle tone and diminished or absent response to stimulation, the rate of HHE observed following HCPDT [14 per 10,000 subjects; 29 per 61,220 (0.047%) doses], administered at 3, 5, and 12 months of age in most subjects, was similar to that observed following a whole cell DTP vaccine. In the Sweden I Efficacy Trial, there was one HHE (described as episode of pallor, lack of muscle tone, and hyporesponsiveness, but not prospectively defined) within 24 hours following DAPTACEL (post-Dose 3) administered to 2,551 subjects (0.039%).

As reviewed in Section 5.1.2.3, using a definition for HHE that is consistent with that used in the pivotal studies of Pentacel, an IMPACT investigation suggested a decreased risk for HHEs associated with pertussis-containing vaccines upon adoption of Pentacel in Canada in place of whole-cell pertussis vaccine.

Other Possible Neurological Events

"Other possible neurological events" were retrospectively identified in the clinical database by the Medical Monitor. According to the applicant, this category included events that may have been normal for age or had a possible convulsive association but for which no further information was available for clinical assessment (e.g., tremors, shaking).

Table 75 provides rates of "other possible neurological events" within 30 days and within seven days after any of Doses 1-3 and Dose 4 of Pentacel or Control Vaccines in the pivotal safety studies.

Table 75. Pivotal safety studies: Incidence of "other possible neurological events[1]" within 30 days and within 7 days after any of Doses 1-3 and Dose 4, Pentacel and Control vaccines, safety population

	Control						Pooled Pentacel[5] Doses 1-3 (any): N=4197 Dose 4: N=5033		
	HCPDT + POLIOVAX + ActHIB[2] Doses 1-3 (any): N=1032 Dose 4: N=739			DAPTACEL + IPOL + ActHIB[3] Doses 1-3 (any): N=1455 Dose 4: N=418[4]					
	N	%	95% CI	n	%	95% CI	N	%	95% CI
0-30 Days									
Post Dose 1-3	0	0.0	(0.0, 0.4)	2	0.1	(0.0, 0.5)	6	0.1	(0.0, 0.3)
Post-Dose 4	0	0.0	(0.0, 0.5)	0	0.0	(0.0, 0.9)	5	0.1	(0.0, 0.2)
0-7 Days									
Post Dose 1-3	0	0.0	(0.0, 0.4)	1	0.1	(0.0, 0.4)	5	0.1	(0.0, 0.3)
Post-Dose 4	0	0.0	(0.0, 0.5)	0	0.0	(0.0, 0.9)	3	0.1	(0.0, 0.2)

[1]"Other possible neurological events", retrospectively identified in the clinical database by the Medical Monitor, included events that may have been normal for age or had a possible convulsive association but for which no further information was available for clinical assessment (e.g., tremors, shaking).
[2] HCPDT + POLIOVAX + ActHIB group from Study 494-01.
[3] DAPTACEL + IPOL + ActHIB groups from Study P3T06.
[4] Dose 4 Group 1: Subjects who received DAPTACEL + ActHIB at 15-16 months of age.
[5]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.
Subjects are classified by randomized treatment for Post-Dose 1-3 (any).
Source: iss.pdf revised, Tables 9.122

Characteristics of "other neurological events" that occurred within 30 days post-vaccination are summarized in Table 76. With the exception of one case of tremors and head lag (graded as severe) in an infant diagnosed with congenital encephalopathy, all cases were considered mild or moderate in severity.

Table 76. Pivotal safety studies: "Other neurological events"[1] within 30 days following Pentacel or Control vaccines[2], safety population

Vaccine/ Study	Subject Number	Literal Term	Action Taken	Last Dose	Days Since Last Dose	Outcome	Other available clinical information
Pentacel/ 494-01	0344	Shaking legs	No action taken	1	0	Recovered, no sequelae	Resolution after 3 days; no neurological events reported after Doses 2 and 3; Voluntary withdrawal prior to Dose 4
Pentacel/ 494-01	1063	Jerking to body	Medical office visit	1	0	Recovered, no sequelae	No treatment reported; same day resolution; voluntary withdrawal
Pentacel/ 494-03	1330	Trembling Trembling Trembling	No action taken No action taken Medical office visit	1 2 2	0 0 7	Recovered, no sequelae	Resolution the same day for first 2 episodes and within 3 days for 3rd episode; 2nd and 3rd episodes accompanied by fever; discontinuation at parental request
Pentacel/ 494-03	0346	Head Lag Tremors	Medical office Visit Discontinuation	1 1	8 8	Not reported	Eventual diagnosis of congenital encephalopathy
Pentacel/ 494-01	0934	Minor head shakes	No action taken	2	0	Recovered, no sequelae	Resolution reported during contact with parent on Day 63 (duration not specified); completed trial, no other neurological events reported
Pentacel/ 494-01	0635	Shaking upon waking	No action taken	3	0	Recovered, no sequelae	Resolution after 4 days; completed trial, no other neurological events reported
Pentacel/ 494-01	0473	Staring into space	No action taken	4	0	Recovered, no sequelae	Resolution after 3 days; completed trial, no other neurological events reported
Pentacel/ 5A9908	2188	Tremor	No action taken	4	0	Recovered, no sequelae	Tremor and mottled skin within 30 minutes post-vaccination
Pentacel/ 494-03	1030	Breath holding spells	No action taken	4	6	Recovered, no sequelae	--
Pentacel/ 494-01	1444	Breath holding spell	Medical office visit	4	12	Recovered, no sequelae	No treatment reported; same day resolution; completed trial, no other neurological events reported
Pentacel/ 494-03	1021	Tremors	Telephone call to physician	4	18	Recovered, no sequelae	--
DAPTACEL/ P3T06	2110	Leg tremors	Medical office visit	2	0	Recovered, no sequelae	Albuterol for concurrent bronchiolitis; resolution documented; duration not specified; completed trial, no other neurological events reported.
DAPTACEL/ P3T06	0916	Shaking episode (probable disinhibition)	Telephone call to physician	2	26	Recovered, no sequelae	Same day recovery; possible seizure 35 days later.

[1]See text for definition of "other neurological events".
[2]Control vaccines: Study 494-01 HCPDT + POLIOVAX + ActHIB; Study P3T06 DAPTACEL + IPOL + ActHIB (Doses 1-3), DAPTACEL + ActHIB (Dose 4).
Source: 49401_addnl_safetyanalyses.pdf, pages 9-11 and pages 20-23; 49403_addnl_safetyanalyses.pdf, pages 8-9; p3t06_addnl_safetyanalyses.pdf, Table 1 page 17 (8 of 273); iss.pdf revised Table 5.24

Serious Adverse Events

Tables 77 and 78 present the rates of any serious adverse event within 30 days following Doses 1-3 and Dose 4, respectively, of Pentacel or Control vaccines. Across the pivotal safety studies, serious adverse events, overall, appeared to occur at a lower frequency in Study 494-01 compared to the other studies. Variability in exposures to childhood infectious diseases due to different geographic sites, as well as variability in proportions of subjects vaccinated during different seasons was offered by the applicant as possible explanations for this finding. In each of the two controlled studies, the frequencies of any serious adverse event within 30 days post-vaccination were similar in the Pentacel and Control groups.

