SUBJECT: **Clinical Review of Biological License Application DAPTACELä (CPDT)**

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DATE: **9 April 2002**

To: **PLA 96-0660**
STN 103666\0

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2. 0 General Information

Product Name:	DAPTACEL™ Component Pertussis Vaccine Combined With Diphtheria and Tetanus Toxoids Adsorbed (CPDT).
STN #:	STN 1036610
Manufacturer:	Aventis Pasteur Limited.
Proposed Indication:	Prevention of diphtheria, tetanus and pertussis in infants and children aged 6 weeks to 6 years (prior to 7th birthday).
Dosage Form:	Liquid, single use vials and mulitidose (5 dose) vials.
Adjuvant:	Aluminum phosphate
Preservative:	2-phenoxyethanol
Route of Administration:	Intramuscular

Product/Formulation:

- Inactivated pertussis toxin (PT) 10 μg
- Filamentous hemagglutinin (FHA) 5 μg
- Pertactin (PRN) 3 μg
- Fimbriae (types 2 & 3) 5 μg
- Diphtheria toxoid 15 Lf
- Tetanus toxoid 5 Lf
- Aluminum phosphate, 0.33 mg of aluminum
- 2-phenoxyethanol, 0.6%
- Formaldehyde, <0.02%
- Glutaraldehyde, <0.1%

Related Products

- Diphtheria and Tetanus Toxoids, DT Adsorbed for pediatric use (STN #103944 approved April 1997)
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2.1 Indication:

For active immunization against diphtheria, tetanus and pertussis in infants and children aged 6 weeks to 6 years (prior to 7th birthday). The vaccine is recommended to be given

at 2, 4 and 6 months of age, at intervals of 6-8 weeks with a fourth dose given at 17-20 months of age.

2.2 Regulatory Review

A summary of the review process is presented below in Table 1. The original application was submitted in May 1996. CBER issued a complete response (CR) letter in May 1997. The sponsor responded in September 1999 and, in their response, included results of the US Bridging Study (USBS). Result of the USBS revealed that US children had lower PRN antibody responses to CPDT as compared to children enrolled in the pivotal efficacy trial conducted in Sweden between 1992-5. CBER issued a 2nd CR letter in March 2000 to which the sponsor responded in August 2000. The application was presented to and discussed by the Vaccines and Related Biological Products Advisory Committee in November 2000. CBER issued a 3rd CR letter in February 2001 following review of information submitted in the August 2000 response and the VRBPAC deliberations. CBER requested, in part, that a study be initiated to evaluate the safety and immunogenicity of four consecutive doses of CPDT vaccine in the US given with routinely recommended childhood vaccines. An interim safety report of this study was submitted for CBER review in January 2002.

Table 1: Chronology of regulatory review

PLA submitted by sponsor	May 1996
CBER complete review letter #1	May 1997
Sponsor submission of complete response to CBER review	September 1999
Pre-approval inspections	November 1999
CBER complete review letter #2	March 2000
Sponsor submission of complete response to CBER review	August 2000
Vaccines and Related Biological Products Advisory Committee	November 2000
CBER complete review letter #3	February 2001
Sponsor submission of completer response to CBER review	January 2002

3.0 General Background

The indication being sought for the CPDT vaccine is the prevention of diphtheria, tetanus and pertussis in infants and children. The vaccine contains four *B. pertussis* antigens, inactivated pertussis toxin, filamentous hemagglutinin, fimbriae (types 2 and 3) and pertactin, as well as diphtheria and tetanus toxoids (see above, vaccine formulation).

Pertussis (whooping cough) is a bacterial infection caused by *Bordetella pertussis* affecting primarily the respiratory system. Typical infection is characterized by onset of an initial catarrhal phase following a 1-3 week incubation period with symptoms of rhinorrea, lacrimation, low grade fever, and conjunctival injection. A dry non-productive cough may develop which evolves, during the paroxysmal phase, into a paroxysmal cough consisting of short expiratory bursts followed by an inspiratory gasp (or whoop). This cough may be long lasting, up to several weeks in duration. Leuckocytosis with a lymphocytic predominance is typical. Complications include pneumonia, secondary bacterial infections, hemorrhages and petechiae resulting from increased intrathoracic and intraabdominal pressures during coughing, and CNS complications that include encephalophathy and seizures. Infants are most susceptible to the severe manifestations and complications of pertussis disease.

Prior to introduction of whole cell DTP vaccine (DTPwc), the annual incidence of pertussis disease was high (>260,000 cases in 1934, highest recorded annual incidences) with ~10,000 deaths. Reduction of pertussis disease was marked following widespread use of DTPwc vaccine, with the fewest number of cases reported in 1976 (1,010). In the early 1980s a steady increase in cases was reported. In the last two years for which data are available, 1999 and 2000, there were 7,288 and 7,867 cases reported, respectively. In 1999, 27% of these occurred in children < 7 months of age, 11% were in children 1-4 years of age and 28% were in children 10-19 years of age. In the pre-vaccination era close to 80% of cases occurred in children 5 years or younger and the shift in epidemiology is thought to be related to waning immunity in an immunized population. Since 1990, the incidence of pertussis among preschool-aged children has not changed, but the incidence among adolescents has increased in some areas (*Clin Inf Dis* 1999; 28:1230-7).

Development of acellular pertussis vaccines was prompted by safety concerns about the DTPwc vaccine. The first DTaP vaccine for use in infants was licensed in 1996 (Tripedia®, manufactured by Aventis Pasteur Inc., Swiftwater, PA). There are currently four DTaP vaccines licensed in the US for use in infants. In addition to Tripedia®, these include Infanrix™, manufactured by Glaxo SmithKline (Philadelphia, PA), ACEL-IMUNE®, manufactured by Wyeth Lederle Vaccines and Pediatrics (Pearl River, NY) and Certiva™ manufactured by Baxter Hyland Immuno Vaccines, Inc. However two of these manufacturers have discontinued production of their DTaP vaccines (Baxter Hyland Immuno Vaccines and Wyeth Lederle Vaccines and Pediatrics). As a result, the CDC issued guidance in March 2001 (MMWR March 16, 2001 / 50(10); 189-190) advising that some vaccine providers may have difficulties obtaining sufficient supplies of DTaP vaccine to vaccinate all children in their practices. The guidance stated that, if providers had insufficient quantities of vaccine, the CDC recommends giving priority to the first three doses and, if necessary, deferring the fourth dose of vaccine. DTaP vaccine is routinely recommended as a five-dose series: three doses given to infants at ages 2, 4,

and 6 months, followed by two doses at age 15-20 months and at age 4-6 years. Of note, Aventis Pasteur Limited is not currently seeking an indication for the 5th dose of DTaP vaccine, which is routinely recommended at 4-6 years of age, with this application.

Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae*. Humans are the only known reservoir and spread is thought to occur by airborne droplets or direct contact with infected secretions or tissues. Symptoms occur in the respiratory tract where the major manifestation is that of a membranous inflammation of the upper respiratory tract and in skin. Cardiac and neurologic complications are not uncommon. In the US, the disease is rare and only a single case was reported in 2000. The recommended schedule for vaccination against diphtheria when given as part of a DTaP combination vaccine is noted above. In the absence of vaccine shortages, booster immunization with a Td vaccine is then routinely recommended at 10 year intervals.

The gram-positive anaerobic spore forming bacillus *Clostridium tetani* produces a toxin that causes tetanus. The organism produces the neurotoxin, tetanospasmin, which causes the clinical manifestations of disease which is divided into four types: generalized, localized, cephalic, and neonatal. Disease is not communicable but is acquired by environmental exposure. The incidence of disease in the US has declined with improved wound care and preventive vaccination. In the year 2000, there were 35 cases of tetanus reported in the US. The recommended schedule for vaccination against tetanus when given as part of DTaP combination vaccines is noted above. In the absence of vaccine shortages, booster immunization with a Td vaccine is then routinely recommended at 10 year intervals.

4.0 Clinical Studies Reviewed

Table 2: Pivotal Clinical Studies in the Product License Application

Study	Study Completion	Vaccine	IND Sponsor	Country	Schedule (months)	# of subjects	Study Objective
Phase IB	1990	CPDT	APL	US	16-20	34	Safety and immunogenicity after whole cell vaccine
	1990	CPDT	Na	Canada	15-18	28	
Phase ID	1991	CPDT	Na	Canada	17-18	30	Safety and immunogenicity after whole cell vaccine
Phase 2	1993/1994	CPDT	Na	Canada	2,4,6	324	Lot consistency
		CPDT			17-18	301	
Phase 2B	1992/1993	CPDT	Na	Canada	2,4,6	34	Safety and immunogenicity, CPDT vs. HCPDT
		CPDT			17-18	28	
Phase 2C	1994	CPDT	Na	Canada	2,4,6	173	Safety and immunogenicity, CPDT vs. HCPDT
		CPDT			17-18	72	
	1993	CPDT	APL	US	2,4,6	118	
	1994	CPDT	Na	France	2,3,4	83	
NIAID Multicenter Pertussis Trials (MAPT), Cycle I	1993/1994	CPDT	NIAID	US	2,4,6	137	Safety and immunogenicity
		CPDT			17-18	75	Safety and immunogenicity
		CPDT			15-18	19	Safety and immunogenicity after whole cell vaccine
Sweden I	1992-5	CPDT	NIAID	Sweden	2,4,6	2,587	Efficacy (absolute*)
Sweden 2 (relative)	1993-6	*HCPDT*	*NIAID*	*Sweden*	*3,5,12 2,4,6*	*18,196 2,549*	*Efficacy (relative)*
US Bridging 470-01	1997	CPDT	APL	US	2,4,6	321	Population and lot bridging

Table 3: Non-Pivotal Clinical Studies in the Product License Application

Phase 1A and 1B	*1990*	*CP4*	*APL*	*USA*	*21-59 yr 16-20 mo*	*15 13*	*Safety and immunogenicity*
Phase 1A	*1990*	*CP3 CP4*	*APL*	*Canada*	*17-18 mo*	*35 33*	*Safety*
Phase 1B	1990	CP3DT CP4DT	APL	Canada	17-18 mo	35 34	Safety
Phase 1E	1991	CPDT	APL	Canada	17-18 mo	35	Safety and immunogenicity
Phase 2B	1991-2	CPDT *HCPDT*	APL	Canada	2,4.6 mo	34	Safety and immunogenicity
Phase 2B	1993	CPDT *HCPDT, DTP*	APL	Canada	17-18 mo	27	Safety and immunogenicity
Phase 2C	n/a	CPDT *HCPDT*	APL	France	2,3,4 mo	80	Safety
PB9301	1993	CPDT	Na	Canada	17-18 mo	50	Safety and immunogenicity,
NIAID Cycle 2	1993	CPDT	NIAID	US	2,4,6 mo	75	Safety and immunogenicity,
PB9401	1994	*HCPDT*	Na	Canada	17-19 mo	425 (all)	Safety and immunogenicity
PB9503	1995	*HCPDT-IPV*	Na	Canada	4-6 years	131	Safety and immunogenicity

5.0 Analysis of Efficacy Against Pertussis

Evidence of protective efficacy of CPDT against pertussis in US infants comes from 3 studies. The Sweden 1 efficacy trial evaluated the efficacy of CPDT in Sweden given at 2, 4, and 6 months of age. The US bridging study compared the immune response of US infants following three doses of CPDT given at 2, 4, and 6 months to that observed in the Sweden I efficacy trial. In addition, the sponsor submitted the results of the Sweden 2 efficacy study in which the relative efficacy of the HCPDT was evaluated. The HCPDT vaccine is related to CPDT in that it contains the same antigens and is manufactured by APL but has higher concentrations of pertussis toxin (PT), and filamentous hemagglutinin (FHA). In the Sweden 2 trial, efficacy was evaluated when the vaccine was given on a 3, 5 and 12 month schedule.

5.1 Sweden I Efficacy Study: Placebo controlled efficacy trial of two acellular pertussis vaccines and of a whole-cell vaccine, a combined three-armed and four-armed study

This study is the pivotal efficacy study of CPDT and was conducted to evaluate efficacy of two acellular pertussis vaccines (DTaP), and a whole-cell pertussis vaccine as compared to a control diphtheria-tetanus toxoid vaccine. The trial was conducted in Sweden where vaccination against pertussis had not been recommended since 1979 because of concerns about the safety and efficacy of whole cell pertussis vaccines. In this study the safety and efficacy of CPDT (Aventis Pasteur, Limited; APL), a two component acellular pertussis vaccine, (DTaP2; SmithKline and Beecham), and a whole cell pertussis vaccine (licensed DTPwc; Aventis Pasteur, Inc; ----), were evaluated.
Location: Sweden (14 sites)
Study Date: March 1992 - January 1995

Investigators: P. Olin, L. Gustafsson, and H.O. Hallander
Study Vaccines:
CPDT: CPDT (Lot-------)
DTaP-2- SmithKline Beecham: 25 mcg PT, 25 mcg FHA, Diphtheria toxoid 17 Lf, Tetanus toxoid 10 Lf.
DTPwc – AP whole cell vaccine: Pertussis 17 protective units, Diphtheria toxoid, 6.65 Lf, Tetanus toxoid, 6.65 Lf
DT - Duplex, NBL: Diphtheria toxoid, 15 Lf, Tetanus toxoid 3.75 Lf
Population: Healthy infants recruited by a letter sent to all parents of newborns in the participating regions.
Eligibility Criteria:
Inclusion criteria:

- Born between January 1 and December 31, 1992.
- Residence within defined study areas at birth.
- Registered at child health centre (CHC).
- Examined by CHC physician/study nurse at 6-8 weeks of age.
- Parental consent.

Exclusion criteria:

- Language difficulties and other circumstances that would interfere with communication and follow-up.
- Planning to move out of the study area within one year, thereby interfering with follow-up.
- Serious chronic illness (with signs of cardiac or renal failure or failure to thrive).
- Progressive neurologic disease.
- Uncontrolled epilepsy/infantile spasms.
- Immunosuppressive therapy, manifest immunosuppression, HIV.
- Previous culture-confirmed pertussis illness.
- > 92 days of age.
- Treatment with gammaglobulin during the first 3 months of life.

Vaccination deferred:

- Fever ≥ 38°C or more.
- On short-term medication.
- Receipt of another vaccination within one week and which was not given simultaneously with study vaccine.
- Antibiotic therapy >3 weeks duration.

Contraindication to the second and third dose:

- Pronounced reaction to the previous dose defined as:
  - Encephalopathy; Seizures with or without fever;
  - Persistent crying for ≥ 3 hrs or more within 24 hours of the dose;
  - Generalized cyanosis within 24 hours of the dose;
  - Fever of ≥ 40°C within 48 hrs of the dose;
  - Generalized allergic reaction within 48 hours of the dose;
  - Shock-like reaction within 48 hrs of the dose (includes HHE)

Events which did not contraindicate participation:

- Down's syndrome.
- Prematurity (healthy babies of low gestational age were to be vaccinated according to their chronological age).
- Recent exposure to pertussis.
- Seizures in a close relative (parent or sibling).
- Anaphylaxis or allergy in a close relative)

Sample size: 9829 (2587 CPDT, 2566 DTaP2, 2574 DT, 2102 DTPwc)

Design: The study was double-blinded, randomized, DT controlled trial. The original trial design was to include the U.S. whole cell vaccine manufactured by Wyeth-Lederle. However, this vaccine was not available at the time the trial was to be initiated. The study was started as a three-arm trial (CPDT, DTaP-2, DT). Two months later the ---- DTPwc vaccine was added as a fourth arm. Separate randomization series were used for the three-armed and four-armed parts of the study.
Initial recruitment was to one of three vaccine: CPDT, DTaP-2 or DT control from March 1992 to April 1992, then to all four vaccines, including the DTPwc vaccine from May 1992 to February 1993.
Schedule: 2, 4 and 6 months

Concomitant Vaccines and Medications: Infants were to receive IPV simultaneously with the study vaccine at 4 and 6 months of age. *Haemophilus influenzae b* conjugate vaccine (HIB) was gradually introduced during the trial. Concurrent vaccinations were to be given either simultaneously with the study vaccine or at least 7 days before or 14 days after any of the study doses.

Monitored Parameters:
Immunogenicity
Serum samples were obtained from a subset of 689 children at one site pre-vaccination and one month post-third dose, and from all children at one year and 2-3 years of age. Antibodies to pertussis toxin (PT), filamentous hemagglutin (FHA), pertactin (PRN), fimbriae 2 and 3 (FIM) and to diphtheria toxin and tetanus toxoid were determined.
Surveillance for pertussis:
Telephone interviews were conducted throughout the study during which parents were asked if the study child or any household member had experienced pertussis or a similar illness since their last contact. These interviews were carried out 14 days after each vaccination, then monthly until the study child was one year old and then every two months until the end of the follow-up period. Additionally, parents were instructed to call the study nurse or physician if the study child had symptoms of an upper respiratory tract illness with a cough of more than seven days duration, if they suspected pertussis in the household. A study physician or nurse examined infants and household members with suspected pertussis. Cough was characterized in terms of duration, spasms, whoops, and vomiting. A nasopharyngeal specimen was obtained for culture and PCR and repeated in one week if the culture was negative. Blood samples on study infants were to be obtained if not more than 14 days had elapsed since the onset of the cough. If a case of pertussis was confirmed by culture, all household members were examined, cultured, and serology was obtained. If secondary cases were documented, follow-up of

the household was to continue for at least 28 days after the last case was diagnosed. Convalescent sera were obtained 6-8 weeks after onset of cough.

Administration of Antibiotics During the Trial: Antibiotic treatment recommendations are not addressed in the study protocol. The technical report states that in Sweden treatment with macrolides is recommended as a prophylactic measure in infants < 6 months of age who are exposed to pertussis and for early treatment of pertussis in the 6-12 month age, and are given less frequently in older age children. If treatment of suspected cases with erythromycin or trimethoprim-sulfamethoxazole occurred, this treatment was documented.

Main Follow-up Period: The day of the third dose was selected as the start date of the main follow-up. The follow-up period for each study child continued until the child developed pertussis, until the termination of the trial (January 8, 1995), or until the last day of contact with the household, if the household left the study during the follow-up period.

Study Objectives:
Primary:
- To estimate the efficacy of acellular pertussis vaccines and whole cell vaccine against typical pertussis as compared to placebo (DT).

Secondary:
- To explore vaccine efficacy using a spectrum of clinical and laboratory measures.
- To explore relative efficacy, specifically to compare the efficacy of the two acellular vaccines.
- To study possible laboratory correlates of protection using sera samples collected at different intervals after vaccination.
- To evaluate the safety of the vaccines.

Pertussis case definitions:
Primary case definition of typical pertussis (WHO criteria):
Twenty-one days or more of spasmodic cough and either culture confirmed *B. pertussis* or serological evidence of *B. pertussis* infection demonstrated by a 100% IgG or IgA antibody rise against FHA or PT in paired sera. Alternatively, if these symptoms were present but serologic and culture data were not available, if there was an epidemiological link to a confirmed cases (i.e. the child was in contact with a case of culture-confirmed *B. pertussis* in the household with onset of cough within 28 days before or after the onset of cough in the study child), then this case met the primary case definition.

Secondary case definitions of pertussis defined as:
- Culture confirmed *B. pertussis* or serological evidence of *B. pertussis* infection demonstrated by a 100% IgG or IgA antibody rise against PT in paired sera or serological evidence of *B. pertussis* infection demonstrated by a 100% IgG or IgA antibody rise against FHA in paired sera, with a positive PCR-test, or in contact with a case of culture-confirmed *B. pertussis* in the household with onset of cough 28 days before onset of cough in the study child

- In an asymptomatic child with 100% rise in IgG or IgA antibody against FHA in paired sera, in contact with a culture-confirmed *B. pertussis* in the household, with onset of cough within 28 days before or after the first two serum samples was taken.
- The following measures of clinical illness were used in combination with the laboratory evidence listed above: cough for ≥1, > 7, ≥ 21, ≥ 30 days, and ≥14, and ≥ 21 days of paroxysmal.

Note: For FHA antibody response in the primary analysis, a significant rise in FHA-antibody alone was regarded as a sign of pertussis only if the child had a paroxysmal cough for 21 days or more and only if the child did not have a positive culture or PCR for *B. parapertussis*.
Culture negative children with significant rises in FHA-antibody only and less than 21 days of coughing spasms were included in the preplanned secondary analysis of efficacy only if other criteria were met (see above).
PCR was included as confirmatory evidence of pertussis to avoid the use of a case definition based on clinical data only and to expand case ascertainment beyond culture and conventional serology. PCR was done on culture negative episodes without significant increase in anti-PT serology with one or more of a) significant serum antibody rise to FHA b) a household exposure to *B. pertussis* c) 21 days or more of paroxysmal cough. Cases confirmed by PCR were included in the preplanned secondary case definitions.

Statistical Analyses: All analyses were performed according to plans outlined in the protocol prior to the unblinding of data.
Efficacy:
Efficacy for the acellular vaccines was calculated for all recipients of three doses using data for all recipients of DTaP or DT (i.e. children from both the three and four-armed part of the trial). Efficacy for the DTPwc vaccine was calculated using data from the four-armed part of the trial.
The true efficacy of all pertussis vaccines studied was assumed to be 80 percent. The null hypothesis to be tested was that the efficacy of the vaccines was 70 percent or less, corresponding to a relative risk (RR) of pertussis of 1.5 or greater for the comparison of the acellular vaccines with the whole-cell vaccine. Hazard ratios obtained by Cox-proportional-hazards regression were used to estimate absolute and relative vaccine efficacy. Person-days estimate of absolute vaccine efficacy (comparison of vaccine to placebo) as well as relative vaccine efficacy (comparison of vaccine to vaccine) were performed. Absolute and relative vaccine estimates of the whole cell vaccine were based on the follow-up from the four-armed trial. Estimates of vaccine efficacy were also calculated for follow up periods beginning 30 days after receipt of the third and for efficacy based on secondary endpoints (less severe disease). Intent to treat analyses (including all children who received at least one dose) of absolute and relative vaccine efficacy were performed using the primary case definition and the secondary case definition of cases with > 7 days cough. Calculations of chi-square, relative risk, and differences of paired proportions with 95% confidence intervals were performed as appropriate.
Immunogenicity: The Kolmogorov-Smirnov two-sample test was used to compare the distributions between groups of IgG antibody levels after vaccination.
Safety: The number of adverse events in each vaccine groups was compared using chi-square test or Fisher exact test.

RESULTS:

Demographics: A total of 9,829 subjects were enrolled in the trial. Families of 14,507 infants eligible for enrollment chose not to participate in the trial. A comparison between these two groups shows no difference in birth dates or sex distributions. The percentage of households with only one child was somewhat higher among participants (44.4% vs. 40.7%) and the percentage of single parents was somewhat higher among the nonparticipants (2.2% vs. 1.4%). Study participation among the twelve sites did vary from 28.2% in Danderyd Stockholm to 55.9% in Jonkoping.

Background information collected on children enrolled in the trial with regard to sex, age, household size, or previous pertussis vaccination in elder siblings revealed no differences in demographics between the trial groups.

Table 4: Demographics of Subject Enrolled in the Sweden I Efficacy Study

Vaccine	Sex (%)		Median age, days, at 1st Dose (95%CI)	Median household Size	% Child care at home only *
	M	F			
DT	51.4	48.6	72 (62-89)	4	29.4
DTaP-2	51.6	48.4	71 (62-89)	4	29.3
CPDT	51.4	48.6	72 (62-88)	4	28.5
DTPwc	51.4	48.6	72 (62-88)	4	28.2
All	51.4	48.6	72 (62-89)	4	31.7

***** Until contact at 2 yrs.

Blinding of vaccine administration:

A questionnaire was administered to parents and study nurses at 14 days after administration of the third vaccine dose in order to assess the blinding of vaccine administration. Results obtained from these questionnaires indicate that while blinding was upheld for the acellular vaccine and placebo groups, this was not the case for the whole cell group. Nurses and parents correctly determined which vaccine was administered in greater than half the whole-cell group. This was felt to be due to a marked rise in reactogenicity following the introduction of the whole-cell vaccine into the trial and to the difficulty in resuspending this vaccine prior to immunization as compared to the other vaccines.

Efficacy:

Among the 9,628 children who received a complete course of three vaccine trial doses, 737 children met the primary case definition of pertussis with at least 21 days of paroxysmal cough and laboratory confirmation and/or epidemiologically linked disease.

Per protocol analysis according to primary case definition: This analysis included all children who had received three doses of trial vaccines and who developed disease that met the primary case definition of pertussis. Subjects with protocol violations were excluded from this analysis at the time of the first protocol violation.