Table 77. Pivotal safety studies: Number (percentage) of subjects with a serious adverse event within 30 days following any of Doses 1-3 of Pentacel or Control vaccines

494-01		494-03	P3T06	
HCPDT + POLIOVAX + ActHIB N=1032 n (%)	Pentacel N=2506 n (%)	Pentacel N=1207 n (%)	DAPTACEL + IPOL + ActHIB N=1455 n (%)	Pentacel N=484 n (%)
11 (1.1)	23 (0.9)	25 (2.1)	50 (3.4)	19 (3.9)

Source: revised iss.pdf, page 2627

Table 78. Pivotal safety studies: Number (percentage) of subjects with a serious adverse event within 30 days following Dose 4 of Pentacel or Control vaccines

494-01		494-03	P3T06		5A9908
HCPDT + POLIOVAX + ActHIB N=739 n (%)	Pentacel N=1862 n (%)	Pentacel N=958 n (%)	DAPTACEL + ActHIB N=418 n (%)	Pentacel N=431 n (%)	Pentacel N=1782 N (%)
2 (0.3)	6 (0.3)	8 (0.8)	4 (1.0)	5 (1.2)	19 (1.1)

Source: revised iss.pdf, page 2627

The controlled pivotal safety studies were not adequately powered to reliably evaluate differences between groups with regard to particular serious adverse events. Across the studies, following Doses 1-3 combined of Pentacel or Control vaccines, the most frequently reported serious adverse events were bronchiolitis, dehydration, pneumonia and gastroenteritis. Across the studies, following the fourth dose of Pentacel or Control vaccines, the most frequently reported serious adverse events were dehydration, gastroenteritis, asthma, and pneumonia.

Medically Attended Fever

In the pivotal safety studies, whether febrile infants sought medical attention for fever was not specifically solicited or systematically assessed. Limitations in the ability to capture medically attended fever from the pivotal studies safety database include: 1) potentially missing non-hospitalized cases if they were not considered serious adverse events, and 2) missing any case in which the actual reported diagnosis did not include the term fever or pyrexia. Thus, for example, an infant who underwent diagnostic studies to evaluate the cause of fever for whom the only reported diagnosis was “viral illness” may not be captured in an analysis of medically attended fever.

Extensive Limb Swelling

In the pivotal safety studies, the occurrence of extensive or whole proximal limb swelling was not specifically solicited. Overall, eight subjects who received Pentacel and six subjects who received DAPTACEL 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 vaccination site was not always specified and reporting terms were often non-specific with regard to size and extent of swelling. In at least two subjects, the description 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 "legs are swollen more than twice the normal size" was noted for one subject who received the first doses of Pentacel and Prevnar in opposite thighs.

In the pivotal safety studies, limb circumference was monitored following the fourth dose of Pentacel or Control DTaP vaccines. Overall, of 25 subjects with an increase in limb circumference >40 mm within three days following Pentacel, the maximum reported percent increase over baseline was between 20%-49% in 23 subjects and was 111% and 133%, respectively, in two subjects. For three subjects who reported an increase in limb circumference >40 mm within three days following DAPTACEL, the maximum reported percent increase over baseline was approximately 30% in two subjects and unknown in one subject.

Relatively Common Systemic and Local Adverse Events

Within each of the pivotal safety studies, temperatures were not uniformly measured by the same route. The main analyses of fever were performed using all temperatures recorded, irrespective of route of measurement. Within the two controlled studies, routes of temperature measurement and rates of fever following vaccination were generally similar between the Pentacel and Control groups. In both Pentacel and Control groups, rates of fever post-vaccination tended to increase with consecutive doses from Dose 1 to Dose 3.

In the controlled pivotal safety studies, rates of relatively common systemic adverse events such as decreased activity, inconsolable crying, and fussiness appeared generally similar following Pentacel and Control vaccines. These events tended to be most frequent following the first dose and to decrease with consecutive doses.

In the controlled pivotal safety studies, rates of relatively common local adverse events (i.e., injection site redness, swelling and tenderness) appeared generally similar following Pentacel or the Control DTaP vaccine. Local adverse events tended to be most frequently reported following the fourth dose of Pentacel or Control DTaP vaccine than following previous doses.

7.3.3 Dropouts

For each of the pivotal safety studies, Tables 79, 80, and 81 provide summaries of reasons for termination before the 60-day follow-up post-Dose 3, between 60 days post-Dose 3 and prior to Dose 4, and before the 60- or 180-day follow-up post-Dose 4, respectively.

Table 79. Pivotal safety studies: Reasons for termination in subjects who did not complete the 60-day follow-up post-Dose 3[1], safety population

	494-01		494-03	P3T06	
	Pentacel N=255	HCPDT N=152	Pentacel N=146	Pentacel N=32	DAPTACEL N=105
	n (%)	n (%)	n (%)	n (%)	n (%)
Adverse event	4 (1.6)	2 (1.3)	13 (8.9)	1 (3.1)	5 (4.8)
Contraindication	4 (1.6)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	27 (10.6)	8 (5.3)	8 (5.5)	9 (28.1)	18 (17.1)
Non-compliance	83 (32.5)	54 (35.5)	28 (19.2)	9 (28.1)	21 (20.0)
Voluntary withdrawal	137 (53.7)	87 (57.2)	97 (66.4)	13 (40.6)	60 (57.1)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

[1]Subjects have been classified by the treatment to which they were randomized.
Source: iss.pdf, page 50

Table 80. Pivotal safety studies: Reasons for termination in subjects who completed the 60-day follow-up post-Dose 3 but terminated before Dose 4, safety population

	494-01		494-03	P3T06	
	Pentacel N=356	HCPDT N=175	Pentacel N=105	Pentacel N=22	DAPTACEL N=27
Adverse event	9 (2.5)	2 (1.1)	5 (4.8)	0 (0.0)	4 (14.8)
Contraindication	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	18 (5.1)	11 (6.3)	14 (13.3)	7 (31.8)	7 (25.9)
Non-compliance	56 (15.7)	25 (14.3)	15 (14.3)	3 (13.6)	7 (25.9)
Voluntary withdrawal	273 (76.7)	136 (77.7)	71 (67.6)	12 (54.5)	9 (33.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.00)

[1]Subjects have been classified by the treatment to which they were randomized for Dose 1.
Source: iss.pdf, page 52

Table 81. Pivotal safety studies: Reasons for termination in subjects who received Dose 4 but did not complete the 60-or 180-day[1] follow-up post-Dose 4[2], safety population