Table 5: Sweden I Efficacy Results, Three and Four Arms Combined

	DTPa2	**CPDT**	Control (DT)
# who received 3 doses	2,487	2,488	2487
Pertussis cases meeting primary case definition	157	58	358
VE% 95% CI	**58.0** 49.3-65.1	**84.9** 80.1-88.6	
RR (DTPa2/DTPa5) 95% CI	2.78 2.06-3.76	1	

Table 6: Sweden I Efficacy Results, Four Armed Study

	DTPa2	**CPDT**	DTPwc	Control (DT)
# rec. 3 doses	2,039	2,013	1,949	2,024
Pertussis cases meeting primary case definition	126	45	141	275
VE% 95% CI	**56.1** 45.8-64.5	**84.6** 78.8-88.7	**48.4** 36.8-57.9	
RR (DTPa2/DTPwc) RR (DTPa5/DTPwc) 95% CI	0.85 0.67-1.08	 0.30 0.21-0.42	1	
RR (DTPa2/DTPa5) 95% CI	2.83 2.02-3.98			

Vaccine efficacy analysis according to the primary case definition: This analysis included all children who received three doses of trial vaccine and who developed disease that met the primary case definition. Cases occurring after protocol violations were not excluded from the analysis. Thus, an additional 16 cases were included in this analysis but the estimates of efficacy did not differ significantly from those obtained in the per protocol analysis. The point estimates and 95% CI for efficacy in the four-armed trial were 57.2% (47.3, 65.3) for DTPa2, 85% (79.5, 89) for CPDT, and 48.3% (37, 57.6) for DTPwc.

Vaccine efficacy estimates for the secondary case definitions:

Efficacy estimates for all three trial vaccines were somewhat higher for severe disease. The combined three and four armed trial analyses for the efficacy of DTPa2 and CPDT did not differ significantly from the four-armed trial analyses. Listed below are the point estimates of efficacy with CI for the secondary case definitions in the four-armed trial.

Table 7: Sweden I Efficacy Trial Estimates of Efficacy for Secondary Endpoints

	DTPa2	DTPa5	DTPwc	DT
Children who got 3 doses and at risk	2,082	2,069	2,001	2,068
Clinical Severity	Cases N **VE%** 95% CI			
Cough ≥ 1day	201 **40.1** 28.5-49.7	83 **76.0** 69.4-81.1	190 **41.2** 29.7-50.9	324
Cough > 7 days	196 **41.6** 30.3-51.1	81 **76.6** 70.1-81.6	189 **41.6** 30.1-51.2	324
Cough ≥ 21 days	156 **52.0** 41.0-60.4	67 **79.9** 73.8-84.5	172 **44.8** 33.5-54.2	312
Cough ≥ 30 days	125 **59.1** 49.6-66.9	42 **86.6** 81.4-90.3	155 **47.0** 35.6-56.4	293
Paroxysmal cough ≥ 14 days	144 **54.8** 44.9-62.9	61 **81.2** 75.3-85.8	159 **47.8** 36.8-56.9	305
Paroxysmal cough ≥ 21 days	129 **57.2** 47.3-65.2	47 **84.7** 79.2-88.8	150 **48.0** 36.6-57.3	290

Efficacy estimates from 30 days after the 3rd dose using the primary case definition
Three and four armed trial combined: efficacy did not differ significantly from those obtained with follow-up beginning at the time of the third dose. The point estimates for efficacy and 95% CIs were: 59.7% (51.3, 66.6) for DTPa2 and 85.0% (80.3, 88.6) for CPDT in the three-arm trial. Efficacy estimates were also similar in the four-armed trial in with point estimates of 58.4% for DTPa2, 84.8% for CPDT, and 48.0% for DTPwc.
Efficacy estimates in the intent to treat analysis using the primary case definition:
This analysis included all randomized children. No significant differences were noted in efficacy in this analysis as compared to the per protocol analysis. The point estimates and 95% CI for the three and four-armed trial combined were 58.8% (50.5, 65.7) for DTPa2 and 84.3% (79.6, 88.0) for CPDT. In the analyses of the four-armed trial, point estimates and 95% CI were 56.8% (47.0, 64.7) for DTPa2, 84.2% (78.7, 88.2) for CPDT, and 48.3% (37.3, 57.3) for DTPwc.
Efficacy estimates in the intent to treat analysis using a case definition of cough >7 days:
Efficacy estimates for all three trial vaccines in these analyses were somewhat lower than in analysis using the primary case definition. Point estimates in the combined three and four armed trials were 44.4% for DTPa2 and 77.7% for CPDT and in the four-armed trial analysis the point estimates were 42.1% for DTPa2%, 76.1% for CPDT, and 40.7% for DTPwc.
Vaccine efficacy over time:
Estimates of vaccine efficacy were also calculated for 90 day intervals from the 3rd dose, up to 810 days following the 3rd dose. Vaccine efficacy at ~85% was maintained for the CPDT group throughout the end of the trial.

Isolation of *B. parapertussis:* There were a total of 50 cases of *B. parapertussis* cases that made up 8.4% of all *Bordetella* isolates. These cases were not included in the efficacy analysis.

Antibiotic use:
Antibiotic usage per episode of suspected pertussis during the trial (macrolides and/or trimethoprim-sulfamethoxazole) was similar across vaccine groups during the first year of life. Antibiotic use declined in the CPDT group following 12 months of age. Antibiotic use in the DT and DTPwc groups appeared higher between 12-24 months than in the CPDT group (e.g. 12 - <18 months: CPDT: 12%, DT: 16%, DTPwc: 18%). The impact of this difference in antibiotic usage between vaccine groups on efficacy, if any, cannot be determined.

Immunogenicity:
Children enrolled from one site (Linkoping), n=689, had sera collected for pre and post-vaccination antibody level determinations. The following results, expressed as geometric mean of ELISA units, were obtained.

Table 8: Sweden I Trial Immunogenicity Results for Pertussis Antigens

	Pre-vaccination	**Post-vaccination**			
		DTPa2	**CPDT**	**DTPwc**	**DT**
Anti-PT IgG					
No. tested	689	186	178	144	181
GMC	**2.99**	**59.98**	**49.43***	**1.88**	**0.98**
(95% CI)	(2.78 – 3.21)	(54.45, 66.1)	(44.77, 54.45)	(1.53, 2.32)	(0.89, 1.09)
Anti-FHA IgG					
No. tested	689	186	178	144	181
GMC	**4.30**	**111.43**	**34.12***	**8.73**	**0.81**
(95% CI)	(3.97, 4.63)	(100.9-123.3)	(30.83-37.76)	(7.36-10.35)	(0.73, 0.90)
Anti-fimbriae OG					
No. tested	688	186	178	144	181
GMC	**5.01**	**0.85**	**350.75**	**15.0**	**0.91**
(95% CI)	(4.41, 5.69)	(0.75-0.96)	(301.3-408.3)	(10.07-22.39)	(0.8-1.04)
Anti-pertactin IgG					
No. tested	688	186	178	144	181
GMC	**1.55**	**0.58**	**116.41**	**12.62**	**0.62**
(95% CI)	(1.41-1.70)	(0.55-0.63)	(102.6-132.1)	(9.86-16.14)	(0.57-0.68)

*The geometric mean units of anti-PT and anti-FHA are significantly lower in the 5-component vaccine arm than in the 2-component vaccine arm ($p < 0.001$ with the Kolmogorov-Smirnow two sample test).

Comment: In this randomized, controlled study CPDT efficacy was 85% (79.5, 89) against WHO defined pertussis disease when given according to US schedule at 2, 4, 6 months of age. Efficacy was also demonstrated for secondary endpoints assessing less severe disease, although at somewhat efficacy rates. Efficacy was observed throughout the duration of the study period (~810 days post dose 3).

5.2 Safety and Immunogenicity in Healthy Infants of Diphtheria and Tetanus Toxoids and Five-Component Acellular Pertussis Vaccine (US Bridging Study).
This study was designed to assess the safety and immunogenicity of five lots of CPDT: Lot ------ (efficacy lot, manufactured at APL, Canada) and Lot ----- (manufactured in 1995 at APL, Canada) and three lots manufactured at ---------- in US children.

The purpose of the study was 1) To bridge of the results of the Sweden I efficacy study (in which Lot ----- was administered) to US children 2) To assess the immunogenicity of the more recently manufactured Lot ------ – a recently manufactured lot at the APL facility at the time of the study 3) To assess the safety and immunogenicity of three lots manufactured at the ---------- for a possible transfer of technology and 4) To assess the safety and immunogenicity of other routinely recommended childhood vaccines when administered concomitantly with CPDT.
The sponsor provided an interim report that includes the immunogenicity and safety analysis of lots ---- and ----- in a June 24, 1999 submission to the PLA. The immunogenicity comparison in the Sweden I trial was accomplished by testing serum samples from the efficacy trial in parallel with the US samples using a newly validated assay for pertussis antibody responses. The report from this analysis was submitted to the PLA in September 1999.
Location: USA
Study Date: 20 November 1995 – 14 March 1997
Investigators: W. Andrews, MD, Marietta, GA; Gerald Bader, MD, Vancouver, WA; Stephen Chartrand, MD, Omaha, NE; Kathy Edwards, MD, Nashville, TN; Terry Jefferson, MD, Little Rock, AR; Michael Pichichero, Rochester, NY; Margaret Rennels, MD, Baltimore, MD.
Lot Numbers: Lots ---------- (----- manufactured lots), Lot ------ (Swedish efficacy lot, ----), Lot ----- (-----).
Study Objectives:

- To compare the safety and immunogenicity of three consecutive lots manufactured at ---- (------- to two lots manufactured at APL (---- and ----).
- To bridge study of the Stockholm I efficacy study to the US population.
- To assess the safety and immunogenicity of CPDT with the concomitant administration of routine childhood immunizations.

Population: Healthy children 6 -12 weeks of age.
Sample size: 321 (lot ----=161; lot ----=160)
Design: Double blind, randomized, active control study. Vaccines were given at 2, 4, 6 months of age. Sera were collected pre-vaccination and 4-6 weeks post vaccination.
Study Conduct: There were 161 subjects randomized to Lot ---- and 160 to lot ------. For the immunogenicity analysis, thirty-three subjects did not complete the study per protocol in the ---- lot and 26 in the ---- lot. Most of these were due to missing the allowable window for the post-dose three blood draw (mostly blood drawn outside the windows).

Concomitant Vaccines and Medications:
Routine pediatric immunizations (Polio, HepB and Hib) were to be administered according to standard immunization practices. PRT-T (OmniHib) was the *H. influenzae* conjugate vaccine used most frequently in this trial. Hepatitis vaccine was not required to be given according to a particular schedule and the manufacturer was not specified. Concomitant medications on days 0-3 post-vaccination were to be recorded on the case report form (CRF).

Serologic monitoring (see above) Serum samples were collected pre-vaccination and 4-6 weeks after the third dose.

Demographics: The participants in the ---- and ---- groups had similar demographics. The mean age at entry, overall, was 8.5 weeks, 51.1% were male, 94.1% were Caucasian, 1.9% African American, 1.6 percent Asian.

Immunogenicity Results:
Pertussis Antigens:
Antibodies to pertussis antibodies were assayed twice. Sera from the US study were initially assayed at APL using assays that were not adequately validated. Subsequently, as part of the US bridging study (USBS), samples were assayed at APL, using validated assays, side by side with stored samples from the Swedish I efficacy trial. However, approximately 20% of samples did not have sufficient serum left for these second measurements of antibody levels.

Results from USBS (validated assays):
All sera (ITT) population – This population included any subject who had received all three doses of CPDT vaccine. All available sera regardless of vaccine or adherence to blood sample time windows were included in this dataset.
Paired sera only subpopulation - Included only children for whom pre and post-vaccination serum samples were available.
Sample Size Considerations – Data from the Sweden I trial were used to estimate the power for the statistical analysis planned in this project. The results from the Sweden I trial had shown that the standard deviations of log titers were between 0.7 and 1.4. The largest standard deviation, 1.4, was used in the sample size consideration. The evaluation criteria for comparing the GMCs between two groups was defined using the two-sided equivalence approach of the ratio of GMCs. The consistency boundaries for the GMCs were set at 0.5 and 2. Two groups were considered consistent with respect to a particular antibody response if the 90% confidence interval for the ratio of GMCs was within these boundaries (i.e., the lower limit of the 90% confidence interval was greater than 0.5 and the upper limit was less than 2).
For paired samples, the 4-fold rises in antibody rates are summarized by lot and pertussis antibody. The 90% confidence intervals on the difference between the rates in two groups were calculated for each antibody.

Table 9: USBS Pre-Immunization Pertussis Antibody Titers
GMCs and Comparisons for all Available Sera

	SW Lot -- N=83		US Lot -- N=111		US Lot -- N=122		US Lot -- vs. -- Lot --	US Lot -- vs. US Lot --
	N	GMC	N	GMC	N	GMC	Ratio of GMCs and 90% CIs	Ratio of GMCs and 90% CIs
PT	76	5.76	109	4.42	120	4.59	0.77 (.62, .95)	1.04 (.87, 1.24)
FHA	76	7.36	110	5.82	121	7.39	0.79 (.62, 1.00)	1.27 (1.01, 1.6)
FIM	50	16.05	107	14.73	119	16.11	0.92 (.72, 1.16)	1.09 (.9, 1.32)
PRN	61	2.53	106	3.93	111	4.14	1.55 (1.21,1.99)	1.05 (.82, 1.36)

CI: 90% Confidence Interval on Ratio of GMCs
*CI is out of the consistency boundaries (0.5, 2)

Table 10: Post-Immunization Pertussis Antibody Titers – GMCs and Comparisons for all available sera

	SW Lot - N=83		US Lot -- N=107		US Lot -- N=108		US Lot -- vs. SW Lot --	US Lot -- vs. US Lot --
	N	GMC	N	GMC	N	GMC	Ratio of GMCs (90% CIs)	Ratio of GMCs and CIs
PT	83	72.61	107	89.05	108	62.54	1.23 (1.01,1.49)	.7 (.6, .83)
FHA	83	43.17	107	42.51	108	47.85	.98 (.84, 1.16)	1.13 (.96, 1.32)
FIM	83	323.9	106	376.0	107	303.2	1.16 (.91, 1.49)	.81 (.65, 1.0)
PRN	**83**	**121.21**	**107**	**65.65**	**108**	**47.14**	**.54 (.43, .69)***	**.72 (.54, .95)**

CI: 90% Confidence Interval on Ratio of GMCs

*CI is out of the consistency boundaries (0.5, 2)

All titers are expressed as EU/ml

Results of GMCs for paired sera were similar to ITT analysis.

Table 11: USBS Four-Fold Pertussis Antibody Rates

	Sweden I		US Bridging				Comparisons					
	Lot --		Lot --		Lot --		US Lot -- vs. SW Lot --			US Lot -- vs. Lot --		
	N	%	N	%	N	%	Diff in %	Lower CI	Upper CI	Diff in %	Lower CI	Upper CI
PT	76	82.9	82	89	86	87.2	6.1	-3	15.2	-1.8	-10	6.4
FHA	76	63.2	83	63.9	87	60.9	.7	-11.9	13.3	-2.9	-15.2	9.3
FIM	50	84	79	84.8	85	83.5	.8	-10	11.6	-1.3	-10.7	8.1
PRN	**61**	**96.7**	**80**	**72.6**	**79**	**67.1**	**-24.2**	**-33.2**	**-15.2**	**-5.4**	**-17.4**	**6.5**

*CI: 90% Confidence Interval

Table 12: USBS Pertussis Antibody GMCs with initial assay of sera using the not validated assay.

	Antibody GMC				4-fold Increases			
	US Lot --		US Lot --		US Lot --		US Lot --	
	N	GMC	N	GMC	N	%	N	%
PT	126	62.43	133	48.96	119	89.1	128	86.7
FHA	126	41.65	133	44.91	121	62.8	130	58.5
FIM	126	323.9	133	213.46	120	83.3	130	81.5
PRN	**126**	**37.65**	**133**	**24.34**	**121**	**67.8**	**130**	**62.3**

Further information provided to the FDA on 3/21/2000 revealed that, in the initial assay, the point estimate for the PRN GMC ratio (Lot ----/ Lot ----) for all samples tested initially was 1.6, the point estimate of this ratio for samples that were rested was 1.36, and the point estimate for those samples that were not re-tested was 2.4. Thus, the difference in PRN antibody levels between the lots apparent in the USBS using validated assay may have been larger had all samples been re-tested.

The sponsor provided the following additional information regarding percent of infants who had PRN antibody concentrations < 5, 10, 20, and 50 EU/mL 1 month after Dose 3, indicating that a substantial number of infants in the USBS had PRN levels below 20 EU/mL.

Table 13: USBS Percent of Infants Achieving Various EU/mL Levels of PRN Abs

Study	Vaccine	N	%<5 EU/mL	%<10 EU/mL	%<20 EU/mL	%<50 EU/mL	%≥50 EU/mL
Sweden I	----	83	0.0	0.0	0.0	9.6	90.4
USBS	----	107	4.7	10.3	16.8	34.6	65.4
	----	108	7.4	13.9	22.2	41.7	58.3

Comment: In the USBS, lower antibody levels of PRN were noted following 3 doses of CPDT at 2, 4, 6 months of age as compared to levels observed in Sweden Trial I. This was noted in the vaccine group that received the efficacy lot (Lot ---- – used in Sweden I trial) and, to an even greater degree, in the vaccine group that received a more recently manufactured lot (Lot ----). The study conduct, results, and interpretation are complicated by the fact that sera were assayed twice, once in an assay that was not adequately validated. Subsequently the sera with sufficient remaining volume were reanalyzed in a validated assay along side sera from Sweden Trial I. While ~167 subjects were enrolled in each of the USBS vaccine groups, sera were only available from 107 and 108 subjects/group. Of the 178 sera from Sweden I, 83 samples were available for this bridging study. GMC results for FIM and PRN were similar in the ------- assay of the 178 samples and the APL assay of the subset of ~80 samples. PT and, to a lesser extent, FHA GMCs were higher in the in APL assay of the subset of ~80 samples.

5.3 Sweden 2 Efficacy Trial: A comparison of the relative risk of pertussis in recipients of acellular pertussis vaccines and of a whole-cell vaccine (Pertussis Vaccine Efficacy Trial 2).

Background and Rationale:

The Pertussis Vaccine Efficacy Trial 2 conducted in Sweden was designed to obtain an estimate of the relative efficacy of three acellular pertussis vaccines compared to a whole-cell pertussis. The study was conducted prior to introduction of the acellular pertussis vaccines into the general population.

One of acellular pertussis vaccines included in this study was APL's "hybrid" vaccine (HCPDT). This vaccine contains the same antigens as CPDT ("classic formulation"), but the PT and FHA components are present in higher concentrations. Specifically, the vaccine contains twice the amount of PT and four times the amount of FHA (see below). Trial 2 was to start after completion of enrollment into Trial I, if the vaccines being tested in Trial I showed acceptable safety profiles.

The large sample size needed to compare relative efficacy of vaccines allowed for only simplified surveillance for disease and adverse events. In such a trial design, vaccines would be tested in a "field setting" which would more closely approximate conditions present in a post-marketing phase. Parents' reports of pertussis would be used to validate estimates of relative risk of pertussis based on culture confirmed typical pertussis. The larger sample size would allow for a better comparison of rare SAEs between whole cell recipients and recipients of acellular vaccines.

The main aims of the study, then, were to estimate the protection of the acellular pertussis vaccines as compared to the whole-cell preparations against typical culture-confirmed pertussis, against all culture-confirmed disease and against parentally reported pertussis, as well as to evaluate the safety of the vaccines.

Location: Sweden

Study Date: September 1993 – October 1996

Investigators: P. Olin, L. Gustafsson, F. Rasmussen, H. Hallander, H. Heijbel, P. Gottfarb.

Study Vaccines:
HCPDT (APL hybrid acellular pertussis vaccine) Lot Number:-------; PT, 20 μg FHA, 20 μg, 69 kDa Pertactin, 3 μg Fimbriae 2 and 3/6, 5 μg Diphtheria toxoid 30 IU, 15 Lf Tetanus toxoid, 40 IU, 5 LF 2-phenoxyethanol, 0.61% v/v Aluminum phosphate, 1.5 mg Glutaraldehyde, 0.1%.
DTaP-2- SmithKline Beecham: 25 mcg PT, 25 mcg FHA, Diphtheria toxoid 17 Lf, Tetanus toxoid 10 Lf.
DTaP-3 Biocine-Sclavo PT-9K/129G, 5 μg FHA, 2.5 μg 69 kDa Pertactin, 2.5 μg Diphtheria toxoid, 25 Lf Tetanus toxoid, 10 Lf, Thimerosal, ~0.01% v/v Aluminum hydroxide, ~1 mg.
DTPwc – Pertussis 4 IU, Diphtheria toxoid, 30 IU, 32.5 Lf, Tetanus toxoid, 60 IU, 4.4 LF, Thimerosal, 0.01% w/v, Aluminum phosphate, 0.6 mg aluminum/dose.
Population: Infants born after June 1, 1993 born in designated counties and registered at child health centers (CHC) were eligible for enrollment. Healthy infants were recruited by a letter sent to all parents of newborns in the participating regions.
The study was performed in most counties in Sweden. Gothenburg and surrounding counties, where other pertussis vaccine trials were carried out, did not participate. The vaccines were mainly administered at 3, 5, and 12 months of age according to the Swedish vaccination schedule for DT, IPV and Hib vaccine. Only four areas in the south of Sweden, Malmo, Malmohus County S, Malhomus County N, and Kristianstad County V, a 2, 4, 6 month schedule was used to bridge to Trial I.
Eligibility Criteria:
Inclusion criteria:

- Born between June 1, 1993 and May 31, 1994 (in Malmo and Malmohus County until June 30, 1994).
- Registered at a CHC within the defined study regions at the time of the first vaccination.
- Residing within defined study areas
- Age of 1st vaccination at least 8 weeks, and not more than 6 months.
- Examined by a CHC physician after 4 weeks of age.
- Verbal informed consent from parents.

Exclusion criteria:

- Parental language difficulties and other circumstances that could interfere with communication and follow-up
- Planned move from study area within one year, if the move would interfere with follow-up
- Received a dose of DT vaccine.
- Known or suspected:
  - Serious chronic illness (with signs of cardiac or renal failure, failure to thrive, or immunosuppressive therapy, manifest immunosuppression, HIV).
  - Progressive neurologic disease.
- Uncontrolled epilepsy/infantile spasms.
- Previous culture-confirmed pertussis illness.
- The first dose was not to be given later > 92 days of age.

Vaccination deferred:

- Fever of ≥ 38°C.
- Other vaccination (i.e. polio of Hib) given within one week and not given simultaneously.

Contraindication to the second and third dose:

- Pronounced reaction to the previous dose defined as:
  - Severe neurologic symptoms (within 72 hours of the dose)
  - Rectal fever of 40.5°C or more (within 24 hours of the dose)
  - Systemic allergic reactions (within 48 hours of the dose)
  - Shock-like reaction, including HHE (within 48 hours of the dose)
  - Seizures, with or without fever
  - Received DT vaccine since the previous vaccination

Events which did not contraindicate participation:

- Down's syndrome.
- Prematurity (healthy babies of low gestational age are to be vaccinated according to their chronological age).
- Recent exposure to pertussis.
- Seizures in a close relative.
- SIDS in a sibling.
- Anaphylaxis or allergy in a close relative.
- Strong reaction to vaccination in a close relative.

Sample size: 82,892 (20,747 HCPDT; 20,697 DTaP-2, 20,728 DTaP-3, 20,720 DTPwc)

Design: Multicenter, double blind randomized study.

Schedule: Vaccines were given at 3, 5 and 12 months of age (2, 4, 6 months in some counties). The first dose was not to be given prior to 8 weeks of age or after 6 months of age. The recommended interval between dose 1 and 2 (for most children) was 8 weeks and 7 months between the 2nd and 3rd dose. Dose 2 and 3 could be deferred as long as the interval between doses was at least 4 weeks and all three doses had been given by 18 months of age.

Randomization: Subjects are assigned to one of four vaccine groups by means of a computer generated randomization schemes. The proportion within blocks is 1:1:1:1 and the size of the blocks was not known to the investigators. Vaccine vials were labeled with the unique randomization number, which was also the study number for each study child.

Concomitant Vaccines and Medications: Vaccinations were given IM on the venterolateral side of the thighs. A 0.6 x 25 mm needle was recommended. Infants received IPV and Hib vaccine simultaneously at 3, 5, and 12 months of age. If they were not given simultaneously, they were to be given at least one week before or two weeks after any of the study doses. It was recommended that IPV (SBL-vaccinAB) and Act-HIB (PMC) be mixed in the same syringe and given intramuscularly in the opposite limb. In study groups who received DTP vaccines at 2, 4, and 6 months of age, IPV and Act-HIB was to be given at 2, 4 and 12 months of age.