	494-01		494-03	P3T06		5A9908
	Pentacel N=13	HCPDT N=8	Pentacel N=11	Pentacel N=14	DAPTACEL[3] N=13	Pentacel N=9
	N (%)	n (%)	n (%)	n (%)	N (%)	n (%)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)
Contraindication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	3 (23.1)	0 (0.0)	7 (63.6)	8 (57.1)	7 (53.8)	2 (22.2)
Non-compliance	5 (38.5)	3 (37.5)	2 (18.2)	2 (14.3)	3 (23.1)	0 (0.0)
Voluntary withdrawal	5 (38.5)	5 (62.5)	2 (18.2)	3 (21.4)	3 (23.1)	6 (66.7)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)

[1]The follow-up was 60 days for Studies 494-01, 494-03, and 5A9908, and 180 days for Study P3T06.
[2]Subjects have been classified by the actual treatment received at Dose 4.
[3]Stage II Group 1 (DAPTACEL + ActHIB)
Source: iss.pdf, pages 52-53

Across the pivotal safety studies, the most common reason for withdrawal due to an adverse event or contraindication following Pentacel was seizures, convulsions or epilepsy in 15 subjects (including one with "potential seizures" and one with "R/O seizure disorder"), followed by crying and/or fussiness in seven subjects (including one who also reported fever, pallor, lethargy and loss of appetite). Among Control subjects, the most common reasons for withdrawal due to an

adverse event or contraindication were seizures and chickenpox (3 subjects each). One subject withdrew due to crying following Control vaccines. [Source: revised iss.pdf, pages 60-65.] Other adverse events leading to withdrawal were summarized in the sections on each of the pivotal studies.

Although withdrawals due to seizures or crying and/or fussiness were somewhat more frequent among Pentacel than control subjects, in the controlled studies, rates of prolonged inconsolable crying, prolonged fussiness, and seizures did not appear to be more frequent following Pentacel relative to Control vaccines.

7.4 Other Safety Findings

7.4.1 Product-Demographic Interactions

None of the pivotal studies of Pentacel were designed to address demographic characteristics that might predict greater risk of adverse events.

7.4.2 Product-Disease Interactions

The safety of Pentacel in subjects with underlying illnesses cannot be addressed because only healthy subjects without known immune deficiency, developmental delay, neurological disorders, or chronic underlying medical conditions were enrolled in the clinical studies.

7.4.3 Product-Product Interactions with Regard to Safety

In the three pivotal safety studies in which subjects received four consecutive doses of Pentacel, Prevnar was administered concomitantly with the first three doses of Pentacel in most subjects. The second and third doses of the hepatitis B vaccine series (using RECOMBIVAX HB) also were administered concomitantly with the first and third doses of Pentacel in most subjects. In one study, some subjects who had not previously received the first dose of hepatitis B vaccine received three doses of RECOMBIVAX HB and Pentacel concomitantly. In the pivotal safety studies, the fourth dose of Pentacel was given alone in the majority of subjects, concomitantly with Prevnar in a subset of approximately 200 subjects, or concomitantly with MMR_{II} and VARIVAX in a subset of approximately 200 subjects.

In Study 494-03, the fourth dose of Pentacel administered concomitantly with either Prevnar or with MMR_{II} and VARIVAX was non-inferior (based on criteria specified in Section 6.2.1.5) to Pentacel administered alone, with regard to the occurrence of at least one severe solicited adverse event within three days post-vaccination.

The BLA does not contain safety data on Pentacel administered concomitantly with Rotavirus vaccine.

7.5 Safety Conclusions

In the pivotal safety studies of Pentacel, a total of 4,197 subjects were enrolled to receive four consecutive doses of Pentacel; an additional 1,782 subjects who had previously received three doses of Pentacel received a fourth dose. In one study, the safety of four doses of Pentacel (N=2,506 subjects) was compared to four doses of separately administered HCPDT, POLIOVAX and ActHIB (N=1,032 subjects). In one study, the safety of four doses of Pentacel (N=484 subjects) was compared to separately administered DAPTACEL, IPOL, and ActHIB (N=1,455 subjects for Doses 1-3, overall, and 418 subjects for Dose 4 DAPTACEL + ActHIB). As described in Section 6.1.3, CBER previously agreed to the use HCPDT, the DTaP component of Pentacel, as the control DTaP vaccine in one of the pivotal studies, although this vaccine is not licensed in the U.S.

Within the constraints of the sample sizes of the pivotal safety studies, the available data did not raise any particular concerns with regard to the occurrence of adverse events following Pentacel relative to separately administered Control vaccines and no concerning safety signals were identified. Given the number of subjects evaluated, the ability of the pivotal studies safety database to evaluate rare adverse events is limited.

Supportive post-marketing safety data from spontaneous adverse event reports received by the applicant, reflecting distribution of approximately 13.5 million doses of Pentacel over a 9-year period, primarily in Canada, did not identify any concerning safety signals. While the limitations of passive surveillance for vaccine adverse events, particularly underreporting, is well recognized, these data provide some assurance of the overall safety of Pentacel in the general population.

Data from a Canadian nationwide hospital-based program of active surveillance for certain targeted vaccine adverse events also provided some assurance of the safety of Pentacel with regard to febrile seizures, HHEs and encephalopathy.

8. Additional Clinical Issues

8.1 Directions for Use

The proposed directions for use, which involve reconstitution of lyophilized ActHIB with the DTaP-IPV component, are consistent with the statements of use during the clinical trials. The proposed labeling recommends immediate use of Pentacel after reconstitution of ActHIB with the DTaP-IPV component.

8.2 Dose Regimens and Administration

Consistent with the pivotal clinical studies, the proposed dosage regimen is administration of a single injection of 0.5 mL of Pentacel by the intramuscular route at ages 2, 4, 6, and 15 to 18 months of age.

Of note is that a child who receives the proposed schedule of Pentacel will receive 4 doses of IPV during the first two years of life. While this schedule is generally consistent with the ACIP recommendations for IPV immunization, including acceptable ages at vaccination and spacing between doses, the routinely recommended age for administration of the fourth dose of IPV is 4-6 years. Some State immunization requirements for school entry include receipt of the last dose of IPV after the fourth birthday.[9] Thus, some children who receive four doses of Pentacel according to the proposed schedule may be required to receive an extra (fifth) dose of IPV at 4-6 years of age.

Children who receive four doses of Pentacel at ages 2, 4, 6, and 15-18 months of age will need to receive a fifth dose of DTaP vaccine at 4-6 years of age to complete the 5-dose DTaP series, as recommended by the ACIP. The applicant has committed to submit clinical data to support use of DAPTACEL as the fifth dose in the DTaP series at 4-6 years of age, following four previous doses of Pentacel (see Section 9.3).