Monitored Parameters:

Immunogenicity:

Serum was to be collected from all infants residing in defined geographic areas within three study sites. The following parameters were to be studied: 1) the antibody

responses one month after the third dose and 2) the decline of antibodies 6 months after the 3rd dose (given at 6 months of age and 12 months of age) and 3) the antibody response at seven months of age after two doses and three doses (2, 4, 6 month schedule and 3, 5, 12 month schedule).
Samples sizes for the serology subset were based on the following calculations: 80% power (α=0.05, β=0.02) to demonstrate an approximate 50% difference in GMC of the anti-PT post-vaccination levels between vaccine groups. The proportion of incomplete paired samples was expected to be 5% and the percent with very high titers due to boosting from subclinical exposures was expected to be between 7.5 and 15 % for the 7, 13, and 19 months of age. Analyses were to be done with and without outlier samples.

Table 14: **Sweden Trial 2, Schedule for Collecting Serum Samples**

	2 months	3 months	7 months	13 months	19 months
Pre samples	Pre a 306	Pre s 531			
Post-dose 3			Post s 2 = 276 Post d 3 = 307	Post s 3 =237	
6 months post-dose 3				Late a 3 = 198	Late s 3 = 238

a = 2, 4, 6 month schedule; s= 3, 5, 12 month schedule. Measurements of IgG and anti-PT, anti-FHA, anti-pertactin, anti-2, 3 fimbriae, IgG anti-diphtheria toxin, and anti-tetanus toxin were done by ---------

Surveillance for pertussis:
Parents were made aware of the importance of getting laboratory verification of suspected cases of pertussis through letters and educational leaflets. Pediatricians and primary care physicians were encouraged to collect nasopharyngeal specimens when pertussis was suspected in children born after 1 June 1993.
Reports of positive cultures for *B. pertussis* in the routine surveillance system at the ---------- were matched with the file of study children through a computerized system. The file of cases of laboratory confirmed pertussis at ------- was updated daily and linked daily to the Trial 2 file containing data of study children. In the event of a match, a study nurse contacted the family for clinical follow-up. The onset of cough and of cough with spasms and whoops was documented. The course of the illness was followed until the end of daily coughing spasms or the end of daily coughing, whichever came first.
At the time of the MMR vaccination (18 months of age), the parents were asked if the child had had a whooping cough illness since the last trial dose and, if so, when. In October 1996 at the end of the follow-up period, the parents in the three still blinded vaccine groups were contacted by letter with a question about whooping cough during the entire study period.
Serologic confirmation of cases was not attempted and cases with adequate serologic documentation without positive cultures were not included in the primary or secondary case definitions.

Main Follow-up Period: Follow-up: For the per protocol analysis, follow-up began at the time of receipt of the 3rd dose. The follow-up ended at a) day of onset of cough in cases; b) October 1996 in non-cases for primary analyses of efficacy [comparison of two remaining acellular pertussis groups to DTPwc – see below]; c) last day of follow-up contact in households that left the study.

End Points:

Primary:

To estimate protection of acellular pertussis vaccines against typical culture-confirmed pertussis as compared with a whole-cell vaccine. Typical pertussis disease was defined as 21 days or more or spasmodic cough and culture confirmed pertussis.

Secondary:

1. To estimate the relative protection against pertussis, as reported by parents, of acellular pertussis vaccines as compared with a whole-cell vaccine.
2. To estimate the relative protection against all culture-confirmed pertussis.

   Separate estimates of relative protection are presented for follow-up from 12 months of age and from six months of age, and for the entire follow-up from the first dose and from the second and third doses in the trial. Separate estimates were also calculated for recipients of three doses at 3, 5, and 12 months of age and at 2, 4, and 6 months of age.

3. To evaluate the safety of the vaccines with regard to serious adverse events.
4. To evaluate the immunogenicity of the vaccines as measured in a subset of recipients. Sera in this subset were collected pre-vaccination, at 7 months, 13 months and 19 months of age.

Pertussis case definitions:

Primary:

a) Culture confirmed B. pertussis and twenty-one days or more of spasmodic cough (WHO criteria).

b) Culture confirmed B. pertussis regardless of symptoms.

Secondary:

a) The set of clinical definitions used in Trial I (≥ 1 day of cough, > 7 day of cough, ≥ 14 day of cough, ≥ 21 day of cough, ≥ 14 days of paroxysmal cough, ≥ 21 days of paroxysmal cough).

b) Parental report of whooping cough
   - Yes, certain
   - All yes answers

Statistical Analyses:

Efficacy: The Hazards (Cox) Regression method was used for estimation of RR. The 95% CI were calculated along with point estimates. For each of the acellular vaccines compared to the whole cell vaccine, the null hypothesis that the true relative risk of pertussis is equal to or greater that 1.5 was tested against the alternative that the true relative risk is less than 1.5. Approximately 330-380 cases would be needed to have 80% power to reject the null hypothesis of a relative risk of 1.5% against the alternative – an equal risk of pertussis in acellular and whole-cell vaccine recipients. The following assumptions were made in determining sample size: 1) During the assumed enrollment period of 12 months, there would be an expected 106,000 newborns in the study regions and a predicted enrollment rate of 65%, or 68,000 subjects to be randomized into four separate groups; 2) The duration of follow-up from 12 months of age corresponding to the time for the 3rd dose of vaccine, until the end of follow-up would be 15 months. 3) The risk of disease in unvaccinated infants in 12 months of follow-up was 2.2%; 4) The true vaccine efficacy of the whole-cell vaccine was 80%. 5) The true risk for pertussis is the same for the acellular vaccines and the whole cell vaccines.

Separate estimates of RR were to be calculated for secondary analyses of efficacy (see below)

RESULTS:

Table 15: Sweden 2 Efficacy Trial Demographics (Gender):

		All (%)	DTaP2 (%)	DTaP3 (%)	HCPDT (%)	DTPwc (%)
Sex	M	51.0	51.0	51.2	51.0	50.8
	F	49.0	49.0	48.8	49.0	49.2

The median age at enrollment for the 2, 4, 6 month vaccine schedule was 69 days for all groups and for the 3, 5, 12 month schedule was 96 days. Background information collected on children enrolled in the trial with regard to sex, age, household size, or previous pertussis vaccination in older siblings revealed no differences in demographics between the trial groups.

Total enrolled: 82,864 of a total of 100,471 eligible subjects enrolled. The enrollment rate varied between study sites. The overall participation rate was 82% of the eligible population and varied from 74% in Vastmanland to 90% in Gotland. Reasons for nonparticipation were not recorded.

Study conduct: There were 1024 protocol violations in 914 children or 1.1% of the enrolled children. The number of infants by vaccine groups with protocol violations were as follows:
SKB DTaP2 = 142; Biocine DTaP3 = 137; PMC HCPDT = 108; DTPwc = 129. The most frequent protocol violations were: Dose 2 or 3 given at > 18 months of age (n = 381); Dose 1 given at > 6 months of age (n = 153) and parent did not sign vaccination record form at dose 1 (n = 139). Protocol violations were evenly distributed among the vaccine groups.

Efficacy:
Results of Trial I in Sweden revealed that the efficacy of the SKB-2 component DTaP vaccine had lower than expected efficacy (58.0%, 95%CI 45.8, 64.5), and results from both Trial I and the Italian efficacy trial revealed that the whole-cell vaccine used in those studies had very low efficacy when given at 2, 4 and 6 months of age.
As a result of the poor efficacy results of the 2-component vaccine, recipients of this vaccine in Trial 2 were offered a booster dose of the SKB-3 component DTaP in the fall of 1995 and an interim analysis of efficacy was performed to ascertain if the efficacy of the DTPwc vaccine given in Trial 2 was acceptable. The interim analysis was carried out by the DSMB in March 1996 and continuation of the trial was recommended.
The number of culture confirmed cases in Trial 2 was lower than expected and efforts were made to increase the detection rate of cases by newsletters to primary care and laboratory personnel. A letter was sent to the parent with an offer of free visits to doctors "if a pertussis culture was taken". However, the number of cases in the three still blinded groups continued to be low, almost half of the cases occurred in the unblinded 2-component group. These findings indicated that the blinded vaccines were highly efficacious. Thus, in August 1996 the DSMB recommended the trial be terminated in fall 1996**.**

Per protocol analysis of efficacy, according to the two primary case definitions: There were two primary case definitions: culture confirmed cases with cases with $\geq$ 21 days of paroxysmal cough and all culture confirmed cases. Relative risks (RR) of disease were

calculated using the DTPwc vaccine group as a reference. Follow-up was from Dose 3 until 7 October 1996 for children assigned to the 3, 5, and 12- month schedule. Mean follow-up after Dose 3 was 22 months. There were 94 culture-confirmed cases of pertussis, 49 of which were associated with ≥ 21 days of paroxysmal cough, among the 52,818 children with a completed vaccination series according to the 3, 5, and 12 month-schedule. Subjects with protocol violations were excluded from the analysis.

Table 16: Efficacy Results From Sweden 2 Efficacy Trial ATP Analysis

	HCPDT	**Chiron DTaP-3**	**DTPwc**
Children who got 3 doses Person days of f/u	17,509 11,515,719	17,463 11,538,640	17,261 11,374,282
# of culture confirmed cases			
With or without cough	26	49	19
≥ 21 days of paroxysmal cough	13	21	15
RR **95% confidence interval**			
With or without cough	**1.35** (0.75-**2.43**)	**2.55** (1.5-4.33)	**1**
≥ 21 days of paroxysmal cough	**0.85** (0.41-**1.79**)	**1.38** (0.71-2.69)	**1**

Based on the upper limits of the CIs above (2.43 and 1.79) for HCPDT, it is clear that the null hypothesis of a RR greater than 1.5 cannot be rejected for either case definition. The ITT results below, yielding upper confidence limits of 1.75 and 1.89, are consistent with these findings. Clearly, the trial did not achieve its desired goal of demonstrating the alternative hypothesis.

Vaccine efficacy analysis according to the primary case definition: This analysis included all children who received three doses of trial vaccine and who developed disease which met the primary case definition. Cases occurring after protocol violations were not excluded from the analysis. RR calculations for the HCPDT group were unchanged although one additional case in "with or without cough" was included. For the DTaP-3 group RR for the "with or without cough" was 2.55 (95%CI, 1.5-4.33) and in the "≥ 21 days of paroxysmal cough" analysis was 1.39 (0.71-2.69).

Intent to treat analysis of efficacy: This analysis included all children randomized who received their first dose of vaccine. Follow-up continued until 7 October 1996. The results of this analysis were similar as the results as the ATP analysis. For all cases of culture confirmed pertussis there were 79 cases in the HCPDT group vs. 50 cases in the DTPwc group (RR 1.25; 95%CI 0.9-1.75); For cases of culture confirmed pertussis with ≥ 21 day of paroxysmal cough there were 50 cases in the HCPDT group vs. 40 cases in the DTPwc group (RR 1.25; 95%CI 0.82-1.89)

Intent to Treat Analysis of Vaccine efficacy using the SKB DTaP-2 vaccine as a control: Following release of result from Trial I, a decision was made to unblind the SKB 2-component group. This was done on 29 July 1995, and almost half the cases of culture confirmed pertussis cases were in the DTaP-2-component group. As a result, a 2nd analysis of efficacy was performed, using follow-up until 29 July 1995, in which the SKB DTaP-2-component group was used as a control. The analysis included all children who received at least one dose of vaccine according to 3, 5, 12 month schedule.

Table 17: Sweden 2 Trial Estimates with SKB DTaP-2 Vaccine Group as Control Arm

	SKB DTaP-2	**HCPDT DTaP-5**	**Chiron DTaP-3**	**DTPwc**
Children who got 3 doses Person days of f/u	18,138 9,075,582	18,183 9,114,455	18,175 9,097,731	18,159 9,116,739
# of culture confirmed cases				
With or without cough	145	56	82	45
≥ 21 days of paroxysmal cough	99	38	50	26
RR **95% confidence interval**				
With or without cough	1	0.38 (0.28-0.52)	0.56 (0.43-0.74)	0.31 (0.22-0.43)
≥ 21 days of paroxysmal cough	1	0.38 (0.26-0.56)	0.50 (0.36-0.71)	0.26 (0.17-0.40)

Intent to Treat Analysis of Vaccine efficacy using the SKB DTaP-2 vaccine as a control with follow up beginning 30 days after Dose 3: A 2nd analysis of efficacy was performed, using follow-up beginning 30 days post-dose 3 and ending 29 July 1995, in which the SKB DTaP-2-component group was used as a control. The analysis included all children who received at least one dose of vaccine according to 3, 5, 12 month schedule. Results indicate that for all groups, the majority of cases occurred within the first 30 days post-vaccination. In the DTaP-2 group there were 31 cases of culture confirmed pertussis, 14 with ≥ 21 days of paroxysmal cough, for the HCPDT group there were 5 (all cases, RR 0.16, 95%CI 0.06- 0.41) and 3 cases (≥ 21 days paroxysmal cough, RR 0.21, 95%CI 0.06, 0.74) and for the DTPwc group there were 2 cases, RR 0.06 0.02-0.27), 1 with ≥ 21 days paroxysmal cough (0.07, 95%CI 0.01, 0.55).

Efficacy Between Dose 2 and Dose 3: An efficacy analysis for the time period between dose 2 and 3, for the two primary case definitions of culture-confirmed pertussis cases was performed. Relative risk estimates were calculated using the SKB DTaP-2 vaccine group as a comparison.

Table 18: Sweden 2 Trial Efficacy Estimates for Time Period Between Doses 2 and 3

	SKB DTaP-2	**HCPDT DTaP-5**	**Chiron DTaP-3**	**DTPwc**
Children who got 3 doses Person days of f/u	17,898 3,832,794	17, 952 3,838,465	17,940 3,825,626	17,794 3,825,286
# of culture confirmed cases				
With or without cough	71	16	37	19
≥ 21 days of paroxysmal cough	55	10	22	7
RR **95% confidence interval**				
With or without cough	1	0.22 (0.13-0.39)	0.52 (0.35-0.77)	0.27 (0.16-0.45)
≥ 21 days of paroxysmal cough	1	0.18 (0.09-0.36)	0.40 (0.24-0.66)	0.13 (0.06-0.28-)

Vaccine efficacy over time: The incidence of cultured confirmed pertussis per million person days was calculated for 6-month intervals starting at the time of third dose. The incidence for all cases and for cases with ≥21 days, was 2.2 and 0.94 respectively of the 0 - < 6 month time period; 1.26 and 0.63 for the 6 - < 12 month post -dose 3 time period; 2.6 and 1.3 for the 12 to < 18 month period and 3.7 and 1.86 for the ≥ 18 month time period.

Vaccine efficacy for cases of pertussis of varying degree of severity: relative risk estimates for culture confirmed pertussis according to varying severity was compared to the SKB DTaP-2 groups was calculated for the other vaccine groups. These analyses included children who received vaccine on the 3, 5, and 12-month schedule. Follow-up was from Dose 3 through 28 July 1995. The RR risks estimates group along with 95% CI for:

≥ 1 day of cough: HCPDT: 0.21 (0.1, 0.46); DTPwc: 0.08 (0.03, 0.26)
> 7 day cough: HCPDT: 0.23 (0.1, 0.49); DTPwc: 0.09 (0.03, 0.28)
≥ 14 days of cough: HCPDT: 0.22 (0.1, 0.51); DTPwc: 0.1 (0.03, 0.32)
≥ 21 days of cough: HCPDT: 0.25 (0.1, 0.6); DTPwc: 0.08 (0.02, 0.36)
≥ 30 days of cough: HCPDT: 0.42 (0.16, 1.10); DTPwc: 0.14 (0.03, 0.63)
≥ 14 days of paroxysmal cough: HCPDT 0.27 (0.11, 0.67); DTPwc: 0.09 (0.02, 0.39)
≥ 21 days of paroxysmal cough: HCPDT 0.25 (0.08, 0.74); DTPwc: 0.13 (0.03, 0.55)

Analysis of whooping cough according to parents in 18-month questionnaires: Relative risk estimates were calculated based on the proportion of parents who answered, "Yes" to the 18- month questionnaire in response to the question "has your child had whooping cough?" This analysis included children who received vaccine according to the 3, 5, and 12-month schedule and was based on a comparison to the SKB DTaP-2 group. The analysis included all children who received at least one dose of vaccine. Follow-up continued through 28 July 1995.
There were 293 parental reports in the DTaP-2 group, 160 in the HCPDT group (RR 0.54, 95%CI: 0.45-0.66) and 166 cases in the DTPwc group (RR 0.57, 0.47-0.68).

Non-randomized comparisons of 2, 4, 6 and 3, 5, 12 months schedules for HCPDT: RR estimates were calculated comparing the rates of pertussis at in the groups receiving vaccine at 2, 4, and 6 months to the group receiving vaccine at 3, 5, 12 months. However, the two-vaccination schedules used in the trial were implemented in different geographic areas.

The incidence of culture-confirmed pertussis in both study areas declined during the trial from 1993 to 1996. There was very little difference in the incidence between the areas in 1993 and 1995. Areas in which vaccine was given according to the 3, 5, and 12-month schedule had a higher incidence in 1994 and 1996. Follow-up began at receipt of dose 1 until October 7, 1996. The incidence in the 2, 4, 6 group was 5.39 per million days of follow-up and 4.65 in the 3, 5, 12 month group (RR 0.86, 95%CI 0.47, 153). Because this analysis was performed among non-randomized groups in geographically different areas, it is difficult to draw conclusions from the analysis.

Antibiotic use: was not recorded in Trial 2

Culture confirmed pertussis, possible misclassifications

Bias due to differential sensitivity in detecting pertussis by culture is a potential problem in vaccine trials, particularly in placebo-controlled trials where pertussis is more easily cultured from placebo recipients than from vaccine recipients. This potential source of bias should be less of a problem in vaccine-vaccine comparisons. However, in Trial I, culture detected 56% of pertussis meeting the WHO-criteria in the 2-component group but only 42% of the cases in the CPDT group.

Immunogenicity

Table 19: Sweden 2 Efficacy Trial Pre-vaccination Pertussis Antibody GMCs (all groups combined)

IgG Antibody	Schedule	GMC	95% CI
Anti-PT	2,4,6	2.86	2.53-3.24
	3,5,12	2.04	1.86-2.24
Anti-FHA	2,4,6	4.30	3.8-4.86
	3,5,12	3.02	2.75-3.31
Anti-FIM	2,4,6	5.07	4.1-6.27
	3,5,12	3.77	3.25-4.38
Anti-PRN	**2,4,6**	**1.63**	**1.42-1.86**
	3,5,12	**1.38**	**1.24-1.52**

Table 20: Sweden 2 Efficacy Trial Pertussis Antibody GMCs 1 Month Post-Dose 3 for HCPDT Group

Antibody	Schedule	N	GMC	p-value	95% CI
PT	2,4,6	80	51.64		44.8-59.54
	3,5,12	58	54.06	0.87	44.95-65.01
FHA	2,4,6	80	57.02		49.12-66.16
	3,5,12	58	76.74	0.01	64.27-91.6
FIM	2,4,6	80	351.89		272.83-453.84
	3,5,12	59	390.39	0.66	295.53-515.7
PRN	2,4,6	80	134.37		110.89-162.82
	3,5,12	58	212.03	0.001	168.73-266.38

Table 21: Sweden Trial - Immunogenicity at 7 months of Age After 3 Doses (2, 4, 6 mo. schedule) and 2 doses (3, 5, 12 mo. schedule) – HCPDT group

Antibody	Schedule	N	GMC	p-value	95% CI
PT	2,4,6	67	122.9		50.92-74.20
	3.5.12	65	74.2	0.001	57.62-80.37
FHA	2,4,6	67	139.5		132.01-179.8
	3,5,12	65	113.0	0.06	127.06-179.76
FIM	2,4,6	67	1480		44.8-59.54
	3,5,12	65	619	0.001	44.95-65.01
PRN	2,4,6	67	334.0		6.97-14.22
	3,5,12	65	163.0	0.001	8.88-17.64
D	2,4,6	67	1.68		88.76-124.8
	3,5,12	65	1.31	0.001	135.86-207.63
T	2,4,6,	67	7.82		15.54-23.63
	3,5,12	60	5.64	0.001	16.42-26.33

Comment: Data from the Sweden 2 efficacy study were submitted in support of the efficacy of CPDT. The HCPDT vaccine, evaluated in this trial, contains the same antigens as CPDT, but both PT and FHA are present in higher concentrations. HCPDT was given to the majority of infants on a 3, 5, 12 month schedule and it is in this cohort that efficacy was assessed. The null hypothesis of the study was that the RR of pertussis for each of the acellular vaccines compared to the whole cell vaccine would be ≥ 1.5. Based on the upper limits of the CI for both the ATP and ITT analysis, the null hypothesis could not be rejected and the trial did not achieve its objective of demonstrating the alternative hypothesis (i.e RR <1.5 for the DTaP *vs.* DTPwc). This was true for severe disease (≥ 21 days of cough) or any disease.
When results of the Sweden I trial became available, the DTaP-2 arm in this study was terminated because of the low efficacy seen in the earlier trial. An efficacy analysis was performed prior to unblinding of the data for the period of time between the 2 and 3^{d} doses (5 mo – 12 mo of age) using the DTaP-2 as a control. In this analysis, for this window of time, HCPDT was shown to be efficacious as compared to the DTaP-2 vaccine for the two primary case definitions, with or without cough: RR 0.52 (0.35,0.77), and ≥ 21 days paroxysmal cough: RR 0.40 (0.24, 0.66)

5.4 Pertactin Levels in US Infants Receiving Three Doses of CPDT at 2, 4, and 6 Months of Age.
As noted in the USBS, the PRN antibody responses of US infants were considerably lower than those observed in infants enrolled in the Sweden I efficacy trial (both GMC and seroresponse rates). The sponsor was asked to provide data that might explain this finding as well as data that might address the possible impact of lower PRN levels on the efficacy of CPDT in US infants.

The sponsor provided information to address these issues in submissions to the PLA on December 1, 1999 and July 19, 2000. The information contained therein is summarized below.

Possible explanation for lower PRN antibody levels observed in US infants;
The sponsor notes that in all studies using CPDT, Lot ----, in the US and Canada PRN antibody responses have been lower that those observed in Sweden.

Table 22: PRN Ab GMCs in US and Canadian Studies Following Receipt of CPDT Lot ---- as Compared to GMCs in Sweden I Efficacy Trial

Study	Start	Lot	Pre-vaccination		Post-vaccination	
			N	GMC (95% CI)	N	GMC (95% CI)
Sweden I	1992	----	61	2.5 (2.1,3.1)	83	121.2 (102.6, 143.2)
NIAID 2	1992	----	71	4.8 (4.0, 5.7)	70	50.9 (38.2, 67.8)
Phase 2C	1992	----	41	1.5 (1.1, 2.0)	42	71.1 (53.9, 93.8)
US Bridge	1995	----	106	3.9 (3.2, 4.9)	107	65.7 (51.9, 83.0)
		----	111	4.1 (3.3, 5.0)	108	47.1 (37.2, 59.8)

Furthermore, in US and Canadian studies with other lots (except US MAPT Cycle I study, Lot -----) pertactin levels were also lower than observed in Sweden I.

The sponsor hypothesizes that the lower levels observed in US children may be due to higher maternal antibody levels in US mothers and the lower age of immunization of infants in US studies as compared to the same variables in the Swedish studies. The

mean age of the 220 participants from whom pre-immune serum was drawn in the US bridging study was 62.5 days (range 41 to 90 days). In Sweden I, of the 62 infants from whom pre-immune serum was drawn, the mean age was 76.1 (range 61 to 90). This represents almost 14 days difference. Analysis of variance by study indicates that in the US Bridging Study, there was a lower pre-vaccination PRN antibody level with increasing age of infants at the time of 1st immunization (p-values of 0.0114 and 0.0536 for Lot ---- and ---- respectively). However, there was no such correlation in the Sweden I trial.

Table 23: Correlation between pre and post vaccination antibody levels to the PRN antigen for Sweden I Trial and USBS Lots ---- and ----

Study	N	Correlation ρ	Test of ρ=0
Sweden Lot --	62	0.055191	0.6701
U.S. Bridging Lot --	80	-0.48962	0.0001
U.S. Bridging Lot --	79	-0.22462	0.0466

Further analyses were provided by the sponsor in which they examined the correlation of age at 1st immunization on pre-vaccination and post-dose 3 anti-PRN antibody levels in their submission of July 19, 2000. Included in this analysis are the Sweden I study, the USBS, the NIAID MAPT Cycle 1 study, and they NIAID Cycle 2 study (study report for this study was not submitted to the PLA).