8.3 Special Populations: Pediatrics

The applicant requested approval of use of Pentacel in children ages 6 weeks through 4 years (before the 5th birthday). In the clinical development of Pentacel, the rationale for the lower age limit of 6 weeks for administration of Pentacel was based on current immunization practices and the limitations of the neonatal immune response. With the exception of Hepatitis B vaccine, which is routinely administered shortly after birth, in part, to prevent unrecognized perinatal

transmission of hepatitis B virus, the infant immunization program in the U.S. is initiated at a minimum of 6 weeks of age. In general, limitations of the neonatal immune response (e.g., weak and short-lived antibody response and inhibitory influence of maternal antibodies) have been significant barriers to effective immunization earlier in life.

For the age group 19 months through 4 years of age, use of Pentacel would be for catch-up immunization in unvaccinated children and those with delayed vaccinations. The requested upper age limit for administration of Pentacel, 4 years (prior to the fifth birthday), coincides with the age beyond which Hib conjugate vaccines are no longer recommended for routine use.

The BLA includes safety and immunogenicity data on Pentacel administered to children ages 6 weeks through 18 months. Use of Pentacel in children 19 months through 4 years of age is supported by clinical evidence of the safety and effectiveness of Pentacel in children 6 weeks to 18 months of age. Extrapolation of immunogenicity data from children 6 weeks to 18 months of age to older children 19 months through 4 years of age is supported by the generally mature, robust immune response to inactivated vaccines observed in children during and beyond the second year of life. In clinical studies, the safety of Pentacel was evaluated at each of four consecutive doses, administered at 2, 4, 6, and 15-18 months of age, respectively. Although rates of local reactions following Pentacel were generally higher in children 15-18 months of age compared with infants, this finding is thought to represent a higher risk of local reactions with increasing dose number, rather than an age effect. Rates of fever and other solicited systemic adverse events following Pentacel were not higher in children 15-18 months of age compared with infants. Thus, it is anticipated that adverse reaction rates following catch-up vaccination with Pentacel in children 19 months through 4 years would not be meaningfully higher than those observed in younger children and infants following the analogous doses in the four-dose series. Furthermore, DTaP and IPV vaccines are recommended for and routinely administered to U.S. children 6 weeks through 6 years of age. Hib conjugate vaccines are recommended for use among U.S. children 6 weeks through 4 years of age.

In addressing the requirements of the Pediatric Research Equity Act **(**PREA), the applicant submitted a request for a waiver of the requirement to submit pediatric assessments for the age groups 0 to 5 weeks (i.e., before 6 weeks of age) and 5 to 16 years (5 years to prior to 17th birthday).

A recommendation to grant a waiver for assessments of Pentacel in infants 0 to 5 weeks of age and children 5 to 16 years of age is based on the justification presented below.

<u>0 to 5 weeks</u>
For infants from birth to 5 weeks of age, the justification for waiver of studies with Pentacel is based on the following sections of the Pediatric Research Equity Act of 2007:

Section 505B(a)(4)(B)(i): necessary studies are impossible or highly impracticable.

Section 505B(a)(4)(B)(iii): the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group.

<u>Necessary studies are impossible or highly impracticable</u>
Because of the following considerations, it would be difficult to enroll sufficient numbers of subjects from birth to 5 weeks of age in studies of Pentacel and inappropriate to require such studies.

a) Lack of Need
Among the diseases targeted for prevention by Pentacel, neither diphtheria, tetanus, nor poliomyelitis occur in U.S. infants too young to be protected from vaccination with products approved for use beginning at 6 weeks of age.

b) Potential for Diminished Immune Responses to Subsequent Vaccination
Clinical data from one published study suggest that administration of Diphtheria and Tetanus Toxoid (DT) to newborn infants may be associated with suppression of antibody responses to subsequently administered diphtheria toxoid and Hib conjugate vaccines.[10] In another study, neonatal vaccination with an acellular pertussis vaccine interfered with the immune response to a Hib conjugate vaccine.[11] In addition, the applicant has indicated that vaccination with DTaP at birth may suppress the antibody responses to diphtheria toxoid and pertussis antigens.[12]

c) Potential for Clinically Significant Adverse Reactions
As with all preventive vaccines, a high standard of safety would be expected for vaccines administered to healthy neonates. Moreover, the vulnerability of the neonate poses unique safety considerations for clinical studies of preventive vaccines. For example, post-vaccination fever assumes greater clinical significance in neonates than in older infants or children because of the high risk for serious bacterial infection and the difficulty in predicting the presence of invasive disease by physical exam and laboratory testing in the neonatal period. Hospitalization, diagnostic evaluation including cerebrospinal fluid studies, and administration of intravenous antibiotics represent the standard of care in the U.S. for febrile neonates. Administration of Pentacel in infants from birth to 5 weeks of age poses at least a theoretical concern for excess fever due to vaccination. In clinical studies, approximately 5-20% of older infants had fever $\geq$38.0^{o}C within 0-3 days following receipt of Pentacel.

Pentacel does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of infants 0-5 weeks of age
Vaccinating U.S. infants from birth to 5 weeks of age against diphtheria, tetanus, and poliomyelitis does not represent a meaningful therapeutic benefit over vaccination according to the currently recommended schedule which begins at a minimum age of 6 weeks. In view of the potential risks of neonatal vaccination and the lack of added benefit to earlier vaccination against diphtheria, tetanus, and poliomyelitis, Pentacel is not likely to be used by a substantial number of U.S. infants from birth to 5 weeks of age.

5 to 16 years
The justification for waiver of studies of Pentacel in children and adolescents 5 to 16 years of age is based on the following sections of the Pediatric Research Equity Act of 2007:

Section 505B(a)(4)(B)(i): necessary studies are impossible or highly impracticable.

Section 505B(a)(4)(B)(iii): the drug or biological product—(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and (II) is not likely to be used by a substantial number of pediatric patients in that age group (for children 10 to 16 years of age).

Necessary studies are impossible or highly impracticable
In the pediatric population 5 to 16 years of age, necessary studies are impossible or highly impracticable because too few children, geographically dispersed, would need vaccination with all of the antigens contained in Pentacel. Specific considerations are presented below.

a) Too Few Children 5 to 16 Years of Age in Need of Vaccination against Invasive Hib Disease
A fourth dose of Hib conjugate vaccine, administered at age 12 to 15 months, completes the routinely recommended series for this vaccine. Because of the negligible risk of developing invasive Hib disease, catch-up vaccination is not generally recommended for children 5 years of age and older. Vaccination is recommended for children 5 years of age and older who are unimmunized and who have an underlying disease possibly predisposing to invasive Hib disease. Such children are expected to be few in number and geographically dispersed.

b) DTaP Vaccines not Administered to Children 7 Years of Age and Older
DTaP vaccines are not administered to children 7 years of age and older. A single dose of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) is routinely recommended at 11-12 years of age. Tdap vaccines were specifically formulated to contain lower amounts of diphtheria toxoid than DTaP vaccines to reduce the potential for reactogenicity that may be associated with booster vaccination.

c) Limited Need for Polio Vaccination in this Age Group
The routinely recommended IPV series consists of four doses. The school entry requirements for some States require a dose of IPV at age 4 to 6 years. For other States, the last dose in the IPV series may be administered before age 4 years. Thus, many children may fulfill the IPV requirements before 5 years of age. IPV is not routinely recommended for children 7 to 16 years of age.

Pentacel does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used by a substantial number of children and adolescents 10 to 16 years of age
For children and adolescents 10 to 16 years of age, Pentacel does not represent a meaningful therapeutic benefit over Tdap vaccine. Pentacel is not likely to be used by a substantial number of children and adolescents 10 to 16 years of age because Tdap vaccines were specifically formulated to reduce the potential for reactogenicity that may be associated with booster vaccination. Although IPV is not routinely used in this age group, Pentacel does not represent a meaningful therapeutic benefit over IPV.

9. Recommendations

9.1 Approval Recommendation
The safety data in the BLA support a recommendation for approval of Pentacel in infants and children 6 weeks through 4 years of age (prior to the fifth birthday) for active immunization against invasive Hib disease, diphtheria, tetanus, pertussis, and poliomyelitis. The dosage regimen supported by clinical data is a single 0.5 mL dose of Pentacel, administered by the intramuscular route, at 2, 4, 6, and 15 to 18 months of age. Safety of Pentacel in children ages 19 months through 4 years of age whose vaccinations have been delayed is inferred from the available safety data in children 6 weeks through 18 months of age.

This recommendation is based only on the review of safety, and does not take into account the data submitted to support the effectiveness of Pentacel. CBER's review of the effectiveness of Pentacel was conducted by Dr. Theresa Finn.

9.2 Partial Waiver of Pediatric Studies
Based on the justification outlined in Section 8.3, I recommend partial waiver of pediatric studies of Pentacel in infants 0-5 weeks of age and children 5-16 years of age. During their 5/14/08 meeting, FDA's Pediatric Review Committee concurred with this recommendation.

9.3 Postmarketing Actions Pertaining to the Safety Evaluation of Pentacel

The applicant has proposed to conduct a post-licensure passive surveillance study designed to detect serious adverse events and specified, medically-attended neurological conditions, hypersensitivity reactions, and new-onset autoimmune disease following Pentacel. The proposal is to conduct a study at ---------- that would accrue at least 10,000 children who receive Pentacel and an unspecified number of children who receive other DTaP vaccines. For each subject, passive surveillance for specified adverse events through 6 months following the fourth dose of Pentacel or other DTaP vaccine will be conducted by review of computerized medical records and state mortality tapes. This study will also provide safety data on concomitant use of Rotavirus vaccine with Pentacel, which were not available in the BLA. In view of the available pre-licensure clinical data on Pentacel and the post-marketing data on use of Pentacel outside the U.S., a post-marketing study to evaluate the safety of Pentacel in 10,000 children, combined with routine pharmacovigilance activities, is sufficient. In the concept document for the post-marketing safety study, the applicant has proposed some comparative analyses of Pentacel vs. other DTaP vaccines. CBER has conveyed to the applicant that a non-randomized, observational study, as proposed, would not be sufficient to support comparative safety claims in the package insert. The primary review of this study is being conducted by the Office of Biostatistics and Epidemiology.

The applicant has committed to submit clinical data from Study P3T10, conducted under the DAPTACEL IND, to support use of DAPTACEL to complete the DTaP series following four previous doses of Pentacel. In Study P3T10, 989 subjects who previously received four doses of Pentacel in Studies 494-01 and 494-03 were enrolled to receive a dose of DAPTACEL between 4 to 6 years of age. The applicant has committed to submit the final study report for Study P3T10 by 7/31/08.

10. Labeling

Review and revision of the package insert was ongoing at the time this review was finalized. No major labeling issues have been identified. Comments on the draft package insert have been itemized in separate reviews and conveyed to the applicant.

11. Appendices

Appendix 1. Study 494-01 Lot numbers for the concentrates used in the three HCPDT-IPV consistency lots

[redacted]

Source: summary.pdf page 19

Appendix 2. Study 494-01 Summary of changes to safety data, by subjects, for the period up to 60 days after each dose, resulting from the audit of the clinical safety database

Dose / Treatment Group	Solicited Local Reactions (0-7 Days)		Solicited Systemic Reactions (0-7 Days)		Unsolicited Adverse Events (0-60 Days)		Serious Adverse Events (0-60 Days)	
	Pre-audit n/N	Post-audit n/N	Pre-audit n/N	Post-audit n/N	Pre-audit n/N	Post-audit n/N	Pre-audit n/N	Post-audit n/N
Dose 1								
Pooled Pentacel	962/2319	978/2319	1927/2333	1933/2334	1414/2506	1299/2506	-----	-----
Control	491/934	503/935	824/935	827/935	573/1032	500/1032		
Dose 2								
Pooled Pentacel	775/2167	789/2167	1646/2182	1660/2183	1422/2374	1350/2374	9/2374	10/2374 4/945
Control	367/854	371/854	676/853	683/853	558/945	535/945	3/945	
Dose 3								
Pooled Pentacel	707/2018	714/2018	1487/2034	1501/2035	1502/2294	1474/2294	13/2294	12/2294 4/900
Control	347/795	348/795	-	-	581/900	570/900	2/900	
Doses 1-3 Combined								
Pooled Pentacel	1417/2389	1435/2389	2232/2397	2244/2400	2192/2506	2135/2506	38/2506	37/2506
Control	648/966	654/967	910/965	911/965	881/1032	847/1032	15/1032	17/1032
Dose 4								
Pentacel	1005/1658	1006/1659	1142/1663	1144/1663	1094/1862	1075/1862	-----	-----
Control	405/643	406/643	471/643	472/643	421/739	415/739		

Source: 49401si.pdf, page 58 and 49401sii.pdf, page 55

Appendix 3. Study 494-01 Summary of changes in termination classification, by subjects, through 60 days post-Dose 3, resulting from the audit of the clinical safety database, safety population

Termination Reason	Group	Pre-Audit n/N	Post-Audit n/N
Adverse Event	Pooled Pentacel Lots	1/2507	4/2507
Contraindication	Pooled Pentacel Lots	6/2507	4/2507
Lost to Follow-Up	Pooled Pentacel Lots	26/2507	27/2507
Non-Compliance	Pooled Pentacel Lots	45/2507	83/2507
	Control	26/1036	55/1036
Voluntary Withdrawal	Pooled Pentacel Lots	67/2507	138/2507
	Control	57/1036	90/1036
Other	Pooled Pentacel Lots	111/2507	0/2507
	Control	62/1036	0/1036