Table 24: PRN Antibody Levels with CPDT Vaccination - Correlation of Age at 1st Vaccination to Pre-vaccination anti-PRN, and Age at 1st Vaccination Age to Post-Dose 3 results

Study	Vaccine	N	Mean Age (Range)	Age vs. Pre		Age vs. Post	
				Correlation	P-value	Correlation	P-value
Sweden I	CPDT----	61	76.1 (61, 90)	0.07868	0.5467	-0.----84	1.000
USBS	CPDT----	80	61.5 (41, 84)	-0.25046	0.0250	0.22442	0.0454
	CPDT----	79	62.6 (42, 90)	-0.20566	0.0690	0.22029	0.0511
NIAID I	CPDT----	136	63.6 (46, 82)	-0.10076	0.2715	0.04472	0.6248
NIAID 2	CPDT----	75	63.4 (44, 88)	-0.08162	0.4986	0.05637	0.6430

As the sponsor notes, a significant correlation between age at 1st immunization and the pre-immunization PRN antibody level was only observed in the USBS. The correlation between age at 1st immunization and post-dose 3 Ab level was not significant for NIAID 1 or 2 studies, and the Sweden 1 trail. Furthermore, the sponsor has provided information showing that the age of immunization in the Canadian studies (Phase 2, 2B and 2C) was higher than in the US studies (exact means and ranges not provided), and as previously noted the anti-PRN results from these studies revealed low PRN antibody responses as well. (Note: assays were not validated as recommended by CBER at the time the sera were assayed for Canadian studies).

The sponsor has also analyzed the correlation between the pre-immunization and post-immunization PRN GMCs and the age at 1st immunization and the post 3rd dose immunization PRN antibody level.

Table 25: PRN Antibody Levels with CPDT Vaccination - Correlation of Age at 1st Vaccination to Pre-vaccination anti-PRN, and Age at 1st Vaccination Age to Post-Dose 3 results

Study	Vaccine	N	Mean Age (Range)	Pre vs. Post		Age vs. Post	
				Correlation	P-value	Correlation	P-value
Sweden I	CPDT----	61	76.1 (61, 90)	0.03640	0.7806	-0.----84	1.000
USBS	CPDT----	80	61.5 (41, 84)	-0.48962	0.0001	0.22442	0.0454
	CPDT----	79	62.6 (42, 90)	-0.22462	0.0466	0.22029	0.0511
NIAID I	CPDT---	136	63.6 (46, 82)	-0.03235	0.7247	0.04472	0.6248
NIAID 2	CPDT----	75	63.4 (44, 88)	-0.28459	0.0170	0.05637	0.6430

Of note, the NIAID cycle I sera were assayed at the FDA, the NIAID cycle 2 at UCLA (a study report for this study has not been submitted to the FDA so results can not be adequately evaluated), and the sera from Sweden I and USBS were assayed by APL using the validated assay as recommended by the FDA.

A significant negative correlation can be seen between level of "maternal antibody" in pre-immunization sera and post 3rd dose response in the USBS and the NIAID cycle 2 study, while a positive correlation exists between the age at the 1st immunization and the post 3rd dose response in the USBS.

Thus, the sponsor has provided some information which suggests that age of 1st immunization and pre-immunization antibody levels to PRN may impact the post-vaccination antibody levels in US children. However, the findings were not consistent throughout all studies and data on the effect of pre-immunization PRN levels on post-vaccination levels in Canadian studies was not provided. In these studies the age of immunization was higher than US studies, but results revealed similarly low post-vaccination levels. Furthermore, analysis of the data is complicated by the fact that sera from these studies were assayed in different laboratories,

Impact of Lower PRN Antibody Levels in US Children on Efficacy of CPDT:
Whether or not the lower post-vaccination PRN antibody levels are related to high pre-immunization PRN levels, to the age of the child at the time of the first dose, the effect of the lower post-vaccination levels on the efficacy of CPDT in US children remains of concern. To address this concern, the sponsor has provided the following information and rationale in support of the efficacy of CPDT in US children:

Level of Antibody Response Required for Protection:
Within the Sweden I efficacy study, a nested household contact study was conducted which had the specific objectives to 1) estimate the absolute vaccine efficacy after household exposure to *B. pertussis* for study children who had received a full three-dose primary series with the study vaccines and 2) to investigate possible correlates of protection by relating clinical outcome after exposure for individual children to their antibody levels against PT, FHA, PRN, and FIM at the time of exposure. A study protocol and study report for this study has not been submitted to the PLA, but a reprint of a publication of the results was provided (Storrsaeter, J., Hallander, HO, Gustafsson, L., Olin, P. *Vaccine* 1998, **16**, 1907-16).

Results of this study are provided below. Vaccine efficacy against typical pertussis (≥ 21 days spasmodic cough) was above 70% when at least one of the factors anti-PRN or

anti-FIM levels was 'high' (≥ 5 units/mL), with a maximum of 84.9% when both were 'high' **at the time of exposure**.
(see attachment 1 Table A)
Vaccine efficacy against any pertussis was above 67.4% when at least one of the factors anti-PRN or anti-FIM levels was 'high', or just above 20% when both were 'high' **at the time of exposure**
(see attachment 2 Table B)

The sponsor has also provided results from a univariate analysis looking at each of the pertussis antigens in the CPDT vaccine, using data obtained form the household contact study. The relative risk for acquiring typical pertussis disease or for laboratory confirmed cases with ≥ 1day cough for the CPDT group *vs*. DT vaccine group, stratified by antibody levels at the time of exposure in the Sweden I trial are provided.
Vaccine Efficacy *vs*. Pertussis – "Typical disease" in Relation to the Antibody Levels at the Time of Exposure in the Sweden Household Contacts Study.

Table 26: Sweden I Efficacy Trial; Household Contact Study, Risk of Acquiring WHO Defined Pertussis Disease in Relation to Antibody Levels at Time of Exposure for CPDT Group (Comparison with DT Group Provided).

Antibody to			CPDT Antibody Levels at Time of Exposure				
		DT	<5	5-10	10-20	20-30	≥30
PT	Cases/Subjects	44/65	5/23	0/14	2/17	0/1	0/0
	Risk (%)	67.69	21.74	0.00	11.76	0.00	NE*
	Relative Ris	1	0.32	0.00	0.17	0.00	-
FHA	Cases/Subjects	44/65	4/26	2/19	1/8	0/2	0/0
	Risk (%)	67.69	15.38	10.53	12.5	0.00	NE*
	Relative Ris	1	0.23	0.16	0.18	0.00	-
PRN	Cases/Subjects	44/66	3/7	0/6	2/15	2/14	0/13
	Risk (%)	66.67	42.86	0.00	13.33	14.29	0.00
	Relative Ris	1	0.64	0.00	0.2	0.21	0.00
FIM	Cases/Subjects	44/66	2/4	1/6	0/12	0/5	4/28
	Risk (%)	66.67	50.0	16.67	0.00	0.00	14.29
	Relative Ris	1	0.75	0.25	0.00	0.00	0.21

Table 27: Sweden I Efficacy Trial; Household Contact Study, Risk of Acquiring Mild Disease (³ 1 day) Pertussis Disease in Relation to Antibody Levels at Time of Exposure for CPDT Group (Comparison with DT Group Provided).

Antibody to			CPDT Antibody Levels at Time of Exposure				
		DT	<5	5-10	10-20	20-30	≥30
PT	Cases/Subjects	57/66	6/23	5/14	6/17	0/1	0/0
	Risk (%)	86.36	26.09	33.71	35.29	0	NE*
	Relative Ris	1	0.30	0.41	0.41	0.00	-
FHA	Cases/Subjects	57/66	9/26	3/19	5/8	0/2	0/0
	Risk (%)	86.36	34.62	15.79	62.5	0	NE*
	Relative Ris	1	0.40	0.18	0.72	0.00	-
PRN	Cases/Subjects	57/66	4/7	1/6	6/15	5/14	1/13
	Risk (%)	86.36	57/14	16.67	40	35.71	7.69
	Relative Ris	1	0.66	0.19	0.46	0.41	0.09
FIM	Cases/Subjects	57/66	2/4	2/6	3/12	2/5	8/28
	Risk (%)	86.36	50.0	33.33	25	40	28.57
	Relative Ris	1	0.58	0.39	0.29	0.46	0.33

*NE = not evaluable

The sponsor states that the data presented above suggest that antibody level of either PRN or FIM of > 5 EU/mL correlates with efficacy and that levels ≥ 5 EU/mL do not correlate with increased efficacy.

While these data suggest an association with anti-PRN antibody levels and anti-FIM levels with protection against disease several points need to be kept in mind. The number of cases available for these analyses was low and the confidence intervals around estimates of protection are wide. Furthermore, there is not an accepted correlate of protection for pertussis and vaccines lacking FIM and/or PRN have been shown to be efficacious in field trials. Finally, the data for protection against mild disease would suggest that antibody levels ≥ 5 U are not sufficient for protection against disease.

Vaccine Redundancy

The sponsor notes that CPDT contains a number of pertussis antigens (PT, PRN, FHA, and FIM 2/3). The sponsor suggests that while lower antibody responses to PRN may be observed in US children, these are of less concern than they might otherwise be because responses to other antigens should ensure that children with low PRN antibody levels would be protected from disease.

To address the question of how infants with a low response to PRN respond toother vaccine antigens in CPDT, the sponsor summarized the responses of these children from several trials.

Table 28: Pertussis Antibody Responses in Children Receiving CPDT or HCPDT Stratified by Response to PRN Antigen < 5 EU/mL or ³ 5 EU/mL

Post 3rd Dose PT, FHA, FIM Antibody Levels Stratified by Post 3rd Dose PRN Ab Levels of < 5 EU/mL or ≥5 EU/mL						
Study	Vaccine	PRN		PT	FHA	FIM
			N	GMC (95%CI)	GMC (95%CI)	GMC (95%CI)
Sweden I	CPDT----	≥5	83	72.6 (61, 86.4)	43.2 (37.7,49.4)	323.9 (258.1, 406.5)
USBS	CPDT----	<5	5	36.6 (13.5,99.2)	21.9 (15.0, 31.9)	273.6 (112.6, 664.8)
		≥5	102	93 (79.7,108.6)	43.9 (38.0, 50.7)	381.9 (314.1, 464.4)
	CPDT----	<5	8	43.2 (26.6,70.2)	25.9 (17.3, 38.9)	109.1 (28.7, 414.5)
		≥5	100	64.4 (57.3,72.5)	50.3 (44.2, 57.2)	325.7 (273.6, 387.7)
Sweden 2 2 months*	HCPDT-----	<5	5	13.0 (9.1,18.6)	22.4 (6.2, 80.8)	33.5 (10.2, 109.7)
		≥5	60	28.6 (24.0,34.1)	46.4 (38.0, 56.7)	113.7 (79.4, 162.7)

Table 29: Pertussis Antibody Responses in Children Receiving CPDT or HCPDT Stratified by Response to PRN Antigen < 20 EU/mL or ³ 20 EU/mL

Post 3rd Dose PT, FHA, FIM Antibody Levels Stratified by Post 3rd Dose PRN Ab Levels of < 20 EU/mL or ≥ 20 EU/mL						
Study	Vaccine	PRN		PT	FHA	FIM
			N	GMC (95%CI)	GMC (95%CI)	GMC (95%CI)
Sweden I	CPDT----	≥20	83	72.6 (61, 86.4)	43.2 (37.7,49.4)	323.9 (258.1, 406.5)
USBS	CPDT----	<20	18	36.9 (22.2, 61.2)	25.3 (18.6, 34.2)	204.7 (129.5, 323.4)
		≥20	89	106.4 (93.2,121.6)	47.2 (40.6, 54.9)	422.3 (345.2, 516.6)
	CPDT----	<20	24	45.5 (35.4, 58.5)	34.0 (25.9, 44.4)	181.6 (108.0, 305.4)
		≥20	84	68.5 (60.5, 77.6)	52.8 (46.0, 60.6)	348.9 (291.3, 417.8)
Sweden 2 2 months*	HCPDT----	<20	21	17.7 (13.7, 22.9)	32.3 (21.2, 49.1)	49.5 (25.3, 97.2)
		≥20	44	32.8 (26.8, 40.2)	50.8 (40.9, 63,2)	147.1 (101.6, 212,9)

*Tested in Swedish Laboratory, 2 months after 2nd dose.

These studies reveal, that overall children with low antibodies to PRN as defined as < 5 and < 20 EU/mL also appear to have a somewhat lower response to other pertussis antibodies.

The sponsor also provided line listings for the 42 infants in the USBS who had PRN antibody levels < 20 EU/mL showing their responses to other pertussis antigens. Of these 42, four (~10%) had anti-FIM levels < 20 EU/mL, an additional subject had a FIM antibody level of 22.46 EU/mL. Three children had PT levels of < 20 EU/mL, with an additional 3 children with levels of 20.16, 20.6 and 21.3). Ten children (~20%) had anti-FHA levels of < 20 EU/mL. Only one child had antibody levels < 20 EU/mL for three antigens (PT, PRN, FIM) and this child had an anti-FHA antibody level of 22.57 EU/mL.

Bridge to Sweden Trial 2 Efficacy Study

In December 1999 the sponsor requested that the efficacy and immunogenicity results obtained from Sweden 2 Trial be viewed as supportive of the PLA for CPDT (see summary of Trial above). This study was designed to compare the safety and efficacy of three acellular pertussis vaccines to a whole pertussis vaccine. One of the acellular vaccines was the APL "hybrid' (HCPDT) vaccine which contains the same antigens as CPDT but in different concentrations. Specifically, the hybrid vaccine contains 20 mcg of PT (vs. 10 mcg in CPDT) and 20 mcg of FHA (vs. 5 mcg in CPDT). All other components are present in the same concentration.

A correlate of protection for pertussis does not exist and FDA has not accepted an immunogenicity bridge across pertussis vaccines in lieu of clinical efficacy data. Antibody responses following vaccination with the same vaccine have been used, with FDA concurrence, to bridge populations and/or manufacturing changes. The sponsor contends that antibody responses to CPDT can be compared to those from HCPDT since both vaccines contain components manufactured using the same processes. Furthermore, they contend antibody responses to the two vaccines have been shown to be sufficiently similar to allow for the proposed bridge to the Sweden 2 efficacy trial. In support of this they provide the following comparison of immunogecinicty results from Sweden Trial I (2, 4, 6 months) and Sweden Trial 2 (subset of cohort that received the vaccine at 2, 4, 6 months)

Table 30: Comparison of Pertussis Antibody GMCs in the Sweden I Efficacy Trial (CPDT given at 2, 4, 6 Months) to those Obtained in the Sweden 2 Efficacy Trial (HCPDT given at 2, 4, 6 Months)

Antibody to	Sweden Trial I CPDT		Sweden Trial 2 HCPDT	
	N	GMC (95% CI)	N	GMC (95% CI)
PT	178	49.43 (44.77, 54.45)	80	51.64 (44.8, 59.54)
FHA	178	34.12 (30.83, 37.76)	80	57.02 (49.12, 66.16)
FIM	178	350 (301.3, 408.32)	80	351.89 (272.83, 453.84)
PRN	178	116.41 (102.57,132.13)	80	134.37 (110.89, 162.82)
D	178	0.83 (0.72, 0.95)	80	0.66 (0.55, 0.80)
T	95	3.75 (3.15, 4.48)	80	3.19 (2.64, 3.85)

As noted this is a non-randomized comparison between the two efficacy trials. Nevertheless, with the exception of FHA antibody levels, the GMC responses in the two trials were quite similar.

A number of other studies compared CPDT to the hybrid formulation of the APL pertussis vaccine (see review). In most of these studies, antibody responses to FHA were higher following receipt of the hybrid vaccine. PT antibody responses tended not to be significantly elevated, in spite of the increase PT antigen concentration in the hybrid concentration. Antibody responses to FIM have been higher in some studies (Phase 2C, NIAID Cycle 2) following receipt of CPDT even though both vaccines contain the same amount of FIM antigen.
In the Sweden 2 trial, most children received study vaccine at 3, 5, and 12 months of age, unlike Sweden I in which vaccine was administered according to the US schedule at 2, 4, and 6 months of age.

Comment: As noted above an immunologic correlate of protection against pertussis disease has not been defined. Two publications addressing serologic markers associated with of protection against disease concluded that antibodies to PRN, (FIM [Storrseaeter et al] and to a lesser extent PT were associated with protection whereas antibodies to FHA were not. (Storrsaeter, J., Hallander, HO, Gustafsson, L., Olin, P. *Vaccine* 1998, **16**, 1907-16; Cherry, JD, Gornbein, J. Heininger, U., Klemens, S. *Vaccine* 1998, **16**, 1901-1906). Data from other studies have demonstrated an efficacy benefit derived from the inclusion of FHA in DTaP vaccines (Storrsaeter, J., Hallander, HO, Olin, P. *Vaccine* 1992, **10**, 142-144). Furthermore, the relative importance of cell mediated immunity in protection against disease is not well characterized and precise levels and antibodies and relative contribution of the pertussis antibodies to protection is not dearly defined. Thus, while the two vaccines, CPDT and HCPDT, contain the same antigens manufactured by the same processes, the differing concentration of antigens in the two formulations adds an additional level of uncertainty in accepting immunologic (antibody) data to bridge efficacy results obtained from studies of these two formulations.

Nevertheless, the antibody and efficacy data from HCPDT studies that the sponsor views as supportive of CPDT efficacy in the US, in spite of lower PRN antibody levels observed in US children, include the following. In the Sweden 2 trial, efficacy was calculated for the period between dose 2 and dose 3 as part of a secondary analysis of efficacy. This comparison was done using the DTaP-2 vaccine as the control, as that arm was terminated when it was revealed that this vaccine had demonstrated low efficacy in the Sweden I efficacy trial. The relative risk for typical pertussis in the HCPDT group between dose 2 and 3, as compared to DTaP-2 group was 0.18 (95 CI: 0.09, 0.36) and for all cases 0.22 (95 CI: 0.13, 0.39). The sponsor notes that these are conservative estimates of efficacy, as they assume no efficacy for the DTaP-2 vaccine.

The sponsor notes that antibody responses from the USBS obtained **one** month after the third dose (2, 4, 6 month schedule) are higher, in general, than those obtained **two** months after the second dose of the HCPDT vaccine in Sweden 2, when given on a 3, 5, 12 months.

Table 31: Comparison of Pertussis Ab GMC Responses in USBS (CPDT – Sera Collected 1 Month Post-Dose 3 of 2, 4, 6 Month Schedule to Those Obtained in Sweden 2 Efficacy Trial – Sera Collected 2 Months Post-Dose 2 (3, 5, 12 months)

Antigen	Study	Vaccine	Post	
			N	GMC (95% CI)
PT	US Bridging	CPDT ----	107	89.1 (76.3, 104)
		CPDT----	108	62.5 (55.8, 70.1)
	Sweden 2	HCPDT----	65	26.9 (22.7, 31.9)*
FHA	US Bridging	CPDT ----	107	42.5 (36.9, 48.9)
		CPDT----	108	47.9 (42.2, 54.3)
	Sweden 2	HCPDT----	65	43.9 (35.9, 53.6)*
FIM	US Bridging	CPDT ----	107	376 (311.3, 454)
		CPDT----	108	303.3 (252.5, 364.2)
	Sweden 2	HCPDT----	65	103.5 (73.3, 146.2)*
PRN	US Bridging	CPDT ----	107	65.7 (52, 83)
		CPDT----	108	47.1 (37.2, 59.8)
	Sweden 2	HCPDT----	65	30.8 (22.3, 42.4)*
* 7 months (i.e. 2 months after dose two)				

The sponsor states that since efficacy was demonstrated between dose 2 and 3 in Sweden 2 (age 5 months – 12 months), efficacy should be comparable in US children in the period following three doses of CPDT and before the fourth dose (i.e. between 6 months and age 15-20 months).

In order to address whether the antibody level at 15-20 month of age in US children would be comparable to those observed at 12 months of age in the Sweden 2 trial, the sponsor constructed antibody decay curves based on data from the Sweden I efficacy trial, where sera were assayed at 1, 7 and 23 months post-dose three of CPDT.

Table 32: Sweden I Efficacy Trial Post-vaccination Pertussis Ab Levels, GMCs at 1, 7, & 23 Months after Dose 3

Antibody to	N	1 month after dose 3	7 months after dose 3	23 months after dose 3	Antibody decay rate
PT	170	49.8	13.3	2.3	-0.951
FHA	170	33.3	9.9	2.9	-0.763
FIM	170	352.4	81.8	16.9	-0.947
PRN	170	116.7	29.6	10.4	-0.765

*Antibody decay rate in log (month)

Using the antibody decay rates, the GMCs of Sweden Trial 2 at one month post-dose 2 were estimated (from available results obtained at 2 months post-dose 2). The data were then used to estimate the GMCs of both the USBS and Sweden Trial 2 prior to the next immunization (15 months and 12 months, respectively).

To calculate the antibody level "n" months post immunization the following formula was used,

$$\text{Log } (GMC_n) = \log (GMC_1) + \log (n) * \text{antibody decay rate}$$

Where GMC_n is the "n" months post-immunization and GMC_1 us the GMC one month post-immunization.

Antibody levels prior to the Booster (4th) Dose at 15 Months of age in the USBS and prior to Dose 3 at 12 Months of Age in Sweden Trial 2 using Ab decay rates derived from Sweden Trial I

Table 33: Comparison of Estimates of Pertussis Ab GMCs at 15 Months of Age (pre-Dose 4) in Children Enrolled in USBS to Estimates of GMCs from Sweden 2 at 12 months of Age (pre-Dose 3). Estimates Based on Decay Rates Calculated from Data Obtained in Sweden I (see Above)

Antigen	Antibody Decay Rate	Study	Vaccine	N	GMC		
					Age 7 months	Pre(e)	Pre(o)
PT	-0.951	Serology	CPDT----	24	99.3	12.3	10.7
		Bridging	CPDT----	32	59.2	7.3	8.7
			----/----*	56	73.9	9.1	9.5
		Sweden 2	HCPDT----	65	26.9†	8.2††	-
FHA	-0763	Serology	CPDT----	24	42.1	7.9	6.8
		Bridging	CPDT----	32	56.9	10.6	10.6
			----/----*	56	50.0	9.4	8.8
		Sweden 2	HCPDT----	65	43.9†	16.9††	-
FIM	-0.947	Serology	CPDT----	24	417.5	58.9	31.9
		Bridging	CPDT----	32	273.5	34.1	33.7
			----/----*	56	327.9	40.9	32.9
		Sweden 2	HCPDT----	65	103.5†	31.6††	-
PRN	-0.765	Serology	CPDT----	24	85.7	16.0	13.9
		Bridging	CPDT----	32	42.6	7.9	9.9
			----/----*	56	57.5	10.7	11.5
		Sweden 2	HCPDT----	65	30.8†	11.8††	-

† Observed at 7 months (2 mo after 2nd dose)

†† Estimated for 12 months (prior to 3rd dose)

Pre(e) Estimated Ab levels using Ab decay rates prior to the next dose of vaccine (age 15 months in USBS and age 12 months in Sweden Trial 2).

Pre(o) Ab levels at age 15 months in the Serology Bridging Booster Study obtained from laboratory testing.

* Lots CPDT---- and CPDT---- (combined average)

For this analysis the sponsor has used GMC results from a limited number of subjects enrolled in the USBS from whom pre-booster (4th dose) sera were available. Five lots of vaccine were used in the US study designed to bridge to the Sweden I efficacy study: Lots ---- and ---- manufactured by APL and 3 lots manufactured at ---- (---). A subset of subjects in the USBS were who had received CPDT Lot ---- or ---- (----------) were boosted with the a lot of "CPDT" manufactured at ----, ----------and had "pre-booster" serology available. [Immunogenicity data from the three groups of children immunized in the primary series with the lots manufactured at ---- have not been submitted to the PLA and therefore, booster data obtained using these lots can not be evaluated because it is unknown whether these lots have a similar immunogenicity profile as the vaccine manufactured by ----].

Comment: The sponsor has calculated antibody decay rates from sera obtained from CPDT recipients at a limited number of time points in the Sweden I efficacy study and has applied these data to estimate rates of decay for the hybrid product at 12 months when given on a 3, 5 and 12 month schedule. These estimates have been compared to

observed values at 15 months from a very limited subset of subjects enrolled in the USBS who received CPDT at 2,4, and 6 months of age. While "estimated" 12 month HCPDT GMCs were found to be similar those observed at 15 months in the CPDT group, the validity of this comparison and of the estimated values is unknown because of the following deficiencies: The small sample sizes at 15 months in the USBS, the limited number of time points for serum collection in the Sweden I trial on which decay rates are based, extrapolation of antibody data obtained following receipt of the CPDT formulation to the HCPDT formulation and from data obtained following a 2, 4, 6 month schedule to a 3, 5 12 month schedule.

As noted in the summary of Sweden 2 trial contained within this review, sera were collected one month and 6 months post-dose 3 from subsets of children enrolled in Trial 2 who received vaccine at 2, 4, and 6 months and at 3, 5, and 12 months of age. Results of the 6 month post 3rd dose serology have not been submitted to the PLA. These might be useful to further assess the validity of the antibody decay rate obtained analysis of serology results in Trial I with CPDT and its applicability to predicting antibody decline following vaccination with the hybrid vaccine.