Source: 49401si.pdf, page 59

Appendix 4. Study 494-01 Summary of changes in termination classification, by subjects, prior to the fourth dose for subjects who completed the 60-day follow-up post-Dose 3, resulting from the audit of the clinical safety database, safety population

Termination Reason	Group	Pre-Audit n/N	Post-Audit n/N
Total Discontinued	Pentacel	-	-
	Control	181/880	182/880
Adverse Event	Pentacel	0/2251	9/2251
	Control	0/880	2/880
Contraindication	Pentacel	6/2251	0/2251
	Control	3/880	1/880
Lost to Follow-Up	Pentacel	-	-
	Control	10/880	11/880
Non-Compliance	Pentacel	33/2251	61/2251
	Control	13/880	27/880
Voluntary Withdrawal	Pentacel	155/2251	278/2251
	Control	82/880	141/880
Other	Pentacel	154/2251	0/2251
	Control	73/880	0/880

Source: 49401sii.pdf, page 56

Appendix 5. Study 494-01 Summary of changes in termination classification, by subjects, for the period 60 days post-Dose 4, resulting from the audit of the clinical safety database, safety population

Termination Reason	Treatment	Pre-Audit n/N	Post-Audit n/N
Total Discontinued	Pentacel	-	-
	Control	7/706	8/706
Non-Compliance	Pentacel	-	-
	Control	2/706	3/706
Voluntary Withdrawal	Pentacel	3/1895	5/1895
	Control	3/706	5/706
Other	Pentacel	2/1895	0/1895
	Control	2/706	0/706

Source: 49401sii.pdf, page 56

Appendix 6. Study 494-01 Seizures and possible seizures that occurred anytime during the study, safety population

Pentacel (N=2506)					
Subject Number	Afebrile, Febrile, or "Possible"	Literal Term	Last Dose	Days Since Last Dose	Outcome
2126	Afebrile	Seizure activity	1	6	Recovered without sequelae
1230	Afebrile	Hypoxic ischemic encephalopathy[1]	1	30	Recovered with sequelae
1958	Afebrile	Seizures	3	29	Recovered without sequelae[2]
0858	Afebrile	Seizure	3	139	NR
1336	Afebrile	Seizure	3	149	Recovered without sequelae
1218	Afebrile	Seizures	3	256	Death[3]
0178	Afebrile	New onset seizure	3	296	Recovered without sequelae
0961	Afebrile	Seizure[4]	4	27	Recovered without sequelae
0521	Febrile	Febrile seizure	2	42	Recovered without sequelae
0541	Febrile	Febrile seizure	3	99	Recovered without sequelae
1584	Febrile	Febrile seizure	3	106	Recovered without sequelae
3983	Febrile	Febrile seizure	3	113	Recovered without sequelae
2387[5]	Febrile	Febrile seizure	3	198	Recovered without sequelae
0856	Febrile	Febrile seizure	3	220	Recovered without sequelae
1203	Febrile	Febrile seizure	3	226	Recovered without sequelae
		Febrile seizure	4	14	Recovered without sequelae
		Possible febrile seizure[6]	4	24	Recovered without sequelae
3537	Febrile	Tonic-clonic febrile seizure	4	14	Recovered without sequelae
0800	Febrile	Febrile seizure	4	53	Recovered without sequelae
1888	Possible	Rule out seizure	2	20	Recovered without sequelae
0364	Possible	R/O seizure disorder	2	52	Recovered with sequelae
1453	Possible	Shaking episodes R/O seizure	2	57	NR
0441	Possible	R/O seizure	3	0	Recovered without sequelae
3710	Possible	(Questionable seizure) Infant spasms	3	26	Recovered without sequelae
0858	Possible	Myotonic jerking movement	3	138	Recovered without sequelae
1562	Possible	Potential seizure	3	237	Recovered without sequelae
Control Vaccines (N=1032)					
0008	Afebrile	Intermittent seizures	1	44	Recovered without sequelae
3449	Afebrile	Migraine variant	2	0	Recovered without sequelae[7]
2501	Afebrile	Seizures	4	14	Recovered without sequelae
3942	Febrile	Febrile seizure	1	21	Recovered without sequelae
0693	Febrile	Possible febrile seizure[6]	3	221	Recovered without sequelae
0955	Febrile	Febrile seizure	3	290	Recovered without sequelae
0066	Febrile	Possible febrile seizure[6]	4	6	Recovered without sequelae
1943	Febrile	Febrile seizure	4	7	Recovered without sequelae
1286	Possible	R/O Seizure disorder -normal exam	2	14	Recovered without sequelae

[1] This subject experienced seizure disorder secondary to anoxia and ischemic encephalopathy, as a post-operative complication of cardiac surgery.
[2] This subject continued with seizure episodes (undetermined number) attributable to an intracranial lesion.
[3] This subject experienced seizure activity while hospitalized and died one day later. The cause of death was noted as secondary to neuroblastoma.
[4] Subject 0961 experienced afebrile seizure activity sometime after the 60-day follow-up post-Dose 3 Pentacel. The event was reported in the CRF Comments section but not entered as an adverse event.
[5] Subject 2387 was randomized to Pentacel but received HCPDT for the fourth dose.
[6] The Investigator reported the event as a possible febrile seizure. However, after evaluation of the event, the Medical Monitor categorized it as febrile seizure.

[7] In a letter to the Sponsor from the Investigator approximately 2.5 years after the event, it was noted that the child has continued to have seizures.
NR = information not reported
Other than Subject 2387 (see table), no seizures or possible seizures were reported by subjects not receiving study vaccines as randomized.
Source: 49401_addnl_safetyanalyses.pdf, pages 7-11; questions1_133.pdf pages 38-41

Appendix 7. Study 494-01 "Other neurological events"[1] that occurred anytime following Pentacel or Control vaccines, safety population

Pentacel (N=2506)						
Subject Number	Literal Term	Severity	Action Taken	Last Dose	Days Since Last Dose	Outcome
0121	Breath holding spells	Moderate	Emergency room visit	3	152	No information reported
0344	Shaking legs	Mild	No action taken	1	0	Recovered without sequelae
0473	Staring into space	Mild	No action taken	4	0	Recovered without sequelae
0475	Shaking	Mild	Phone call to physician	1	37	Recovered without sequelae
0635	Shaking upon waking up	Mild	No action taken	3	0	Recovered without sequelae
0736	Myoclonus	Mild	Medical office visit	2	35	Recovered without sequelae
0934	Minor head shakes	Mild	No action taken	2	0	Recovered without sequelae
0965	Myoclonic jerks	Mild	Medical office visit	2	34	Recovered without sequelae
1063	Jerking to body	Moderate	Medical office visit	1	0	Recovered without sequelae
1444	Breath holding spell	Mild	Medical office visit	4	12	Recovered without sequelae
1562	Holding breath	Severe	Discontinuation	3	237	Recovered without sequelae
2320	Benign myoclonic jerks	Mild	Phone call to physician / Medical office visit	1	45	No information reported
3053	Pre-meal shaking	Mild	Phone call to physician	3	38	Recovered without sequelae
3764	Holding breath	Mild	Medical office visit	4	56	Recovered without sequelae
Control Vaccines (N=1032)						
Subject Number	Literal Term	Severity	Action Taken	Last Dose	Days Since Last Dose	Outcome
0873	Infantile spasm[2]	Mild	Medical office visit	2	62	Recovered without sequelae