Additional immunogenicity data provided in support of this bridge to the Sweden 2 efficacy study includes a comparison of the percentage of infants in Sweden 2 trial and the USBS who had PRN antibody concentrations less than 5, 10, 20 and 50 EU/mL (see below). Efficacy was demonstrated between dose 2 and dose 3 in the Sweden 2 trial, in spite of the fact that there were a number of subjects with low PRN levels. Of note, these sera were drawn two months after the second dose and those for the USBS were obtained 1 month after the third dose.

Table 34: Percent of Subjects with PRN Antibody Responses < 5, 10, 20, 50 and 50 EU/mL 2 Months the Sweden 2 Efficacy Trial and in the USBS [3]

Vaccine	Schedule	Serology timepoint	N	% < 5 EU/mL	% < 10 EU/mL	% < 20 EU/mL	% < 50 EU/mL	% ≥ 50 EU/mL
HCPDT	3, 5, 12	7 months	65	7.7	20.0	32.3	63.1	36.9
		13 months	58	0	0	1.7	6.9	93.1
	2, 4, 6	7 months	80	0	1.3	2.5	13.8	86.2
USBS lot ----	2, 4, 6	7 months	107	4.7	10.3	16.8	34.6	65.4
USBS Lot ----			108	7.4	13.9	22.2	41.7	58.3

Response to Fourth Dose in US Children

Children in the USBS were not immunized with the APL CPDT vaccine at 15-20 months of age so responses of these children, and in particular the children with a low response to PRN following the primary series can not be evaluated. Several other trials (NIAID MAPT Cycle I, Phase 2B, Phase 2C) studied the immune response to a fourth dose of CPDT in children who had received three doses as part of their primary studies. However, none of these studies were sera assayed prior to validation of the APL pertussis antibody assays in 1999.

The sponsor was able to obtain frozen serum from the children who received a fourth dose of CPDT following a primary series of CPDT in a lot consistency study). Pre and post-booster dose sera were re-assayed using the validated assays in 2000. Results are presented below:

Table 35: Pertussis Antibody Responses to 4th Dose of CPDT from Phase 2 Lot Consistency Study – Sera Re-tested Using Validated Assay

Antibody Responses to Pertussis Antigens in Phase 2 Study compared to those in Sweden Trial I at 7 Months of Age								
	PT		FHA		FIM		PRN	
Bleed	N	GMC	N	GMC	N	GMC	N	GMC
2 mth	274	25.8	268	4.2	265	11.6	266	1.2
6 mth	272	46.8	268	24	268	51.1	268	2.9
7 mth	274	87.5	272	45.6	271	238.2	272	26.9
PreB	271	6.8 (6 0,7.7)	269	10.8 (9.6 12.1)	276	26.6 (23 ,30.1)	276	11.3 (10 12.7)
PostB	273	171 (15 ,191.1)	273	117.6 (107 ,128.6)	275	518 6 (451.2, 96.1)	275	241.7(21 2,272.8)
Swed	83	72.6 (61 1,86.4)	83	43.2(37.7 49.4)	83	323 9 (258.1, 06.5)	83	121.1(10 6,143.2)

Sera re-tested using recently validated (1999) assays
PreB – Pre 4th do
PostB – Post 4th dose
Swed – Sweden Trial I (post 3rd dose)
N – Number of assay results available for analysis. The number is less than 278 due to insufficient sera.

The results of the primary series are provided only for the sake of comparison as these sera were assayed prior to validation of the APL assays and a number of inconsistencies noted between center and lots could not be adequately explained. Results following four doses compare favorably to the response observed following three doses of vaccine in the Sweden I efficacy trial.

The sponsor also provided line listings for all infants with PRN antibodies level < 5 EU/mL following a primary series of CPDT who received a fourth dose of CPDT at 15-20 months of age (n = 41). All but one had anti-PRN response following fourth dose, all but three had levels > 50 EU/mL. An analysis of post-booster dose responses stratified by post 3rd dose PRN antibody level of < or ≥ 20 EU/mL is provided below.

Table 36: PRN Antibody Responses To 4th Dose of CPDT Stratified by Response to 3rd Dose for Several US and Canadian Studies

Ab Levels Post Booster 4th Dose Stratified by Post-Dose Post 3rd Dose PRN Antibody Level of < 20 EU/mL or ≥ 20 EU/mL						
Study	Vaccine	Post Dose 3	Pre Dose 4		Post Dose 4	
			N	GMC	N	GMC
Pha e 2*	CPD T------- -----	< 20	91	3.3	35	1 8.5
		≥ 20	180	15.2	234	2 6.7
NIAID I	CPDT----	< 20	2	3.0	1	23.2
		≥ 20	38	10.2	39	187.8
Phase 2B	CPDT----	< 20	2	8.3	0	293.4
		≥ 20	25	18.5	28	281.0
	HCPDT---	< 20	8	11.6	3	298.5
		≥ 20	20	22.2	25	446.8
Phase 2C	CPDT----	< 20	3	1.8	0	51.2
		≥ 20	36	9.9	39	209.9
	HCPDT	< 20	18	3.0	2	83.6
		≥ 20	209	14.6	226	254.3

* Re-testing with validated (1999) assay

For most studies, the number of children with < 20 EU/mL is small, but the Phase 2 study provides evidence indicating that these children do respond to the fourth dose, though perhaps not as well as children with post-dose three levels of ≥ 20 EU/mL.

5.5 Summary, Conclusions, and Recommendations Regarding The Efficacy Data Submitted in Support of CPDT Vaccine Against Pertussis Disease.

CPDT was demonstrated to be highly efficacious against WHO defined pertussis disease in a randomized, comparative (DT controlled) study when given at 2, 4 and 6 months of age. Efficacy estimates for the primary ATP analysis for the vaccines tested were 57.2% (47.3, 65.3) for DTPa2, **85% (79.5, 89) for CPDT**, and 48.3% (37, 57.6) for DTPwc vaccine. Similar estimates of efficacy were obtained in an analysis which excluded subjects with protocol violations (Table 6). Efficacy, while somewhat lower, was also demonstrated for secondary endpoints against less severe disease. The efficacy estimate for CPDT against laboratory confirmed disease with cough of ≥ 1 day was **76.0%** (69.4-81.1). Further, in an analysis of efficacy over time with estimates calculated for 90 day intervals for a period of up to 810 days following the third dose, CPDT vaccine efficacy estimate of ~85% was maintained.

In the USBS, which was designed to bridge the efficacy data obtained from the Sweden I trial to the US population using immunogenicity data as the bridge, it was noted that antibody levels to PRN were significantly lower in US children as compared to those observed in Swedish children who participated in the efficacy study. Furthermore, data from a number of other studies suggest that lower responses to PRN can be expected in Northern American children. In only one Northern American study, NIH MAPT cycle I, were PRN antibody levels similar to those observed in the Sweden I following immunization at 2, 4, and 6 months of age. A number of explanations/reasons for this finding have been put forward such as lower age at time of first immunization in US/North American children and higher maternal antibodies in this population. But the data are not consistently supportive of these explanations.

The sponsor has attempted to bridge the immunogenicity following 3 doses of CPDT in the US given at 2, 4, 6 months of age to the efficacy demonstrated following 2 doses of HCPDT in Sweden 2, given at 3 and 5 months of age. However, this bridge is complicated by the use of two different vaccine formulations, the timing at which sera were obtained (1 month post-dose 3 in US, 2 months post-dose 2 in Sweden 2) and the lack of robust antibody decay data. Furthermore, even if one were to accept the data with all these caveats, the duration of efficacy which could be bridged is only 7 months.

The redundancy of the vaccine (i.e. four antigens) might provide some reassurance that even with lower PRN antibodies, efficacy of CPDT in US infants should be high. However, while only 1 of 42 children in the USBS with a PRN Ab level of <20 EU/mL had a similarly low response to all other antigens, ~20% had low FHA Ab levels, ~ 10 % had low FIM Ab levels, and 7% had low PT Ab. Similarly, when GMC results to other antigens are stratified by response to PRN, subjects with low levels of PRN Ab have lower GMCs to the other components as compared to those with higher PRN Ab levels.

Insufficient data are available on Northern American “low responders” to PRN following 3 doses at 2, 4, 6 months and who receive a fourth dose from sera assayed using validated procedures to determine how these subjects can be expected to respond to a fourth dose

In the Phase 2 lot consistency study conducted in Canada four consecutive doses of CPDT were given and pertussis antibody levels before and after the 4th dose were recently re-assayed using validated procedures. A historical comparison of PRN levels following a 4th dose in this study reveal that responses are at least as high as those obtained from children who received 3 doses of CPDT in Sweden I (assayed in same laboratory). Additionally similar PRN GMCs were observed post-dose 3 in the Sweden 2 trial on the 3, 5, 12 month as were observed post-dose 4 in the lot consistency study (assayed in different laboratories).

In all, the efficacy data would appear to support a four dose schedule of CPDT in US children given at 2, 4, 6 and 17-20 months of age. Additional data in a post-marketing setting should be obtained from a large US cohort who receives four consecutive CPDT doses so that pertussis antibody responses following the 3rd and 4th dose from a single cohort can be followed. These data will provide more insight into the antibody responses of "low post-dose 3 PRN responders" to a fourth dose and to their responses to the other vaccine components.

6.0 Analysis of Efficacy Against Diphtheria and Tetanus

In April 1997, APL received licensure for Diphtheria and Tetanus Toxoids, Adsorbed (STN #103944 approved) for use in infants and children. The manufacturing of the diphtheria and tetanus toxoids used in the CPDT is the same as that used in the licensed DT vaccine.

The Diphtheria toxoid (D) is prepared from *C. diphtheriae* strain ---------- grown in ---------- ----------. The culture is treated with ---------- and toxin is ---------- ---------- produce D toxoid.

Tetanus toxoid (T) is prepared from *C. tetani* strain ---------- grown in ---------- ----------. T toxoid is produced by addition of ---------- ----------

I have summarized the results immunogenicity results for D and T antigens following receipt of CPDT at 2, 4, 6 months of age in the Sweden I efficacy trial, the Canadian Multicenter Lot consistency trial, the US Bridging Study.

6.1 Sweden I Efficacy Trial – D and T Immunogenicity Results

Geometric mean antibody titers to the D and T components for all vaccine groups were provided in the Technical Report of the efficacy study, submitted with the 5/1996 PLA submission.

The DT vaccine used in the study was a Swedish manufactured vaccine containing 15 Lf of D, 3.75 Lf of T, and 2.5 mg of aluminum phosphate per dose.

Serology testing was performed at ---------- – SOP for assays not submitted with the Technical Report. ---------- were used for determination of antibodies to both tetanus and diphtheria antibody levels. Results are expressed as IU/mL.

Table 37: Sweden I Efficacy Trial GMT responses to Tetanus and Diphtheria

	Pre-vaccination	Post-vaccination			
		DTPa2	**CPDT**	**DTPwc**	**DT**
Tetanus anti-toxoid					
No. tested **	689	100	95	66	90
GMT (IU/ml)	**0.314**	**2.14**	**3.75**	**4.39**	**4.07**
(95% CI)	(0.277-0.356)	(1.84-2.5)	(3.15-4.48)	(3.47-5.56)	(3.63-4.57)
Diphtheria anti-toxoid					
No. tested	689	186	178	144	181
GMT (IU/ml)	**0.019**	**0.61**	**0.83**	**0.62**	**0.97**
(95% CI)	(0.017-0.021)	(0.55-0.68)	(0.72-0.95)	(0.51-0.74)	(0.86-0.93)

** Sera of infants who received Hib conjugated to tetanus toxin were not evaluated.

In response to CBER CR letter 21 March 2000 percent of children achieving anti-T and anti-D levels of ≥ 0.1 IU/mL for CPDT group were provided

Table 38: Diphtheria and Tetanus Toxoid Seroresponse Rates in CPDT Group Post-Dose 3:

Antibody	Criteria*	N	%
Diphtheria	≥ 0.01	178	99.4
	≥ 0.1	178	98.3
Tetanus	≥ 0.01	178	99.4
	≥ 0.1	178	99.4

* IU/mL

In Sweden Trial I an ---------- assay was used for assessing responses to the D and T components. Samples were not assayed using ---------- assays and the details of the ---------- were not provided, including relevant data on use of standardized reference sera.

The GMT responses to T for the CPDT group are somewhat lower to those obtained in the group which received a DT vaccine approved in Sweden and to the GMC results in the US licensed DTPwc group. The significance of this difference was not analyzed and the clinical relevance is difficult to evaluate. High seroprotection rates are observed at the ≥ 0.01 IU/ml and the ≥ 0.1 IU/ml in the CPDT group.

The GMT responses to the D component were a little lower than those observed in the DT group, but somewhat higher than those observed in the group that received the licensed DTPwc vaccine. The significance of this difference was not analyzed and the clinical relevance is difficult to evaluate. High seroprotection rates are observed at the ≥ 0.01 IU/ml and the ≥ 0.1 IU/ml in the CPDT group.

6.2 Phase 2 Canadian Multi-Center Lot Consistency Trial – D and T Immunogenicity Results.

The study was a multicenter, randomized, double blind study. Study children were randomized to receive one of the three lots of CPDT (----------) or a whole cell pertussis vaccine (DTPwc) with the same formulation as a licensed DTPwc vaccine in Canada except that it had a reduced diphtheria content and contained 0.6% 2-phenoxyethanol as a preservative. A total of 432 subjects (108 per arm) were enrolled between November 1990 and July 1991. Overall, 49.5 percent were male; among CPDT recipients 52.5% were male.

The fourth dose study included subjects who completed the primary series study and were eligible to receive a fourth dose at 18 months of age. The original primary series assignments were retained for the booster dose. The study remained double-blinded. Of the 423 subjects who completed the primary series, 398 (94%) participated in the fourth-dose study. The study was conducted between February and July 1992.

Pertussis antibody assays for the infant series were performed prior to assay validation and a number of inconsistencies in antibody responses were noted between center and lots, which could not be adequately explained. Thus, for the purpose of demonstrating lot consistency for CPDT CBER did not accept the study.

The D and T results are presented here. Details of assay validation for D and T assays were submitted to CBER in a 12/1998 response to CR letter of 5/97 and subsequent clarifications were provided in response to CBER CR letter of 3/00 in 6/00. Assays were performed at Aventis Pasteur Limited. Dr. Chandler has reviewed these submissions and assay validation was felt to be adequate. Serum samples were tested for antibodies to tetanus toxin using an --------- and for antibodies to diphtheria toxin using a ----------
---

Table 39: Seroresponse Rates to D and T at 7 Months and following 4th Dose in Lot Consistency Trial

			Lot ------		**Lot -----**		**Lot -----**	
Age	Ab To	Criteria	N	%	N	%	N	%
7 Months	Diphtheria*	≥ 0.01	106	100	103	100	104	100
		≥ 0.1	93	87.7	80	77.7	92	88.5
		GMT	0.39		0.28		0.36	
	Tetanus**	≥ 0.01	106	100	102	100	105	100
		≥ 0.1	106	100	102	99.0	105	100
		GMT	1.58		1.28		1.43	
4th Dose	Diphtheria*	≥ 0.01	98	100	99	100	99	100
		≥ 0.1	98	100	99	100	99	100
		GMT pre	0.17		0.09		0.10	
		Post	7.08		5.53		6.18	
	Tetanus**	≥ 0.01	98	100	99	100	99	100
		≥ 0.1	98	100	99	100	99	100
		GMT pre	0.19		0.17		0.20	
		Post	3.45		3.65		3.43	

** Tetanus Ab concentration, EU/mL
*Diphtheria Ab concentration IU/mL

The GMT results to the T component in the Lot consistency study appear lower than those observed in the USBS or the Sweden I efficacy trial. Of note, the same bulk concentrate was used for all three lots of tetanus in the lot consistency study. High seroprotection rates are observed at the ≥ 0.01 EU/ml and at the ≥ 0.1 EU/ml level. The GMT in these to studies to the D component are somewhat lower than in the Sweden I trial, of note the assays were not performed by the same lab. Seroprotection rates at the ≥ 0.1 IU/ml level are also lower than those observed in the Sweden I trial.

Fourth dose data are available from the lot consistency study. While a "booster effect" cannot be evaluated because data on percent of subjects with a pre-specified fold increase in antibodies levels (e.g. 4-fold) have not been provided, a notable increase from pre to post 4th dose GMTs was demonstrated for both D and T. High seroprotection rates were observed at the ≥ 0.1 IU/ml and EU/ml level, respectively.

6.3 US Bridging Study – D and T Immunogenicity Results.
Seroresponse rates and GMTs to D and T antigens are provided for recipients of CPDT Lots ---- and ----. Assays were performed at APL as described above for Phase 2 Lot consistency study.

Table 40: USBS GMC and Seroconversion Rates to Diphtheria

Vaccine Group	**Lot ---- (95% CI)**	**Lot ---- (95% CI)**
Pre-Vaccine	N=125	N=134
GMT EU/mL	0.047 (0.038, 0.059)	0.051 (0.040, 0.065)
Post-Dose 3	N=127	N=134
GMT	0.34 (0.27, 0.42)	0.26 (0.21, 0.32)
% ≥ 0.01 IU/mL	99.2 (95.7, 100)	99.3 (95.9, 100)
% ≥ 0.1 IU/ml	85.0 (77.6, 90.7)	76.1 (68.0, 83.1)

The percent responders with ≥ 0.1 IU/mL of antibody to Diphtheria is lower than observed in the Sweden I efficacy trial. However, different assays were used in the to measure antibody levels.

Table 41: USBS GMC and Seroconversion Rates to Tetanus

Vaccine Group	**Lot ---- (95% CI)**	**Lot ---- (95% CI)**
Pre-Vaccine	N=121	N=131
GMT	0.55 (0.44, 0.69)	0.74 (0.61, 0.90)
Post-Dose 3	N=127	N=134
GMT	4.85 (4.13, 5.69)	3.76 (3.28, 4.35)
% ≥.01 EU/ml	100 (97.1, 100)	100 (97.3, 100)
% ≥ 0.1 EU/ml	100 (86.3, 96.5)	100 (92.4, 99.2)

6.4 Summary, Conclusions, and Recommendations Regarding The Efficacy Data Submitted in Support of CPDT Vaccine Against Diphtheria and Tetanus Toxoid

The gold standard for measuring an immune response to tetanus toxoid is the serum toxin neutralization test. For Diphtheria, the *in vitro* ---------- assay is a well established test for measuring an immune response to diphtheria toxoid. Other serological tests for both D and T such as ----------, are useful provided that a correlation with toxin neutralization has been demonstrated.

It is generally accepted that 0.01 IU/ml of tetanus antitoxin is the minimum level needed to ensure protection, and that this level confers protection in most situations. Probably no level of circulating antitoxin confers absolute protection. However, available data indicate that in most circumstances, an antitoxin level of 0.01 IU/ml is the lowest giving some degree of protection, and 0.1 IU/ml is considered a protective level of circulating antitoxin. Levels of 1.0 IU/ml and above are thought to confer long-term protection.

Efficacy data for CPDT against D and T Toxoids rely on immunogenicity responses measured in such serologic assays. Different assays were used in the Sweden I Trial (performed at --------) as compared to the Northern American study (performed at APL, Inc.) This reviewer has not reviewed the validation of the assays used in both laboratories for the D and T component of the CPDT vaccine. Differences in the results obtained may, in part, explain some of the observed differences between studies. The reason(s) for markedly lower GMTs observed post-dose 3 to the Tetanus toxoid component in the Lot Consistency study as compared to the Sweden I Trial and the USBS is not clear.

In all studies, high seroprotection levels were noted to both components at the 0.01 IU/ml or EU/ml for the tetanus toxoid. High seroprotection rates to diphtheria toxoid at the 0.01 IU/ml were observed in all studies. Seroprotection rates to D at the $\geq$ 0.1 IU/ml were higher in the Sweden I study than in the Lot Consistency and USBS. Whether this reflects a difference in the assay or population is not clear.

This can be evaluated further in a post-marketing study conducted to assess responses of infants and toddlers to components of CPDT vaccine.

7.0 Manufacturing Consistency – Clinical Lot Consistency

In order to demonstrate consistency of manufacturing, the sponsor conducted a study entitled "Safety and Immunogenicity of the Connaught Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed (CPDT), in Calgary, Alberta; Surrey, Maple Ridge and Coquitlam, British Columbia, Canada – Lot Consistency Study".

The study was conducted between November 1990-July 1991. In this study, infants were randomized to receive three lots of CPDT vaccine ---------- or a DTPwc vaccine [lot was ---------- which contained a reduced amount of diphtheria (15 Lf vs. 25 Lf) from the licensed vaccine available in Canada and a different preservative (0.6% 2-phenoxyethanol)].

The study objective, to demonstrate consistency of manufacturing, was to be accomplished by comparing the immunogenicity and safety of three consecutively manufactured lots. The inclusion of DTPwc arm was to allow for a comparison of safety and immunogenicity of the three CPDT lots to a DTPwc vaccine.

The study population included healthy 2 month old infants who were to receive vaccine at 2, 4, and 6 months of age (subsequently, children from this study whose parents consented were enrolled in a 4th dose study in the randomization assignment was maintained. A total of 432 infants were enrolled (108 per arm). All children were to receive OPV concurrently at 2 and 4 months of age.

The safety data from this study were reviewed in the safety section and re-analysis of fourth dose sera following assay validation are summarized in the efficacy section as part of the discussion of decreased responses to PRN observed in US and Canadian infants. Diphtheria and Tetanus Toxoid responses are reviewed in the section on the analysis of efficacy to the D and T components.

Analysis of the pertussis antibody responses in the infant series revealed unexplained variations among centers. In particular, large differences were noted among the centers in PT antibody as measured by ---------- at the 2 month old time point. Levels at the Calgary site were substantially higher than those at other centers (GMC at Calgary at 2 months for Lot -----: 221 EU/mL, Lot ------ 215 EU/mL, Lot ------: 161 EU/mL. At Alberta 2 month GMCs for PT for Lot -----: 9 EU/mL; Lot ------: 4 EU/mL; Lot ----: 5 EU/mL. At Surrey, for corresponding lots GMCs to PT were 24 EU/mL, 21 EU/mL, and 25 EU/mL. Additional center effects were noted in responses to some of the lots with regards to the PRN antibody response at 7 months, i.e. at two of the centers Lot ---- elicited responses that were 40 to 50% higher than the other two lots. This effect was not seen at the 3rd center.

In the May 27, 1997 CR letter, CBER requested clarification regarding the predefined clinical criteria to demonstrate lot consistency. The sponsor acknowledged that such criteria had not been predefined. CBER also requested details regarding the performance of the assays and handling of the samples and possible explanations for the observed center effects. These responses were reviewed by Ms. Frejya Lynn and Dr. Bruce Meade who concluded that the assays were not adequately validated at the time that antibody responses were measured, that the variation noted between centers remained unexplained and that there was a lack of documentation of adequate handling of the serologic samples. Thus, the serologic data from this study are not accepted for the evaluation of lot consistency.

In the 21 March 2000 CR letter, the sponsor was asked to provide a summary of available clinical data and animal immunogenicity data to support consistency manufacturing. Information from five sources were requested 1) manufacturing consistency data; 2) laboratory characterization or recently manufactured lots; 3) animal immunogenicity; 4) other clinical immunogenicity data in support of lot consistency 5) clinical efficacy in two different studies using two different lots.

I have reviewed the efficacy data from Sweden Trial I (CPDT ----) and Sweden Trial 2 (HCPDT Lot ----) – see above. Substantial efficacy was noted in Sweden Trial I with CPDT ----. Relative efficacy for the period between dose 2 and 3 (5 months and 12 months) was demonstrated in the HCPDT group as compared to the SKB DTaP 2 group. This analysis had not been planned at the beginning of the study but was possible after the SKB DTaP-2 arm was terminated when results from the Trial I study became available showing a low efficacy of this vaccine. However, the primary endpoint of efficacy for the HCPDT group was not met (r/o a RR of > 1.5 as compared to the DTPwc arm). Additionally, because relative efficacy was measured a comparison of the estimates of efficacy obtained in the Sweden I trial with CPDT and in the Sweden 2 trial with HCPDT cannot be made. Finally, as noted in the discussion of PRN responses, the different formulations of the two products and the lack of an immunologic correlate of protection against pertussis disease, adds a level of uncertainty when one uses the

results of studies with the hybrid product (HCPDT) to predict the performance of the classic (CPDT) product.

Additional data from several other lot studies using CPDT or HCPDT and CPDT containing vaccines (i.e. combination vaccine products) are provided as additional supportive data for demonstrating manufacturing consistency. None of the studies were designed as equivalence studies. Retrospectively, lot consistency was defined as being met if the 90% CI of the ratio of the GMCs was not less than 0.5 or not greater that 2.0 and for seroconversion rates (4-fold increase), the 90% CI of the difference did not exceed ±18%. The units of measurement are not provided, but it is assumed that they are EU/mL for the pertussis and T antigens and IU/mL for the D antigen. Of note, all of the assays for pertussis antigens from these studies were performed at APL prior to assay validation in 1999.

1) The US Bridging study – results have been previously reviewed. Children were randomized to receive CPDT Lot ---- or ----. Lot ---- was manufactured ---------- later than Lot ---- (see table 10). The number of children included varies slightly from those presented in table 10. For GMCs, none of the 90% CI of the ratio of GMCs were less than 0.5 or exceeded 2. However the upper bound of CI (----/----) exceeded the more stringent criteria of 1.5 for Diphtheria (1.88), PT (1.67), PRN (1.84), FIM (1.55). For seroconversions only the ratio of Lot ----/---- exceeded 18% only for D ≥ 0.1 (18.4). Using the more stringent criteria of 10%, this was exceeded for FHA (15.2), PRN (17.4) and FIM (10.7).

2) Study ---------- HCPDT-mIPV/PRP-T (n = 105-109). Three lots were studied, Lots ---- ---------- (n= 106-109/group). This study was conducted between 1995 –6. Details of the study design and conduct are not provided.
GMC results:
D: GMT 90 Upper bound CI ratio ----------: 1.54, ----------: 1.82; Lot ----------: 1.63.
T: GMT 90% CI ratios were within 0.5/1.5
PT: GMC 90% CI ratios were within 0.5/1.5
FHA: GMC 90% CI ratios were within 0.5/1.5
PRN: GMC 90% UB CI ratio----------: 1.96, ----------: 2.03;
FIM: GMC 90% CI ration were within 0.5/1.5
Seroconversion:
D: 90% CI upper bound for rates >0.1 ---------- 19.1----------: 19.8, ----------: 10.7
T: 90% CI all within 10% for both 0.01 and 0.1.
PT: ----------: -14.2; ----------: -14.1
FHA: ----------: -11.3; ---------: -10.8
PRN: ----------: 18.6; ----------: -10.4; ----------: -16.0
FIM: ----------: -16.6; ----------: -17.6;

3) Study --------- HCPDT-PRP-T-IPV (Pediacel). – Lot ---------- (N = 105-109/group). This study was conducted between 1995 –6. Details of the study design and conduct are not provided.
GMC Results
D: GMT 90 Upper bound CI ratio all within 0.5/1.5
T: GMT 90% CI ratios were within 0.5/1.5
PT: GMC 90% CI ratios were within 0.5/1.5
FHA: GMC 90% CI ratios were within 0.5/1.5
PRN: GMC 90% UB CI ratio ----------: 1.87, ----------: 1.54;

FIM: GMC 90% UB CI ratio ----------: 1.61, ----------: 1.59;
Seroconversion:
D: 90% CI upper bound for rates >0.1 ---------- 11.7, ----------: 11.0,
T: 90% CI all within 10% for both 0.01 and 0.1.
PT: ----------: -10.3, ----------: -13.7
FHA: ----------: -18.7, ----------: -17.7;
PRN: ----------: 10.8; ----------: ----------: -11.6
FIM: ----------: 11.1; ----------: -11.6

4) Study ---------- CPDT-mIPV/PRP-T – Lots ---------- (n=110 -116). This study was conducted between 1996 –7. Details of the study design and conduct are not provided.
GMC Results
D: GMT 90 Upper bound CI ratio ----------: 1.52, ----------: 1.57
T: GMT 90% CI ratios were within 0.5/1.5
PT: ----------: 1.86, ----------: 1.80;
FHA: all 90% CI ratios were within 0.5/1.5
PRN: all 90% CI ratios were within 0.5/1.5
FIM: GMC 90% UB CI ratio ----------: 1.82, ----------: 2.34; ----------: 1.73.
Seroconversion:
D: 90% CI upper bound for rates >0.1 ---------- -18.9, ----------: 12.8----------: 21.5 for ≥ 0.1
T: 90% CI all within 10% for both 0.01 and 0.1.
PT: ---------- 11.0----------: 19.8; ----------: 16.3
FHA: ---------- 12.1, ----------: -15.2; ----------: -18.3
PRN: ---------- –12.3, ----------: -11.1; ----------: 11.1
FIM:, ----------: 23.8; ----------: 23.1

5) Phase 2C Multicenter Bridging Study of CPDT and HCPDT – CPDT Lot ---- and HCPDT Lot ----
. This study was conducted between 1992 and 1994. Details of the study design and conduct reviewed in the clinical study section. Serology data were available only from between 40-42 subjects for the CPDT group and for 244-250 for the HCPDT group. Thus, because of the small size of the CPDT group, results are not easily interpretable for the purpose of demonstrating lot consistency. With these small numbers, the GMCs for FHA and FIM did not meet the specified criteria. The FHA response, not surprisingly, was greater in the HCPDT group, the FIM response was greater in the CPDT group. [Of note: This increased FIM response in the CPDT vs. HCPDT groups, in spite of equivalent amount of antigen in both vaccine formulations has been noted in other studies]. For seroprotection rates, the FIM responses exceeded the 90% CI of the ratio of the two groups exceeded 18% for the FIM responses.

7.1 Summary, Conclusions, and Recommendations Regarding Data Submitted in Support Of Manufacturing Consistency.
As noted above, the data from the Lot consistency study of CPDT were not accepted in support of manufacturing consistency because of problems with assay validation, large center effects on antibody levels which could not be adequately explained and the documentation of how samples were handled was not adequate.

The sponsor has submitted additional clinical data from studies in which one or more lots of a CPDT or HCPDT containing vaccine were administered in clinical studies. As noted

above, these studies were not designed or powered as equivalence studies and pre-defined criteria for demonstrating lot consistency were not defined. Using retrospective criteria, which would not be accepted today [i.e. 90% CI of the ratio of the GMC was not less than 0.5 or not greater that 2.0 and for seroconversion rates (4-fold increase), the 90% CI of the difference did not exceed ±18%] there were still some parameters that fell outside the criteria. If one were to apply more stringent criteria [90% CI of the ratio of the GMC was not less than 2/3 or not greater that 1.5 and for seroconversion rates (4-fold increase), the 95% CI of the difference did not exceed ±10%] many more of the parameters would have fallen outside of the criteria. Thus, these data are difficult to interpret do to the limitations imposed by the different vaccines and formulations evaluated, the study designs, sizes, and the lack of assay validation at the time the sera were analyzed.

The demonstration of efficacy of the two formulations in two independent efficacy studies, Sweden Trial I and Sweden Trial 2, while encouraging, is also of limited value in demonstrating lot consistency for the following reasons. As noted, two different formulations of the vaccine were evaluated and the applicability of data derived from the HCPDT vaccine to CPDT is in question. The data were not obtained from the same study in which infants were randomized to received one of the two vaccines. Efficacy and the immunogenicty of the two formulations were, therefore, not evaluated in a head to head comparison. Only the relative efficacy of the HCPDT formulation was assessed in Sweden Trial 2, and the primary endpoint of efficacy was not met. In an ITT analysis, HCPDT did appear to have good efficacy as compared to the SKB-2 DTaP formulation between 5-12 months of age. This SKB-2 formulation had been shown in Trial I to have low efficacy as compared to DT control.

In summary, the clinical data submitted in support of manufacturing consistency are not interpretable for this evaluation ---------- Data on manufacturing consistency from ten recently manufactured lots of CPDT, laboratory characterization of recently manufactured lots and animal immunogencity have also been submitted in support of manufacturing consistency. These data are reviewed elsewhere by others on the review committee.

8.0 Analysis of Safety

Safety of CPDT was evaluated in a total of nine clinical trials. Approximately 3,852 infants received 11,435 doses of CPDT as a three dose series; the majority at 2, 4, and 6 months of age. A fourth dose of CPDT was given to 637 toddlers. Five hundred twenty-six of these children had received three dose of CPDT as their primary series and 111 children had received DTPwc in their infant series.

In addition, the sponsor submitted the safety data from the Sweden 2 efficacy trial in which HCPDT was administered to subjects on a 3, 5, 12 month schedule in support of the safety of CPDT.

8.1 Size and Demographics of CPDT Safety Database

Table 42: Safety Database: Number of Subjects Who Received CPDT and the Number of Doses Administered.

Schedule	Number of Subjects	Number of Doses
Infant series		
2, 4, 6 months	3,769	11,191
2, 3, 4 months	83	244
Total infant series	**3,852**	**11,435**
Fourth dose		
15 - 20 months		
After 3 doses of CPDT	476*	476
After 3doses of DTPwc	111	111
Total fourth dose	**587**	**587**
TOTAL	**3,963**	**12,022**

* These 476 toddlers are included among the 3,852 subjects listed for infant series above

Demographics of CPDT Safety Data Base

Age of enrollment for infant series:

The mean age of enrollment in the Sweden I efficacy study (N= 2,587) was 72 days (range 62-88 days). In the US bridging study, the mean age at time of enrollment was 8.5 weeks (range 5 –12 weeks) [While not provided in days by sponsor, this would be equivalent to a mean of ~59.5 days, range 35 – 84]. In the Canadian studies (N = 531), the age of enrollment was ≥ 60 days for all but one of the subjects.

Sex, Race/Ethnic Origin:

In the Swedish efficacy trial, 51.4% of subjects receiving CPDT were male. Information on ethnic origin was not specifically provided. Fifty-one percent of subjects participating in the US bridging study were male. The following information on ethnic origin was provided: 94.1% of participants were Caucasian, 1.9% African American, 1.6% Asian, and 2.5% "other". In the Canadian studies there was a relatively even distribution between males and females; information on ethnic origin was not collected.

Age of enrollment for fourth dose:

The sponsor has requested an age range of 15 - 20 months for the fourth dose indication. However, most of the children who received a fourth dose following a primary series of CPDT were 17 - 20 months at the time of vaccination, with no children receiving vaccine at 15 months and only four receiving vaccine at 16 months. Of the children who received CPDT following a DTPwc vaccination series, two were 15 months of age and twelve were 16 months of age. The remaining children were 17 months or older. All children receiving four dose of CPDT were 17 months or older at the time of receipt of their 4th dose.

This summary will focus on the safety evaluation in the 3 largest studies of CPDT: the Sweden Trial I efficacy study, the Phase 2C lot consistency study, and the US bridging study. However, the review will include data from all clinical studies of CPDT when discussing serious adverse events (SAE) and large local reactions following the fourth dose of CPDT. The sponsor has also submitted safety data gathered from studies of hybrid formulation (HCPDT) of their acellular pertussis vaccines in support of the CPDT

license application and serious adverse events reported from clinical trials with this vaccine will be reviewed.

Case report forms and/or case narratives were provided for subjects who had seizures, hypotonic-hyporesponsive episodes (HHE), and other selected serious adverse events within 14 days of vaccination and for all deaths occurring at anytime in the clinical studies. For events occurring following receipt of CPDT, brief descriptions of these events are provided within this document. Additionally, the four deaths due of sudden infant death syndrome and one case of "sudden death", all of which occurred in clinical studies of HCPDT, are briefly described.

Additional summary data of post-vaccination reactions for other smaller studies submitted in support of the application are presented and reviewed in the section on supporting clinical study summaries.

8.2 Safety Data from the Sweden Trial I Efficacy Study

The largest study to evaluate the safety of CPDT was Sweden Trial I (see study summary, Appendix 1 and publication, Appendix 3). A total of 9,829 infants were enrolled in this study, of which 2,587 were randomized to the CPDT arm. CPDT vaccine was given at 2, 4, and 6 months of age. Inactivated polio vaccine (IPV) was given to most children at 4 and 6 months of age (with second and third doses of CPDT) either alone or as a combination of *Haemophilus b* conjugate vaccine-IPV (HIB-IPV). For further details on use of these vaccines, see section on concurrent immunization.

Safety results from this study were submitted as part of the Technical Report, authored by the investigators from the Swedish Institute of Infectious Disease Control.

Safety Monitoring in Trial I

The following monitoring procedures were followed for the evaluation of safety in the Sweden Trial I:

Local and Systemic Adverse Events:

Diary cards:

Parents were asked to monitor the child for adverse events and record these on a diary card for 14 days after each vaccination. They were asked to record rectal temperature the evening of and the morning following vaccination. If the temperature was >37.9°C, they were instructed to continue to monitor twice daily temperatures until it fell to <38.0°C. Diary cards were not collected as part of the study record.

Telephone interview:

Information about adverse events was collected by study nurses through the use of scripted interviews one day after and on day 14 after vaccination. The day one interviews solicited specific information on the presence of injection site tenderness, redness and nodules, as well as the size of local reactions. Information was specifically requested on the following systemic reactions: temperature, drowsiness, anorexia, vomiting, irritability, crying, limpness, pallor, twitching, and seizures. On the day 14 questionnaires, the duration of a fever, which began on the day of vaccination, was solicited as well as the maximum temperature measurement of that fever. Occurrence of seizures, hospitalizations, and contraindicating adverse events (see below for definition) were queried for. Additionally, the duration of local reactions, but not the maximum size of local reactions, was solicited.

Safety analyses included all children who received at least one dose of vaccine. As noted in the clinical trial summary (Appendix 1), the study began as a three- arm study and approximately two months into the trial, a fourth arm, the DTPwc group, was added. Analyses of adverse reactions include all study participants.

Local Reactions
Local reactions reported on the Day 1 and Day 14 are summarized below. Relative risks for comparisons between the CPDT group and the DTPwc group, along with 95% confidence intervals, are reported.

Table 43: Sweden I Efficacy Trial, Rates of Local Reactions From Day 1 and 14 Questionnaires

Symptom		Total %	DT %	DTaP-2 %	**CPDT %**	DTPwc %	CPDT vs. DTPwc
	Dose 1	9,829	2,574	2,566	**2,587**	2,102	RR 95% CI
	Dose 2	9,713	2,555	2,548	**2,563**	2,040	
	Dose 3	9,630	2,538	2,536	**2,549**	2,001	
Tenderness*	1	19.1	8.4	8.0	**8.0**	59.5	0.14 0.12-0.15
	2	20.8	10.3	10.4	**10.1**	60.2	0.17 0.15-0.19
	3	18.3	10.0	9.3	**10.8**	50.0	0.22 0.19-0.24
	At any 1-3	34.6	22.2	21.8	**22.2**	80.5	0.28 0.26-0.30
Redness	1	16.0	9.5	10.9	**10.1**	37.6	0.27 0.24-0.30
	2	26.1	20.1	22.8	**25.5**	38.6	0.66 0.60-0.72
	3	36.2	30.9	36.8	**33.6**	45.6	0.74 0.69-0.80
	At any 1-3	50.1	42.0	48.0	**46.1**	67.4	0.68 0.65-0.72
Redness ≥ 2 cm*	1	1.5	0.3	0.3	**0.3**	6.0	0.04 0.02-0.10
	2	1.8	0.8	0.7	**1.0**	5.1	0.20 0.13-0.30
	3	3.5	2.4	2.2	**3.7**	6.4	0.58 0.44-0.75
	At any 1-3	6.1	3.5	3.1	**4.8**	14.6	0.33 0.27-0.40
Induration	1	27.4	19.9	20.4	**21.7**	52.1	0.42 0.38-0.45
	2	40.4	37.1	35.6	**37.5**	54.1	0.69 0.65-0.74
	3	49.4	44.6	49.9	**46.2**	59.2	0.78 0.74-0.83
	At any 1-3	64.5	59.8	62.2	**60.6**	77.8	0.78 0.75-0.81
Induration ≥ 2 cm*	1	3.0	0.7	1.2	**0.9**	10.6	0.08 0.05-0.12
	2	3.5	2.0	1.6	**1.6**	10.0	0.16 0.12-0.23
	3	6.1	3.9	4.7	**6.3****	10.5	0.60 0.49-0.73
	At any 1-3	10.1	6.0	6.6	**7.8**	22.3	0.35 0.30-0.41

***Rates from day 1 questionnaire (Tenderness and size and reactions were not queried for on day 14 questionnaire).**
**CPDT vs. DT: RR is 1.62 (95%CI 1.27,2.06)

Comment: Local injection site reactions occurred at similar rates following all three doses of CPDT as compared to the DT control group, with the exception of induration ≥ 2 cm following the 3rd dose which occurred significantly more frequently after the third dose in the CPDT arm. In contrast, injection site reactions following all doses occurred significantly less frequently in the CPDT arm as compared to the DTPwc arm.

Systemic Reactions:
Systemic reactions reported on Day 1 and 14 post-vaccination are summarized below. Relative risk estimates for adverse events in the CPDT group as compared to the DTPwc group are provided along with 95% confidence intervals.

Table 44: Sweden I Trial Rates of Systemic Reactions, Day 1 and 14 Questionnaires

Symptom		Total %	DT % (N)	DTaP %(N) †	DTPwc % (N) °	CPDT vs. DTPwc	
	Dose 1	9,829	2,574	2,566	2,102	RR	95% CI
	Dose 2	9,713	2,555	2,548	2,040		
	Dose 3	9,630	2,538	2,536	2,001		
T ≥ 38°C *	1	21.6	7.6	7.8	72.3	0.11	0.09-0.12
	2	30.3	18.4	19.1	74.3	0.26	0.24-0.28
	3	31.5	22.1	23.6	65.1	0.36	0.34-0.39
	All 1-3	47.4	34.8	36.9	90.4	0.41	0.39-0.43
T ≥ 40°C *	1	0.1	(1)	(1)	0.1	**	
	2	0.1	(0)	(0)	0.3	***	
	3	0.2	0.1	(1)	0.7	0.06	0.00-0.04
	All 1-3	0.4	0.1	(2) 0.1	1.3	0.06	0.01-0.26
Received antipyretic	1	17.2	7.4	6.1	56.0	N/A	
Medication*	2	23.6	11.2	12.0	69.1	N/A	
	3	22.5	11.6	20.8	62.5	N/A	
	All 1-3	34	21.1	32.7	81.7	N/A	
Persistent crying	1	5.8	1.6	1.7	11.8	0.15	0.11-0.20
≥ 1 hr *	2	4.1	2.7	2.5	9.3	0.26	0.20-0.35
	3	1.5	1.0	1.2	3.3	0.35	0.23-0.54
	All 1-3	8.3	4.9	4.9	20.1	0.24	0.20-0.29
Cry of “type never	1	13.5	5.8	5.0	43.4	0.11	0.10-0.14
Heard before”*	2	11.0	6.3	6.7	26.2	0.26	0.22-0.30
	3	4.8	3.3	3.3	10.5	0.31	0.24-0.40
	All 1-3	22.2	13.5	12.8.	54.6	0.23	0.21-0.26
Ate less than usual*	1	16.8	10.3	11.2	39.2	0.28	0.25-0.32
	2	12.5	8.1	9.1	25.6	0.36	0.31-0.41
	3	10.0	7.7	8.4	17.5	0.48	0.41-0.56
	All 1-3	30.5	22.3	24.0	56.6	0.42	0.39-0.46
Vomiting more than	1	7.5	6.3	6.9	9.5	0.73	0.60-0.89
Usual*	2	5.7	5.8	5.2	7.4	0.70	0.55-0.87
	3	5.0	5.2	4.3	5.5	-	
	All 1-3	15.6	14.8	14.1	19.2	0.73	0.65-0.84
Pale or gray*	1	1.3	0.4	0.3	4.4	0.08	0.04-0.16
	2	0.3	0.1	0.2	1.1	0.14	0.05-0.42
	3	0.2	0.2	0.1	0.6	0.13	0.030.58
	All 1-3	1.7	0.7	0.6	5.8	0.10	0.06-0.17
Limp, hypotonic*	1	1.5	0.6	0.5	5.1	0.1	0.05-0.20
	2	0.8	0.4	0.3	2.3	0.22	0.11-0.47
	3	0.3	0.1	0.1	1.0	0.07	0.01-0.55
	All 1-3	2.3	1.1	0.9	7.2	0.14	0.08-0.23
Convulsion - 14 day	1	(5)	(1)	(2)	(1)	-	
Questionnaire	2	(5)	(0)	(1)	(2)	-	
	3	0.1	0.2	(3) 0.1	(1)	-	
	All 1-3	0.2	0.2	(6) 0.2	0.2	-	
Hospitalization	1	1.8	1.7	1.8	1.9	-	
	2	1.7	1.1	1.6	1.9	0.84	0.54-1.30
	3	1.7	1.8	1.6	1.5	-	
	All 1-3	4.7	4.4	4.5	4.8	-	
Contraindication to	1	0.7	0.3	0.4	2.2	0.18	0.09-0.35
next dose	2	0.5	0.3	0.3	1.1	0.29	0.13-0.65
	3	0.5	0.5	0.2	1.1	0.19	0.07-0.49
	All 1-3	1.6	1.1	0.9`	4.2	0.21	0.13-0.33

N/A = RR not provided. † for some reactions, percentages not provided; for these total N are listed in ()
* Number of subjects and responses from day 1 questionnaire. **CPDT vs. DTPwc: p value 0.026; *** CPDT vs. DTPwc: p value 0.004.

Comment: Systemic reactions occurred at similar rates following all three doses of CPDT as compared to the DT control group, with the exception of induration ≥ 2 cm following the 3rd dose which occurred significantly more frequently after the third dose in the CPDT arm. Most systemic reactions occurred significantly more frequently following receipt of DTPwc at all doses except for rates of vomiting, convulsions and hospitalizations which were not significantly different between the two groups.

Systemic reactions reported in subject receiving concurrent immunizations:
As noted above, most subjects enrolled in this study were to receive IPV at 4 and 6 months of age (with second and third doses of CPDT) either alone or as a combination of *Haemophilus b* conjugate vaccine-IPV (HIB-IPV). HIB vaccines were introduced during the course of the study.

Table 45: Sweden I Efficacy Trial, Vaccines Given concurrently with CPDT

Vaccines	Dose 1	Dose 2	Dose 3
CPDT	2467	826	732
+ IPV	52	984	881
+ Hib	31	24	44
+Hib –IPV*	37	731	894
Total	2587	2565	2551

*It was recommended that HIB-IPV be admixed and given in the same syringe.

A post-hoc analysis of systemic adverse events in infants who received concomitant vaccines with doses 2 and 3 of their DTP vaccine in the Sweden Trial I was published by Olin et al (*International Journal of infectious Diseases* 1997;1:143-147). A reprint of this publication was submitted to the PLA. Children were either given IPV (SBL-vaccin AB, Sweden) or IPV combined with ActHIB (Aventis-Pasteur) in which case the HIB vaccine was dissolved in the polio vaccine and administered from the same syringe. These vaccines were given intramuscularly in the contralateral thigh as CPDT. Rates of systemic AEs were already high in the DTPwc group, and did not increase with the use of concomitant vaccines. However, rates of systemic reactions did increase in the DT and DTaP groups when administered concurrently with other vaccines. Below are results for the CPDT group.

Table 46: Sweden I Efficacy Trial Rates of Systemic Reactions in Children who Received CPDT Alone or with IPV or IPV/HIB

	Dose	CPDT only	+IPV	IPV/HIB
Number of doses	2	826	984	755
Event	3	732	881	938
Temp ≥ 38°C	2	12.9	17.6	27.7
	3	18.2	23.8	27.6
Antipyretics	2	5.6	4.9	28.4
	3	6.8	5.7	22.1
Fretful	2	29.7	37.0	53.8
	3	30.3	31.7	44.2
Unusual cry	2	3.0	4.0	14.4
	3	1.6	2.0	5.7
Crying ≥ 1hr	2	0.7	2.0	4.9
	3	0.5	1.0	1.8
Anorexia	2	6.9	9.5	11.1
	3	7.0	8.2	9.6
Vomiting	2	5.1	5.0	5.4
	3	4.5	4.4	4.0

Test of significance were not performed as these groups were not randomized. However, as can be seen rates of most systemic reactions were higher when CPDT was administered with concomitant vaccines than when given alone. This was particularly true for children who received CPDT with IPV/HIB. For the first dose, almost all children received CPDT alone.

Serious adverse events (SAE) were collected during the vaccination series until 2 months after the last dose or until 8 months of age if the child only received one or two doses. SAE were defined in the protocol as:

- Sudden death.
- Neurologic adverse events:
  (acute or subacute encephalitis/encephalomyelitis, encephalopathy, collapse or unexplained loss of consciousness, convulsions, infantile spasms, Reye's syndrome).
- General allergic reactions; anaphylactic reactions.
- Invasive bacterial infections.
- Other SAE of unforeseen nature in which the child's life is endangered.
- Onset of serious chronic disease.