[1]See text Section 6.1.1.7 for definition of "Other Neurological Events"
[2]According to the applicant the course was not typical for infantile spasms. The subject recovered without sequelae the same day and completed the study with no other neurological events reported.
Source: 49401_addnl_safetyanalyses.pdf, pages 9-11

Appendix 8. Study 494-03 Summary of changes to safety data, by subjects, for the period up to 60 days after each dose, resulting from the audit of the clinical safety database

Dose	Immediate Reactions		Solicited Systemic Reactions (0-7 Days)		Unsolicited Adverse Events (0-60 Days)	
	Pre-audit n/N	Post-audit n/N	Pre-audit n/N	Post-audit n/N	Pre-audit n/N	Post-audit n/N
Dose 1	-	-	-	-	-	-
Dose 2	-	-	-	-	796/1115	797/1115
Dose 3	-	-	692/881	694/881	724/1077	722/1077
Dose 4 (pooled groups)	23/958	22/958	-	-	662/958	654/958

Source: 49403si.pdf, page 41 and 49403sii.pdf, page 50

Appendix 9. Study 494-03 Summary of changes in termination classification through 60 days post-Dose 3, resulting from the audit of the clinical safety database, ITT safety population

Reason for Discontinuation	Pre-Audit n/N	Post-Audit n/N
Adverse Event	7/1207	13/1207
Contraindication	1/1207	0/1207
Lost to Follow-Up	9/1207	8/1207
Non-Compliance	23/1207	28/1207
Voluntary Withdrawal	106/1207	97/1207

Source: 49403si.pdf, page 42

Appendix 10. Study 494-03 Summary of changes in termination classification for subjects who completed the 60-day follow-up post-Dose 3, resulting from the audit of the clinical safety database, pooled Pentacel groups, ITT safety population

Reason for Discontinuation	Pre-Audit n/N	Post-Audit n/N
Total Discontinued	10/958	11/958
Contraindication	1/958	0/958
Lost to Follow-Up	6/958	7/958
Non-compliance	0/958	2/958
Voluntary Withdrawal	3/958	2/958

Source: 49403sii.pdf, page 52

Appendix 11. Study 494-03 Seizures and possible seizures that occurred anytime during the study, safety population

Vaccine Group[1]	Subject Number	Afebrile or Febrile or "Possible"	Literal Term	Last Dose	Days Since Last Dose	Outcome
Pentacel	1228	Afebrile	Seizure	1	45	Recovered without sequelae
Pentacel	0551	Afebrile	Afebrile seizure	2	54	Recovered without sequelae
Stage II Group 4	0325	Afebrile	Epilepsy	3	87	Recovered without sequelae[2]
Stage II Group 1	0602	Afebrile	Seizure disorder	3	207	Recovered with sequelae
Stage II Group 2	0946	Afebrile	Seizure	3	250	Recovered without sequelae
			Seizure	4	9	Recovered without sequelae
			Seizure	4	21	Recovered without sequelae
Stage II Group 3	0879	Afebrile	Seizure x 2	4	14	Recovered without sequelae
Stage II Group 3	0837	Febrile	Febrile seizure	3	83	Recovered without sequelae
Stage II Group 2	0946	Febrile	Febrile seizure	3	130	Recovered without sequelae
			Seizure (possible febrile)	3	229	Recovered without sequelae
Stage II Group 4	1107	Febrile	Febrile seizure	3	187	Recovered without sequelae
Stage II Group 2	0403	Febrile	Febrile seizure	3	253	Recovered without sequelae
Stage II Group 4	0660	Febrile	Febrile seizure	3	262	Recovered without sequelae
			Febrile seizure	3	284	Recovered without sequelae
Stage II Group 3	1102	Febrile	Febrile seizure	3	265	Recovered without sequelae
			Febrile seizure	4	13	Recovered without sequelae
Stage II Group 1	0338	Febrile	Febrile seizure	4	67	Recovered without sequelae
Stage II Group 2	0376	Febrile	Febrile seizure	4	41	Recovered without sequelae
Stage II Group 4	0385	Febrile	Febrile seizure	4	16	Recovered without sequelae

1For seizures that occurred after Dose 1 or 2, vaccine group is listed as Pentacel. For seizures that occurred after Dose 3 or 4, the Stage II vaccine group is listed.
For Doses 1, 2, and 3, all subjects received Pentacel and Prevnar at 2, 4, and 6 months and RECOMBIVAX HB at 0, 2, and 6 months or 2, 4, and 6 months.
Stage II Group 1 received 4th Dose of Pentacel at 15 months.

Stage II Group 2 received 4th Dose of Pentacel concomitantly with MMRII and VARIVAX at 15 months.
Stage II Group 3 received 4th Dose of Pentacel concomitantly with Prevnar at 15 months.
Stage II Group 4 received MMRII, VARIVAX, and Prevnar at 15 months, and 4th Dose of Pentacel at 16 months.
[2] Although epilepsy is a chronic event, the subject was reportedly recovered without sequelae.
[3] No stop date was recorded at the time of study termination.
Source: 49403_addnl_safetyanalyses.pdf, pages 7-8

Appendix 12. Study 494-03 "Other neurological events"[1] that occurred anytime following Pentacel, safety population

Vaccine Group[2]	Subject Number	Literal Term	Severity	Action Taken	Last Dose	Days Since Last Dose	Outcome
Pentacel	0346	Head Lag	Severe	Medical Office Visit	1	8	No information reported[3]
		Tremors	Severe	Discontinuation	1	8	No information reported[3]
Pentacel	0804	Myoclonus	Mild	Medical office visit	2	55	Recovered without sequelae
Stage II Group 4	1021	Tremors	Mild	Telephone call to physician	4	18	Recovered without sequelae
Stage II Group 2	1030	Breath holding spells	Mild	No action taken	4	6	Recovered without sequelae
Pentacel	1089	Right leg tremor	Mild	Medical office visit	1	49	Recovered without sequelae
Pentacel	1139	Breath holding	Mild	Telephone call to physician	2	39	Recovered without sequelae
Pentacel	1330	Trembling	Mild	No action taken	1	0	Recovered without sequelae
		Trembling	Mild	No action taken	2	0	Recovered without sequelae
		Trembling	Moderate	Medical office visit	2	7	Recovered without sequelae