A total of 48 serious adverse events from all vaccine groups were reported during the study period (Table 12). Overall, SAE were evenly distributed among the vaccine groups. However, five of the six hypotonic hyporesponsive reactions (HHE) occurred in the DTPwc group (Fisher exact test p-value = 0.04 compared to all other vaccine groups). The rate of HHE in the DTPwc group (N= 5) was not statistically different from the CPDT group (N= 1; p-value = 0.096, Fisher exact test). Among the 48 adverse events were two deaths from SIDS, neither one in the CPDT group. As noted above, the surveillance for SAE was censored 60 days after the third dose or at 8 months of age. However contact was maintained with families until the end of the trial (January 1995). Two additional deaths (not included in Table 12) were reported during this period of continued follow-up; neither was in CPDT recipients.

Table 47: Sweden I Efficacy Trial, SAE by Dose and By Vaccine Group

	Dose	Total N (%)	DT N (%)	DTaP-2 N (%)	CPDT N (%)	DTPwc N (%)
	1	9,829	2,574	2,566	**2,587**	2,102
	2	9,713	2,556	2,552	**2,565**	2,040
Reported Event	3	9,630	2,539	2,538	**2,551**	2,002
SIDS	1	2	0	1	**0**	1
	2					
	3					
	All	2	0	1	**0**	1
Acute encephalopathy	1-3	-	-	-	**-**	
HHE	1	4	0	0	**0**	4
	2	1	0	0	**0**	1
	3	1	0	0	**1**	0
	All	6	0	0	**1**	5
Convulsions/infantile	1	5	1	2	**2**	0
spasms	2	7	0	3	**3**	1
	3	12	8	0	**2**	2
	All	24	9 (0.3)	5 (0.2)	**7 (0.3)**	3 (0.1)
General allergic rxn Reye's syndrome	0	0	0	0	**0**	0
Invasive bacterial	1	3	0	1	**0**	2
infections	2					
	3					
	All	3	0	1	**0**	2
Apparent life	1					
threatening event	2	1	0	0	**1**	0
	3	1	0	0	**0**	1
	All	2	0	0	**1**	1
Onset of serious	1	6	3	1	**2**	0
chronic illness	2	2	1	0	**0**	1
	3	3	1	2	**0**	0
	All	11	5	3	**2**	1
Total	1	20	4	5	**4**	7
	2	11	1	3	**4**	3
	3	17	9	2	**3**	3
	All	48(0.5)	14 (0.5)	10 (0.4)	**11 (0.4)**	13 (0.6)

Convulsions and infantile spasms were two distinctive types of SAEs identified in the study. They were presented together in the technical report because of the small numbers in each category. In the CPDT group, there was one case of infantile spasms diagnosed 1½ months after dose 2 and six convulsions, one occurring 8 days after dose 1, one 34 days after dose 1, one 10 days after dose 2, one 47 days after dose 2, and one each 8 and 23 days after dose 3. There was one apparent life-threatening event (ALTE) in the CPDT group. Summaries follow for the ALTE and for the convulsions occurring within 14 days of vaccination:

Subject 1275: Male infant had first convulsion 8 days post-vaccination with 1st dose of CPDT. The infant was not febrile and had no other reactions to vaccination. The episode lasted ~90 seconds. The child was evaluated ~2 hours later and had a normal exam except that his temperature was 38.3°C. Had essentially normal EEG. There were no recurring episodes. The event was judged to be possibly related to vaccine.

Subject 8587: Infant male received his second dose of CPDT, Polio and Hib vaccinations and had convulsion lasting approximately 1 hour ten days post-vaccination. It was unclear if

infant was febrile at the time, but he had been diagnosed with a viral infection the day earlier and with otitis media the following day. He had no subsequent seizures but two months later was diagnosed with diabetes mellitus. The seizure and diabetes were both judged to be unrelated to vaccine.

Subject 9572: Infant male admitted with fever of ~41°C, convulsions, rash 8 days post-dose 3. Diagnosed with febrile seizures and gastroenteritis. He was discharged in good condition 5 days later.

Apparent life-threatening event (ALTE): There was one ALTE in the CPDT groups. A male infant experienced an episode of apnea and cyanosis 41 days post-dose 2, which lasted several minutes. The child was taken to the hospital by his parent and was hospitalized for three days. A work-up which consisted of an echocardiogram, EEG, and ultrasound of his head was unrevealing. The child had a full recovery.

HHE. There was one HHE in the CPDT group and 5 in the DTPwc group.
The rate of HHE in the whole cell group was not statistically different from the CPDT group (p-value = 0.096, Fisher exact test).

Subject 6749: Female infant received third dose of CPDT vaccine with Polio and ActHib. She had an unusual cry approximately four hours later. Eight hours post-vaccination she became limp and unresponsive for about an hour. She was given paracetamol and was able to eat two hours later. Event was judged to be an HHE and related to the vaccine.

Adverse events contraindicating (CAE) further trial doses: Parents were asked about CAE during the day 14 questionnaire, prior to the second and third doses and two months after the third dose. CAE were defined in the protocol as:

- Encephalopathy
- Seizures, with and without fever
- Persistent crying, 3 hours of more, within 24 hours of vaccination
- Generalized cyanosis, within 24 hours of vaccination
- Fever $\geq$ 40°C within 48 hours of vaccination
- Generalized allergic reaction within 48 hours of vaccination
- Shock-like reaction within 48 hours of vaccination

There were 163 events that contraindicated further vaccination (Table 13). These included HHE events, previously discussed under SAE.

Table 48: Sweden Efficacy Trial I, CAEs by Dose and by Vaccine Group

Event	Dose	**Total** N (%)	**DT** N (%)	**DTaP-2** N (%)	**CPDT N (%)**	**DTPwc** N (%)	**CPDT *vs.* DTPwc** RR 95% CI
	1	9,829	2,574	2,566	**2,587**	2,102	
	2	9,713	2,556	2,552	**2,565**	2,040	
	3	9,630	2,539	2,538	**2,551**	2,002	
HHE	1	4	0	0	**0**	4	
	2	1	0	0	**0**	1	
	3	1	0	0	**1**	0	
	All	6	0	0	**1**	5	
Convulsions,	1	9	2	3	**3**	1	
including suspected	2	12	3	3	**4**	2	
	3	15	9	0	**3**	3	
	All	36 (0.4)	14 (0.5)	6 (0.2)	**10 (0.4)**	6 (0.3)	
Protracted cry	1	20	0	0	**3**	17	0.14 0.04-0.49
	2	8	1	2	**1**	4	
	3	2	0	0	**0**	2	
	All	30 (0.3)	1	2 (0.1)	**4 (0.2)**	23(1.1)	0.14 0.05-0.39
Temperature	1	10	2	0	**1**	7	
≥ 40°C	2	10	2	1	**0**	7	
	3	21 (0.2)	3 (0.1)	3 (0.1)	**1**	14 (0.7)	
	All	41 (0.4)	7 (0.3)	4 (0.2)	**2 (0.1)**	28 (1.3)	0.06 0.01-0.24
Cyanosis	1	4	0	0	**0**	4	
	All	4	0	0	**0**	4	
Pronounced local	1	7	0	0	**0**	7	
reaction with general	2	7	0	0	**1**	6	
symptoms	All	14	0	0	**1**	13	
Other symptoms*	1	17	5	2	**4**	6	
	2	9	2	2	**2**	3	
	3	6	1	3	**0**	2	
	All	32 (0.3)	8 (0.3)	7 (0.3)	**6 (0.2)**	11 (0.5)	
Total	1	71 (0.7)	9 (0.3)	5 (0.2)	**11 (0.4)**	46 (22)	0.19 0.10-0.37
	2	47 (0.5)	8 (0.3)	8 (0.3)	**8 (0.3)**	23 (1.1)	0.28 0.12-0.62
	3	45 (0.5)	13 (0.5)	6 (0.2)	**5 (0.2)**	21 (1.0)	0.19 0.07-0.49
	All	163 (1.7)	30 (1.2)	19 (0.7)	**24 (0.9)**	90 (4.3)	0.22 0.14-0.34

"Other" symptoms: For the CPDT group the following events were listed (Table 48) under this category: Post-dose 1: apnea occurring 2½ days post-vaccination; apnea occurring 8 days post-vaccination; Kawasaki disease 34 days post-vaccination; suspected Leigh's disease with onset 26 days after dose 1 (Dose 2 and 3 were given). Post-dose 2: Apnea with cyanosis/ALTE 41 days post-vaccination; petechial rash 4 days post-vaccination.

Table 49: Sweden Efficacy Trial I, Selected SAEs and CAEs by Group By Time of Occurrence Post-Vaccination

		DT	DTaP-2	CPDT	DTPwc
		N N = 2,574	N N = 2,566	N N = 2,587	N N = 2,102
Generalized Cyanosis	<24 hr	0	0	0	4*
SIDS	0-≤ 3d	0	0	0	1
	4-≤ 7d	0	0	0	0
	8-≤ 60d	0	1	0	0
ALTE	0-≤ 3d	0	0	0	0
	4-≤ 7d	0	0	0	0
	8-≤ 60d	0	0	1	1
Other	0-≤3d	2	1	1	7
	4-≤ 7d	2	2	2	0
	8-≤ 60d	4	4	4	4
T ≥ 40° C	0- ≤ 3d	7	4	2	28**
Cry ≥ 3 hrs	<24 hr	1	2	4	23**
Marked local With general sxs	<24hr	0	0	1	13***
HHE	24hr	0	0	1	5

*Fisher exact test, $p < 0.04$
**CPDT vs. DTPwc: RR of rates, upper bound 95% CI < 1 .0
*** CPDT vs. DTPwc: $p < 0.001$, corrected chi square

Summaries follow for the events occurring within 14 days of vaccination:

Subject 2802: Infant female who had only mild erythema/induration at site of injection in first few days post-vaccination. On day 3 post-vaccination she began having crying spells that were felt to be stomach pain/colic. On day 8 post-vaccination, the child would not open her eyes when she was taken out of bed. Shortly thereafter, she started crying loudly and had a bowel movement. After crying she became lifeless/hypotonic, without pallor or cyanosis. This occurred 7-8 more times. The child was hospitalized for three days. Exam and laboratory tests were all normal. The event was judged to be unrelated to vaccine.

Subject 8804: Infant female was hospitalised two days post-vaccination following a 30 second episode of apnea and stiffness. This episode occurred shortly after she had been fed and vomited. Her exam was normal on admission and the discharge diagnosis was "reflex laryngospasm" thought to be unrelated to vaccine.

Convulsions, including suspected: This category includes all the seizures and infantile spasms cases listed under SAE. In addition, suspected seizures are included. For the CPDT group, there were three suspected seizures, one 26 hours after dose 1, one 3 days after dose 2, and one 43 days after dose 3. Summaries follow for those occurring within 14 days of vaccination:

Subject 931: Infant female who experienced two episodes of unresponsiveness post-dose 2, each lasting several seconds (study report states 3 days post-vaccination; case narrative states 1 day). Medical attention was not sought at the time and a decisionwas made not to give a third dose at the time of the next clinic visit.

Subject 991: Infant male who had some "whining" and anorexia in the evening following dose 1. The following day he had some twitching after being fed which was followed by stiffness and seizure like activity, lasting a few seconds. The child cried 15- 20 minutes thereafter. He had a normal exam when evaluated including a normal EEG.

Generalized event:

Subject 2417: Infant female who developed swelling of entire leg, with a blue red color, from thigh to foot in the limb where she had received CPDT on the day of vaccination. Her other foot was also discolored. She had received ActHib in that limb. The reactions resolved within hours, except for some red papules at the site of CPDT injection. The papules resolved several days later. Induration 2 x 4 cm persisted at the site.

Hospitalizations:

Hospital records were collected for all study participants who were hospitalized at any time from entry into the study until two months after the last dose or until the child was at least eighth months of age. The purpose was to identify children with invasive bacterial infections or seizures, and to determine whether the risk of hospitalization was increased among the DTPwc group.

Table 50: Sweden I Efficacy Trial, First Hospitalization From Time of Enrollment by Dose and Vaccine Group Until 60 Days Post-Dose 3 or 8 Month of Age*

	Total N (%)	**DT N (%)**	**DTaP-2 N (%)**	**CPDT N (%)**	**DTPwc N (%)**
Number of Infants	9,829	2,574	2,566	**2,587**	2,102
By Dose	9,713	2,556	2,552	**2,565**	2,040
	9,630	2,539	2,538	**2,551**	2,002
Total	175 (1.8)	44 (1.7)	43 (1.7)	**47 (1.8)**	41 (2.0)
	149 (1.5)	29 (1.1)	52 (2.0)	**34 (1.3)**	34 (1.7)
	134 (1.4)	41 (1.6)	32 (1.3)	**35 (1.4)**	26 (1.3)
	458 (4.7)	114 (4.4)	127 (4.9)	**116 (4.5)**	101 (4.8)

*If series not completed.

There were only three hospitalizations for serious bacterial infections, none in the CPDT group. Rates for all hospitalizations, hospitalizations for acute otitis media, suspected bacterial respiratory infection, lower respiratory infection – no antibiotics, upper respiratory infection – no antibiotics, viral infection, gastroenteritis, urinary tract infection, seizures, trauma/intoxication, surgery were similar among vaccine groups.

Comment: For SAE and CAE, protracted crying, fever ≥ 40°C, generalized cyanosis and generalized cyanosis and marked local reactions with generalized symptoms occurred less frequently in the CPDT group as compared to the DTPwc arm. For SAE (and CAE) HHE rates were higher in the DTPwc arm compared to all other groups combined, but not significantly higher when compared to the CPDT group where one HHE occurred *vs.* 5 in the DTPwc group. Rates of SAE and CAE were similar in the CPDT and the DT groups. Seizure rates were low in all groups and were not significantly different among vaccine groups. Two suspected seizures were reported within 3 days of vaccination in the CPDT group. Rates of first hospitalizations were similar among all groups; this was also true for "all hospitalizations" (data not shown).

8.3 Safety data from US Bridging Study

One of the aims of the US bridging study was to assess the safety and immunogenicity of CPDT with the concomitant administration of routine childhood immunizations. A total of 321 children were enrolled to receive CPDT Lot ---- or ---- at 2, 4, 6 months of age. Routine pediatric vaccines (OPV, HepB and HIB) were to be administered according to standard immunization practices. Parents were provided with diary cards to record rectal daily temperature and any injection site or systemic complaints at 6, 24, 48

and 72 hours following each injection of study vaccine. Telephone contact was made at days 4 and 14 post-vaccination. Information from the diary card was collected during these calls. Safety was also evaluated by interim histories designed to detect unreported events, intercurrent illnesses and severe or unexpected AEs at the time of the second and third doses and at a scheduled clinic visit 4-6 weeks following the third dose.

Table 51: US Bridging Study - Local Reactions Reported Within 72 hours Post-Vaccination by Dose

Symptom (%)	Dose		
	1	2	3
N	321	317	315
Any local reaction	37.4	33.4	31.1
Erythema – any	12.5	15.8	19.7
>1 inch	0.6	0.6	0.9
Swelling – any	14.3	15.5	17.6
>1 inch	0.6	0.9	1.6
Tenderness – any	30.5	19.6	15.9
Pain	18.4	11.3	6.6

Table 52: US Bridging Study - Systemic Reactions Reported Within 72 hours Post-Vaccination by Dose

Symptom (%)	Dose		
	1	2	3
N*	321	317	315
Any systemic rxn	83.8	72.6	65.7
Fever ≥ 38°C	11.8	9.8	9.8
Irritability	72	61.2	56.2
Tired	59.5	41.6	33.3
Anorexia	24.6	13.6	14.9
Rash	0.6	1.6	1.6
Vomiting	6.9	4.7	4.4
Unusual cry	0.6	0	0
Crying > 3 hrs	0.3	0	0
HHE	0.0	0	0

Comment: A comparator arm of either a DT, DTPwc or other US licensed DTaP vaccine was not included in this study. Rates of swelling and redness were somewhat lower than those reported in the Sweden I efficacy trial. Rates of anorexia were higher in the USBS but reports fever ≥ 38°C and of unusual crying were less frequent than in the Sweden I trial.

Serious Adverse Events in the US Bridging Study:

There were 5 reported serious adverse events (SAE). Only one of these, a seizure, was judged to be possibly related to vaccine (lot CPDT-----).

This SAE was a seizure in a male infant and occurred 14 hours post-dose 2. The subject experienced recurrent seizures over the next two days and was hospitalized and started on Phenobarbital. The child received OPV and OmniHIB concurrently with the second dose. The child was not febrile during the first three days post-vaccination. CT, MRI and EEG were

reportedly normal. The Phenobarbital was stopped four months later and the subject had no further episodes within the next 1½ year of available follow-up.

The other SAEs included one case of acute gastroenteritis and dehydration occurring 33 days post-dose 2; RSV infection in a subject beginning 13 days post-dose 1; Fifth disease resulting in hospitalization of a child 24 days post-dose 1; and intussusception in an infant 58 days post-dose 2.

8.4 Safety Results from the Phase 2, Canadian Multicenter Lot Consistency Study – Infant Series and Fourth Dose

This was the largest study in which children received four consecutive doses of CPDT at 2, 4, 6 and ~18 months of age. The study was a double blind, randomized multicenter study that evaluated the safety and immunogenicity of three lots of CPDT and a DTPwc vaccine. The infant series study was originally designed to evaluate consistency of manufacturing of the CPDT vaccine. As noted above, CBER did not accept pertussis antibody data for the purposes of demonstrating lot consistency.

The fourth dose study was designed to assess the safety and immunogenicity of CPDT in toddlers who had received an infant series of CPDT. The safety data from the infant series and fourth dose are presented below. Adverse event rates for the three groups who received CPDT vaccine were similar and the results obtained from the three groups have been pooled.

Design of phase 2 lot consistency study:

Primary series: The study was a multicenter, randomized, double blind study. Study children were randomized to receive one of the three lots of CPDT (----------) or a whole cell pertussis vaccine (DTPwc) with the same formulation as a licensed DTPwc vaccine in Canada except that it had a reduced diphtheria content and contained 0.6% 2-phenoxyethanol as a preservative. OPV was given concurrently with study vaccine at 2 and 4 months of age. A total of 432 subjects (108 per arm) were enrolled between November 1990 and July 1991. Overall, 49.5 percent were male; among CPDT recipients 52.5% were male.

Inclusion/Exclusion Criteria: Healthy 2 month-old children were recruited into the study. Children were excluded from participation if they had: 1) known or suspected disease of the immune system; 2) malignancy or receipt of immunosuppressive therapy; 3) major congenital malformations or conditions; 4) serious chronic illnesses including cardiac or renal disease; 5) personal or immediate family history of developmental delay or neurologic disorders, including seizures; 6) personal history of previous whooping cough.

Fourth Dose:

The fourth dose study included subjects who completed the primary series study and were eligible to receive a fourth dose at 18 months of age. The original primary series assignments were retained for the booster dose. The study remained double-blinded. Of the 423 subjects who completed the primary series, 398 (94%) participated in the fourth-dose study. OPV was given concurrently with study vaccines. The study was conducted between February and July 1992.

Safety Monitoring:

For all four doses, participants were monitored immediately post-vaccination and by telephone at 2-6 hours, 8-12 hours, 24 hours, 48 hours, 72 hours, and 7 days post-

vaccination. Following the first and second doses, information was collected prior to the next vaccination; following the third and fourth doses, information was collected by telephone (or visit) 28 days post-vaccination. Adverse events were collected during a structured telephone interview at each of the interval contacts.

Reactions were grouped into three time periods in the study report: "early", defined as within 48 hours, "delayed", defined as 72 hours to 7 days, and "late", from day 8 until the follow-up visit at 60 day or 28 days (dose 3 and dose 4). At FDA's request, the sponsor subsequently provided a summary of local reactions occurring within 72 hours. CBER reviewers calculated mean rates of reactions for the entire CPDT group from data provided for each lot. Mean rates of systemic reactions occurring within 48 hours, listed below, are those provided by the sponsor in the original submission.

Local Reactions – Phase 2 Lot Consistency Study:
Local reactions (Tables 53 and 54) were reported significantly less frequently in CPDT recipients as compared to DTPwc recipients. This was true for "any" and "clinically significant" swelling, redness, and tenderness.

Table 53: Canadian Lot Consistency Study, Local Reaction Rates (any) Within 72 Hours of Vaccination

AE	Vaccine	N[f]	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)	Dose 4 (%)
Swelling	CPDT	324	4.3	4.4	4.7	18.6
	DTPwc	108	23.1**	32.1**	25**	28.9*
Redness	CPDT	324	12.7	20.6	22.2	36.5
	DTPwc	108	44.4**	57.5**	51.9**	55.7**
Tenderness	CPDT	324	10.2	7.5	8.7	23.9
	DTPwc	108	37.0**	51.9**	48.1**	86.6**

Test of significance not performed for first 3 doses.
[f] Number with data following 1st dose
* Significant at the 0.05 level (Fisher's exact test – CBER statistician, A. Dale Horne, Ph.D.)
** Significant at the 0.01 level (Fisher's exact test – CBER statistician, A. Dale Horne, Ph.D.)

Table 54: Canadian Lot Consistency Study, Rates of Clinically Significant (CS) and Severe (S) Local Reaction Rates Within 72 Hours of Vaccination

		Dose 1 (%)		Dose 2 (%)		Dose 3 (%)		Dose 4 (%)	
AE	Vaccine	CS	S	CS	S	CS	S	CS	S
Swelling	CPDT	1.9	0.3	2.2	0	3.7	0.9	15.9	11.3
	DTPwc	15.7**	6.5**	21.7**	5.7**	14.4**	4.8*	25.8*	15.5
Redness	CPDT	1.2	0.3	7.8	0.3	10	1.6	27.9	21.9
	DTPwc	13.9**	3.7*	22.6**	5.7**	17.3	1.9	36.1	20.6
Tenderness	CPDT	0.9	0	1.2	0.3	1.3	0	3.0	0.3
	DTPwc	13**	4.6**	20.8**	7.5**	17.3**	4.8**	53.6**	12.4**

* Significant at the 0.05 level (Fisher's exact test – CBER statistician, A. Dale Horne, Ph.D.)
** Significant at the 0.01 level (Fisher's exact test – CBER statistician, A. Dale Horne, Ph.D.)
No significant difference noted for clinically significant or severe redness post-dose 3 or 4, or for severe swelling post-dose 4.
Parameters used to define severity of local reactions:
CS: Clinically significant, and includes moderate and severe reactions
Redness and Swelling: Mild <10 mm, Moderate. 10-34 mm, Severe ≥ 35 mm

Tenderness: Mild: momentary whimper/cry with gentle pressure, Moderate: more sustained cry, Severe: cries when leg is moved or with general handling.

Comment: Injection site reactions were significantly greater in the DTPwc group as compared to the CPDT group following all four doses and for most measured parameters. No significant difference was noted for clinically significant or severe redness post-dose 3 or 4, or for severe swelling post-dose 4
Within the CPDT group there was an increase in rates of all injection site reactions following the fourth dose as compared to rates observed following the third dose of vaccine. Specifically, any swelling increased from 4.7% to 18.6%, any redness from 22% to 36.4% and any tenderness increased from 8.6% to 23.9%. Rates of severe redness and swelling following the fourth dose were similar to rates reported following four doses of DTPwc, although rates of severe tenderness remained significantly lower in the CPDT group. Of note, rates of any swelling in the CPDT in this study were considerably lower than those observed in the Sweden I trial and the Phase 2 Lot consistency trial.

Systemic Reactions – Phase 2 Lot Consistency Study
Most solicited systemic reactions within 48 hours of vaccination (Tables 55 and 56) occurred more frequently in the DTPwc group as compared to the CPDT group. However, unlike injection site reactions, rates of systemic reactions did not increase significantly following the fourth dose as compared to the third dose within the CPDT group. Delayed (3-10 days) and late (11-60 days) reactions occurred at similar rates in the CPDT and DTPwc group following all doses.