[1]See text Section 6.1.1.7 for definition of "Other Neurological Events"
[2]For "Other Neurological Events" that occurred after Dose 1 or 2, vaccine group is listed as Pentacel. For events that occurred after Dose 3 or 4, the Stage II vaccine group is listed.
[3]No stop date was recorded at the time of study termination.
For Doses 1, 2, and 3, all subjects received Pentacel and Prevnar at 2, 4, and 6 months and RECOMBIVAX HB at 0, 2, and 6 months or 2, 4, and 6 months.
Stage II Group 1 received 4th Dose of Pentacel at 15 months.
Stage II Group 2 received 4th Dose of Pentacel concomitantly with MMR$_{II}$ and VARIVAX at 15 months.
Stage II Group 3 received 4th Dose of Pentacel concomitantly with Prevnar at 15 months.
Stage II Group 4 received MMR$_{II}$, VARIVAX, and Prevnar at 15 months, and 4th Dose of Pentacel at 16 months.
Source: 49403_addnl_safetyanalyses.pdf, pages 8-9

Appendix 13. Study 5A9908 Summary of changes to the safety data resulting from the audit of the safety database

	Immediate Reactions		Solicited Local Reactions		Solicited Systemic Reactions		Unsolicited Adverse Events		Serious Adverse Events	
	Pre-audit	Post-audit	Pre-audit	Post-audit	Pre-audit	Post-audit	Pre-audit	Post-audit	Pre-audit	Post-audit
All Study Groups Combined	16	9	1325	1325	1366	1336	958	942	31	30

Source: 5a9908.pdf, page 42

Appendix 14. Study 5A9908 Seizures and possible seizures that occurred anytime during the study, safety population

Subject Number	Afebrile, Febrile, or "Possible"	Literal Term	Days Since Vaccine	Outcome
2182	Afebrile	Seizure	9	Recovered without sequelae
1082	Febrile	Febrile seizure	2	Recovered without sequelae
1334	Febrile	Febrile seizure	4	Recovered without sequelae
1231	Febrile	Febrile convulsion	20	Recovered without sequelae
1258	Febrile	Febrile convulsion	26	Recovered without sequelae
5170	Febrile	Possible atypical febrile seizure	27	Recovered without sequelae
1131	Febrile	Febrile seizure	45	Recovered without sequelae
1115	Febrile	Febrile convulsion	47	Recovered without sequelae

Source: 5a9908_addnl_safetyanalyses.pdf, page 6

Appendix 15. Study P3T06 Summary of changes to the safety database resulting from the audit of the clinical safety database, doses 1-3 of DAPTACEL or Pentacel

	Pooled DAPTACEL Lots n/N	Pentacel n/N
Immediate reactions		
pre-audit	8/1455	1/484
post-audit	3/1455	0/484
Solicited local reactions		
pre-audit	999/1429	340/472
post-audit	1002/1429	339/472
Solicited systemic reactions		
pre-audit	1387/1429	-
post-audit	1388/1429	-
Unsolicited adverse events		
pre-audit	1341/1455	454/484
post-audit	1332/1455	455/484
Serious adverse events		
pre-audit	-	23/484
post-audit	-	24/484

Source: p3t06si.pdf, page 52-53

Appendix 16. Study P3T06 Summary of changes in termination classification resulting from the audit of the clinical safety database, doses 1-3 of DAPTACEL or Pentacel

Reason for Discontinuation	Pooled DAPTACEL Lots N=1457	Pentacel N=484
Total discontinued		
pre-audit	117	34
post-audit	105	32
Adverse event		
pre-audit	6	0
post-audit	5	1
Lost to Follow-up		
pre-audit	15	7
post-audit	18	9
Non-compliance		
pre-audit	24	10
post-audit	21	9

Source: p3t06si.pdf, page 54

Appendix 17. Study P3T06 Seizures and possible seizures following Pentacel or Control vaccines, safety population

Pentacel					
Subject Number	Afebrile, Febrile, or "Possible"	Literal Term	Last Dose	Days Since Last Dose	Outcome
0972	Afebrile	seizure disorder, general convulsive	4	139	Recovered without sequelae
2416	Febrile	complex febrile seizure	3	78	Recovered without sequelae
Control (pooled DAPTACEL lots for Doses 1-3; DAPTACEL Group 1 for dose 4)					
Subject Number	Afebrile, Febrile, or "Possible"	Literal Term	Last Dose	Days Since Last Dose	Outcome
1362	afebrile	Seizure with apnea	1	0	Recovered without sequelae
1931	afebrile	Seizure	1	22	Recovered without sequelae
1833	febrile	Febrile convulsion	3	30	Recovered without sequelae
1378	febrile	Febrile seizure	3	190	Recovered without sequelae
2379	febrile	Febrile seizure	4	49	Recovered without sequelae
0916	possible	Possible seizure disorder	2	61	No information available

Source: p3t06_addnl_safetyanalyses.pdf, Table 1 page 16 (7 of 273)

12 References

1. Braun MM, Terracciano G, Salive ME, et al. Report of a US public health service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunization. Pediatrics 1998;102:E52

2. Moore DL, Le Saux N, Scheifele D, et al. Lack of evidence of encephalopathy related to pertussis vaccine: Active surveillance by IMPACT, Canada, 1993-2002. Pediatr Infect Dis J. 2004;23;568-571.

3. Le Saux N, Barrowman NJ, Moore DL, et al. Decrease in hospital admissions for febrile seizures and reports of hypotonic-hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. Pediatrics. 2003;112:e348-353.

4. Marcy SM, Kohl KS, Dagan R, et al. Fever as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2004;22:551-556

5. CDC. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(RR-15):1-48.

6. CDC. Pertussis – United States, 2001-2003. MMWR 2005;54(50):1283-1286

7. Tanaka M, Vitek CR, Pascual FB, et al. Trends in pertussis among infants in the United States, 1980-1999. JAMA 2003;290(22):2968-2975

8. Institute of Medicine, Howson CP, Howe CJ, Fineberg HV, eds. Adverse effects of pertussis and rubella vaccines. Washington, DC: National Academy Press, 1991:86-124

9. http://www.immunize.org/laws/ (accessed 3/26/06)

10. Lieberman JM, Greenberg DP, Wong VK, et. al. Effect of neonatal immunization with diphtheria and tetanus toxoids on antibody responses to *Haemophilus influenzae* type b conjugate vaccines. J Pediatr 1995;126:198-205.

11. Knuf M, Schmitt H-J, Wolter, et. al. Neonatal vaccination with an acellular pertussis vaccine accelerates the acquisition of pertussis antibodies in infants. J Pediatr 2008;152:655-660.

12. Halasa NB, O'Shea A, Shi JR, et. al. Poor immune responses to a birth dose of diphtheria, tetanus and acellular pertussis vaccine. J Pediatr 2008, in press.