Table 55: Canadian Lot Consistency Study, Systemic Reaction Rates (any) Within 48 Hours of Vaccination

AE	Vaccine	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)	Dose 4 (%)
Fever	CPDT	6.5*	4.7*	8.1*	10*
	DTPwc	34	44	43	62.9
Irritability	CPDT	37*	39*	36*	34.6*
	DTPwc	63	69	67	78.4
Prolonged Crying	CPDT	2.2*	3.1*	1.2*	0.7*
	DTPwc	12	12	7.7	7.2
High pitched Crying	CPDT	0.3	0.3	0	N/R
	DTPwc	3.7	2.8	1.9	N/R
Drowsiness	CPDT	42	21*	14*	12.6*
	DTPwc	52	33	33	29.9
Listlessness	CPDT	5.9*	1.6*	3.4*	3.3*
	DTPwc	18	10	14	28.9
Pallor	CPDT	5.2	2.2*	2.2	2.0*
	DTPwc	10	9.4	6.7	11.3
Decreased feeding	CPDT	15	8.1*	9.7*	15.6*
	DTPwc	21	15	22	41.2
Vomiting	CPDT	6.5	5.9	5.3	5.0
	DTPwc	12	8.5	9.6	7.2
Antipyretic Use	CPDT	94	89*	87*	67.1*
	DTPwc	99	99	100	97.9

* Statistically significant; rates between CPDT and DTPwc groups were compared by computing odds ratio and 95% CI. Intervals that did not include 1.00 are statistically significant. N/R: not solicited

Table 56: Canadian Lot Consistency Study, Rates of Clinically Significant (CS) and Severe (S) Local Reaction Rates Within 48 Hours of Vaccination

		Dose 1 (%)		Dose 2 (%)		Dose 3 (%)		Dose 4 (%)	
AE	Vaccine	CS	S	CS	S	CS	S	CS	S
Fever	CPDT	1.3*	0	1.2*	0	2.8*	0	3.3*	0
	DTPwc	14	0	22	0	19	0.9	32	0
Irritability	CPDT	6.8*	0	6.0*	0	4.0*	0	4.3*	0
	DTPwc	19	1.9	22	0	22	0	24.7	2.1
Prolonged Crying	CPDT	0.6	0	1.6*	0.3	0.9	0	0.3*	0
	DTPwc	4.7	0.9	7.5	0	2.9	0.9	5.2	1.0
Drowsiness	CPDT	7.7	0.3	2.2*	0	0.9	0	1.0*	0
	DTPwc	8.6	0	7.6	0	0	0	6.2	0
Listlessness	CPDT	0.9	0	0.3	0	0	0	0	0
	DTPwc	2.8	0.9	2.8	0	1.0	0	8.2	1.0
Pallor	CPDT	0.9	0	0	0	0	0	0.3	0
	DTPwc	2.8	0	0	0	1.9	0	1.0	1.0
Decreased feeding	CPDT	1.3	0	0.3	0	1.2	0	1.7*	0
	DTPwc	3.7	0	2.8	0	1.9	0	13.4	2.1
Vomiting	CPDT	0.9	0	0.7	0	0.3	0	0.3	0
	DTPwc	1.9	0	0	0	2.9	0	2.1	0

* Statistically significant: rates between CPDT and DTPwc groups were compared by computing odds ratio and 95% CI. Intervals that did not include 1.00 are statistically significant.

Parameters used to define severity of systemic reactions

CS: Clinically significant, and includes moderate and severe.

Fever: mild >37.5 - <38.0°C, moderate. ≥ 38.0 - <40.0°C, Severe: ≥ 40.0°C

Irritability: Mild: crying during feeding, require more cuddling, less interested in playing, Mod: more difficult to settle, Severe: persistent crying, unable to console

Prolonged/Unusual cry: Mild: ≥ 30 min, moderate. ≥1 hr -< 3 hrs, Severe: > 3 hours or more

Drowsiness: Mild: Increased sleepiness, moderate: Sleeping through feeds, Severe: Sleeping most of the time, difficult to arouse.

Listlessness: Mild: Less interested in surroundings, moderate: No interest in toys, less interested in feeds, Severe: No interest in surroundings and difficult to arouse.

Pallor: Mild: Lacks usual color; moderate: Very pale, without color; Severe: Severe pallor, looks pasty or gray

Decreased feeding: Mild: Eating less than normal for 1 or 2 feeds, moderate: missed 1 or 2 feeds completely, Severe: Little or no intake for more prolonged time.

Vomiting: Mild: 1 or 2 episodes w/o interfering with routine, moderate: Several episodes inability to keep food down; Severe: Little or no intake for more prolonged time.

Diarrhea: Mild: One or a few soft stools, moderate: Frequent runny stools, Severe: Multiple liquid stools, no solid consistency.

Comment: Rates of any fever prolonged crying, listlessness and irritability were significantly increased in the DTPwc arm as compared to the CDPT arm following all doses. This was also true for CS fever and irritability and for CS prolonged crying after 2nd and 4th doses. Pallor, decreased feeding and antipyretic use occurred significantly more frequently in the DTPwc group after the 2nd, 3rd and 4th doses.

Fever rates in this study (≥ 38°C) were reported at similar rates as in the USBS and less frequently than in the Sweden I trial.

Serious Adverse Events:
There were no serious adverse events, seizures or HHE reported following the infant series. A recipient of the whole-cell vaccine was reported to have had a seizure and HHE episode in the first 48 hours after vaccination following receipt of the fourth dose.

8.5 Additional Information and Summary Information of Local Reactions Following Fourth Dose of CPDT from All Clinical Studies:
As noted above in the Phase 2 lot consistency study, rates of local reactions increased significantly following receipt of a fourth dose of CPDT as compared to reaction rates following the third dose. Similar increases in local reactions were noted in the Phase 2C booster study (Canada), but not in the NIAID MAPT fourth dose study.

FDA requested additional information on severe local reactions following the fourth dose for all subjects in all clinical trials. Specifically, information on size of reactions, duration of reaction, extent of limb involvement, and interference with activity was requested. In their submission of August 2000, the sponsor noted that no specific information on duration of the reaction, extent of limb involvement, or interference with activity was available.

A fourth dose of CPDT was studied in children who had received three doses of CPDT in the infant series in the following studies: Phase 2 Lot consistency, (N = 301); NIAID MAPT cycle I (N = 75); Phase 2C (N = 72); ---------- (N = 29), and Phase 2B (N = 28). Duration of observation for most local reactions in these studies was 72 hours. There was a 10-day follow-up time point in studies 2B and 2C

Line listings of subjects with severe local reactions, which included size of the reactions and, where available, associated pain or tenderness, were provided. Although requested, for subjects enrolled in the NIAID MAPT Cycle I study, the sponsor did not specify whether subjects with severe reactions had received CPDT or DTPwc as infants. For the study ---------- the sponsor included information on children who had received the combination vaccine CPDT/ActHIB and did not identify which children received CPDT alone. The following is a summary of the information contained in line listings for the other three studies (Lot Consistency, NIAID MAPT Cycle I, Phase 2C).

<u>Phase 2, Lot Consistency:</u>
Redness: There were 66 subjects (22% of 301) with severe redness (≥ 35 mm) and 20 of these had redness of ≥ 50 mm in size. In 53 of these subjects the size of redness had decreased or resolved at the time of the last measurement; in the remaining 13 subjects the size of the reaction was either stable or increasing at the 72-hour time point.
Swelling: There were 33 subjects (11% of 301) with severe swelling (≥ 35 mm), 13 of these had swelling of ≥ 50 mm, and 2 had swelling of ≥ 100 mm. In 29 of these subjects the size of redness had decreased or resolved at the time of the last measurement; in the remaining 4 the size of the reaction was either stable or increasing at the 72-hour time point.

<u>Phase 2C:</u>
Redness: There were 11 subjects (15% of 72) with redness ≥ 35 mm; none exceeded 50 mm. In 6 of these subjects the size of redness had decreased or resolved at the time of the last measurement; in the remaining 5, the size of the reaction was either stable or increasing at the 72-hour time point.

Swelling: There were 8 subjects (11% of 72) with swelling ≥ 35 mm; none exceeded 50 mm. In all the size of the reaction was stable or increasing at 72 hours.

Phase 2B:
Redness: There were 5 subjects (18% of 28) with redness ≥ 35 mm; none exceeded 50 mm. In all subjects the erythema had decreased or resolved at 72 hours.
Swelling: Two subjects (7% of 28) had swelling of 35 and 36 mm, respectively. In both subjects the size of the swelling had resolved at 72 hours.

Summary of Injection Site Reactions Following Four Consecutive Doses of CPDT: Of the 401 subjects who are known to have received a fourth dose of CPDT following three doses in infancy, approximately 20% were reported as having redness of ≥ 35 mm within 72 hours of receipt of the fourth dose and 10.7% reported swelling of ≥ 35 mm. In most subjects the size of the local reaction had decreased or resolved by the end of follow-up (72 hours), but in a minority (~4.5% with redness and ~3% with swelling) the size of the reaction was either increasing or remained large at the last follow-up time reported. Information on pain and/or tenderness associated with these severe reactions was difficult to evaluate from the line listings. However, overall rates of tenderness were provided in the study reports for the Phase 2 Lot Consistency Study (23.9% post-dose 4 within 72 hours), for the Phase 2C Study (20.8% post-dose 4 within 24 hours), for the Phase 2B (42.9% post-dose 4 within 72 hours) and for the NIAID MAPT study (20% reported pain post-dose 4 at 72 hours).

8.6 Safety of the Hybrid Formulation (HCPDT):
As noted previously, the pertussis vaccine HCPDT manufactured by APL contains the same components as CPDT but contains twice the amount of PT (20 μg *vs.* 10μg) and four times the amount of FHA (20 μg *vs*. 5 μg).
The sponsor submitted safety data from the HCPDT vaccine in support of the CPDT license application. HCPDT was studied in a number of Phase I and 2 studies in which post-vaccination local and systemic reactions were compared to CPDT. In general, the safety profile for these reactions was similar to CPDT. This review will focus on serious adverse events that occurred following vaccination with the HCPDT vaccine.

Size of Safety Database with HCPDT
Table 57: Safety Database: Number of Subjects Who Received HCPDT and the Number of Doses Administered.

Schedule	Number of Subjects	Number of Doses
Infant series		
3, 5, 12 months	18,196	53,907
2, 4, 6 months	4,416	13,050
2,3,4	500	1,497
Total infant series	**23,112**	**68,454**
Fourth dose 15 – 20 months		
After 3 doses of HCPDT	783*	783*
After 3 doses of DTPwc	288	288
Total fourth dose	**1,071**	**1,071**
TOTAL	**23,400**	**69,525**

* These 783 toddlers are included among the 23,112 subjects listed for infant series above

8.7 Sweden Efficacy Trial 2 Safety Results

This was the largest study in which the safety of the HCPDT vaccine was evaluated. The aim of the study was to estimate the relative efficacy of three acellular vaccines as compared to a DTPwc vaccine (Medeva). The size of the study required to assess relative efficacy precluded active surveillance of local and systemic post-vaccination adverse events. Surveillance for safety was, therefore, directed towards detecting serious adverse events (SAE) and contraindicating adverse events (CAE).

A total of 82,892 infants were enrolled in the study; of these, 20,747 were randomized to the HCPDT arm. The majority of infants, 72,655 (18,183 in the HCPDT group) received vaccine at 3, 5 and 12 month of age. A subset of 10,191 (12% of total) received vaccine at 2, 4, and 6 months of age (2,551 in the HCPDT group).

The investigators recommended that IPV (SBL-vaccin AB, Sweden) and Act-HIB (produced by Aventis-Pasteur) be mixed in the same syringe and given intramuscularly in the opposite limb. In study groups that received DTP vaccines at 2, 4, and 6 months of age, IPV and Act-HIB were to be given at 2, 4 and 12 months of age.

SAEs were to be reported by study personnel to the clinical safety investigator during the primary vaccination series and for up to two months after the receipt of the last dose. These reports were supplemented by active surveillance of all hospitalizations of study participants with any of the following conditions: death, anaphylactic shock, encephalitis/encephalopathy, infantile spasms, invasive bacterial infections, HHE, or loss of consciousness. CAE were identified through spontaneous reporting and reports from Child Health Centers (CHC). Additionally, parents were queried for information regarding events at the time of the second and third vaccinations and at 18 months of age.

In order to describe and to determine the outcome of a reported event, investigators reviewed medical records. For further clarification, some parents, including all parents of children with HHE, were contacted by phone. Vaccines given and time of vaccination were determined from review of CHC medical records. Vaccination Registration Forms with incomplete information on contraindicating events or inconsistent with previously reported events were investigated by contacting the CHC. One of the investigators classified AEs and established date of onset.

The safety analysis included all children who had received at least one dose of vaccine. For the pre-planned analysis of safety, follow-up ended on 4 August 1995 when efficacy results from Trial I became available. Vaccine codes were broken for the 385 children who had experienced an SAE or CAE and for recipients of the 2-component vaccine, DTaP-2.

CAE: Adverse events that contraindicated receipt of a subsequent dose were defined in the protocol as:

- Severe neurologic symptoms (within 72 hours of the dose)
- Rectal fever of 40.5°C or more (within 24 hours of the dose)
- Systemic allergic reactions (within 48 hours of the dose)
- Shock-like reaction, including HHE (within 48 hours of the dose)
- Seizures, with or without fever

There were 300 events that contraindicated further vaccination occurring during the study period, before 4 August 1995, and within 6 months of the last study dose. Of these, 127 were also classified as SAEs (HHE, infantile spasms, convulsions ≥ 30 minute duration).

Table 58: Sweden 2 Efficacy Trial, CAE by Dose and By Vaccine Group

	Dose	Total 82,892 N (%)	**HCPDT 20,745 N (%)**	DTaP-2 20,692 N (%)	DTaP-3 20,725 N (%)	DTPwc 20,716 N (%)
Severe neurological symptoms within 72 hrs 1-3		0	**0**	0	0	0
Fever >40.5°C or more within 24 hrs	1	36	**3**	9	7	17
	2	24	**2**	5	4	13
	3	14	**2**	1	4	7
	1-3	74 (0.9)	**7 (.03)**	15 (0.07)	15 (0.07)	37 (0.18)
HHE	1	87	**20**	22	15	30
	2	13	**8**	0	1	4
	3	1	**1**	0	0	0
	1-3	101 (.12)	**29 (.14)**	22 (.11)	16 (0.08)	34 (.16)
	[# Hosp]	[33]	**[7]**	[7]	[6]	[13]
Infantile spasm	1	3	**0**	1	1	1
	2	9	**2**	1	2	4
	3	0	**0**	0	0	0
	1-3	12	**2**	2	3	5
Convulsions, including suspected	1	40	**3**	8	15	14
	2	61	**13**	15	14	19
	3	13	**2**	3	4	4
	1-3	114	**18**	26	33	37
Total	1	165	**26**	39	36	62
	2	107	**25**	21	21	40
	3	28	**5**	4	8	11
	1-3	300	**56**	64	67	113

Fever > 40.5°C within 24 hours of vaccination – Fever > 40.5°C occurred significantly less frequently in the HCPDT group as compared to the DTPwc group (RR = 0.19, 95%CI: 0.08-0.42).
Convulsions and suspected convulsions - A total of 114 cases were reported. Among all vaccine groups, there were a total of 25 convulsions or suspected convulsions reported within 48 hours of vaccination. Of these, there were 4 in the HCPDT group and 13 in the DTPwc group (RR = 0.31; 95% CI: 0.10-0.94).

SAE: Children were monitored for serious adverse events until 6 months after dose three or until 8 months of age if they had received only one or two doses of trial vaccine. SAE were defined in the protocol as:

- Sudden death.
- Severe neurologic reactions.
  - Acute neurological 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.

- Systemic allergic reactions within 48 hours of vaccinations.
- Invasive bacterial infections.
- Other SAE of unforeseen nature in which the child's life is endangered.

There were 190 SAEs, and 182 occurred within 6 months of the last trial dose and before 4 August 1995. All but one of the children had received Act-Hib and IPV concurrently.

Table 59: Sweden 2 Efficacy Trial, SAE by Dose and By Vaccine Group

Serious Event	Dose	Total 82,892 N	**HCPDT 20,745 N**	DTaP-2 20,692 N	DTaP-3 20,725 N	DTPwc 20,716 N
Death	1 2 3 All	14 14 2 30	**1** **3** **0** **4**	4 3 1 8	4 5 1 10	5 3 0 8
Acute severe neurologic event >30 minutes	1 2 3 All	3 6 3 12	**0** **1** **0** **1**	0 0 1 1	2 2 0 4	1 3 2 6
Infantile spasm	1 2 3 All	3 9 0 12	**0** **2** **0** **2**	1 1 0 2	1 2 0 3	1 4 0 5
HHE (#Hosp.)	1 2 3 All	87 (28) 13 (4) 1 (1) 101	**20 (6)** **8 (0)** **1 (1)** **29**	22 (7) 0 0 22	15 (5) 1 (1) 0 16	30 4 0 34
General allergic rx	0					
Invasive bacterial infections	1 2 3 All	5 12 4 21	**3** **5** **1** **9**	0 3 1 4	1 1 0 2	1 3 2 6
Other life threatening event	1 2 3 All	4 3 0 7	**0** **2** **0** **2**	2 0 0 2	1 0 0 1	1 1 0 2
Total	1 2 3 All	116 56 10 182	**24** **21** **2** **47**	29 7 3 39	24 11 1 36	39 17 4 60

Infantile spasms, acute neurologic events >30 minutes, convulsions >30 minutes were mutually exclusive diagnoses.

There were no statistically significant differences between the four vaccine groups with respect to events classified as SAE: SIDS, other deaths, acute neurologic events with a duration of > 30 minutes, infantile spasms, HHE or other life threatening events.

Deaths: Among all vaccine groups, there were a total of 30 deaths reported through 4 August 1995 (43 through October 7, 1996).
SIDS: There were 13 deaths from SIDS. In a non-randomized post-hoc comparison of participants and non-participants in Trial 2, SIDS occurred at a lower rate in study participants than in non-participants. The cohorts included children born between 1

June 1993 and 31 May1994 (N= 82,892 study participants, 17,607 non-participants). The incidence in participants was 11/100,000 children vs. 85/100,000 infants in non-participants (RR = 0.13, 95%CI: 0.06-0.29).
Other deaths: Five children died of injuries; four died of infections, one of which was an invasive bacterial infection; three children died of congenital heart disease; two died of hepatic disease; and one child died of each of the following disorders: Krabbe's disease, Leigh's disease, and Pompe's disease.

Deaths in HCPDT group: There were 10 deaths in the HCPDT group through October 1996 (end of efficacy follow-up). Case narratives for the deaths occurring in Trial 2 were provided in an August 2000 submission from the sponsor. Summary information about the two cases of SIDS and one case of "sudden death" is provided later in this document. The age of the infants at death was not provided. In the HCPDT group, there also was one case each of accidental strangulation, skull fracture and brain injury, drowning, intestinal dysplasia, metastatic brain ependymoma, congenital heart disease, and Pompe's disease.

Hospitalizations within 30 days of vaccination: Hospitalization information was not specifically collected unless the hospitalization was directly related to contraindicating events or was an SAE as defined in the protocol. The number of SAEs and CAEs within 30 days of vaccination that required hospitalization was 17 in the HCPDT group, 16 in DTaP-2 group, 14 in DTaP-3 and 28 in the DTPwc group.

HHE rates in Sweden Trial 2: There were 101 cases of HHE in Trial 2. The incidence was 16/10,000 children in the DTPwc group, 14/10,000 in the HCPDT group, 11/10,000 in the DTaP-2 group and 8/10,000 children in the DTaP-3 group. The rate of HHE in the DTPwc group (vaccine manufactured by ---------) was similar to that observed in DTPwc group (vaccine manufactured by ----) in Sweden Trial I. However, rates of HHE were higher in the acellular vaccine groups than those observed in Trial I or in other studies of acellular pertussis vaccines (Of note, the DTaP-2 vaccine was included in both Trial I and Trial 2). Possible explanations for this increased rate provided by the investigators in the Ttechnical Report for Trial 2 included:

1) Increased rates of concomitant immunization in Trial 2 vs. Trial I;
2) Variation in pain caused by vaccination. The investigators noted that in a study of a single component pertussis vaccine in which no HHE episodes were reported, vaccines were given subcutaneously (*N Engl J Med* 1995 Oct 19; 333(16): 1045-50). The subcutaneous administration was associated with less pain than had been observed with routine IM administration of the vaccines. However, in Trial I administration of study vaccines was by the IM route and rates of HHE were lower;
3) Variation of case definition. The authors noted that there was no specific definition for HHE. For Sweden Trial I, HHE was not prospectively defined and HHE was described as an episode of pallor, lack of muscle tone, and hyporesponsiveness. For Sweden Trial 2, the case definition was prospectively defined as a condition in which a child had loss of muscle tone and a diminished or absent response to stimulation.
4) In their August 2000 submission, the sponsor stated that they had solicited the opinion of Dr. Olin, the principal investigator for Trial 2. Dr. Olin suggested that the increased rates of HHE observed in Trial 2 might have resulted from better education of study personnel and parents that, in turn, led to increased reporting.

Clinical Characteristics of HHE Episodes and Follow-up of Children with HHE in Trial 2:
The duration of HHE and rates of hospitalization for HHE were not significantly different between vaccine groups. Review of the case report forms revealed that in the HCPDT group, all HHE cases occurred within 24 hours. Twenty of the 29 cases occurring in the HCPDT group resolved in 60 minutes and only two episodes lasted for more than two hours. Fourteen of the 29 children received no medical care. One child received "primary care", fourteen went to the emergency room, and seven of these were hospitalized. All children recovered without sequelae.

One hundred (of the 101) children who experienced an HHE episode were evaluated at 18 months as part of the regular CHC program. The evaluation consisted of a few simple tests and all 100 children were classified as showing normal development. One child who had moved outside the country was not evaluated but was reported to have developed normally at 18 months. Results of the evaluation are summarized below:

Table 60: Sweden Trial 2, Follow-Up Evaluation of Children with HHE

Test	HHE (N=100)			Ref. Population (N=3,126)*		
	Pass	Fail	No info	Pass	Fail	No info
Walking without support	93%	1%	8%	92%	1%	8%
Building a tower with blocks	86%	0%	14%	88%	2%	10%
Simple drawings	87%	0%	13%	87%	2%	11%
Speak and understand simple words	85%	5%	10%	85%	5%	10%
Point to different parts of the body	88%	1%	13%	84%	4%	12%
Take off cap and stockings	85%	2%	13%	86%	1%	12%

*Unpublished material, Department of Pediatrics, Eskilstuna

Comment: There were no significant differences between the vaccine groups for most SAE and CAE events, and in particular between the HCPDT and DTPwc group. However, high fever >40.5°C occurring within 24 hours and for convulsions or suspected convulsions occurring within 48 hours of vaccination were noted significantly more frequently in the DTPwc group as compared to the HCPDT group.

8.8 SAEs Following Receipt of CPDT and HCPDT Vaccines From All Studies:
Deaths:
No deaths were reported in any of the clinical trials following receipt of CPDT.
There were a total of 12 deaths reported following receipt of HCPDT. Ten of the 12 deaths were reported in the Sweden 2 efficacy trial, where the rate of death did not differ as compared to the other vaccine groups. Of these, two children died of SIDS and one of "sudden death". There were two additional cases of SIDS following receipt of the HCPDT vaccine, both in the Phase 2C study. A total of 4 cases of SIDS were reported, and one case of "sudden death." As noted above, this child died 175 days post-dose three, but the age of the child at the time of his death and the vaccine schedule to which he was assigned (3, 5, 12 months vs. 2, 4, 6 months) was not provided.

From Trial 2:
Subject 10756: SIDS, premature infant male born at 34 weeks gestation, birth weight 2.515 Kg. Developed normally except for hospitalization for viral illness on October 4-5, 1993.

Received first dose on ---------- and died in his sleep on ----------, 28 days post-vaccination.
Subject 12019: SIDS. Infant female died 49 days post-dose 2. The infant was found lifeless in bed in the morning. On arrival at the hospital she was pronounced dead.
Subject 84529: "Sudden Death". Infant male died 175 days post-dose 3 of HCPDT ActHIB/IPV. The child was found lifeless in bed and autopsy revealed no abnormal findings.

From Phase 2C study:

Subject US-2C-140. Male infant DOB ---------- received HCPDT, OPV, Hib, HepB on ---------. Post-vaccination course was uneventful except for some mild injection site tenderness at 24 hours and an "unusual crying" on day 14 which was not characterized as high pitched in nature. He was also described as unusually fussy 48 hours post-vaccination that prompted a call to the physician. The child died on ---------- (20 days post-vaccination) of what was presumed to be SIDS at his day care center. An autopsy was performed. The lungs had areas of atelectasis and there were petechial hemorrhages. The child had died while sleeping on a waterbed and these finding were consistent with either a diagnosis of SIDS or suffocation.
Subject HFX-2C-002. Male infant DOB ---------- received first doses of HCPDT, OPV, ActHib on ----------. The child was reported as being mildly fussy 24 hours post-vaccination and having mild diarrhea. The child died 6 days post-vaccination, having been found by his mother between 8-9 am in the morning, cyanotic without respiration or pulse. An autopsy was performed and the death was judged to be related to SIDS.

The sponsor calculated the rate of SIDS for the HCPDT group as 0.17 per 1000 children and 0.06 per 1000 doses. This did not include the "sudden death" case reported in Trial 2. Inclusion of that case would yield a rate of 0.217 per 1000 children and 0.07 per 1000 doses.

HHE

There was a single case of HHE following receipt of CPDT in the Sweden I trial. No other HHE cases were reported in studies with CPDT. The overall rate for the infant series was 0.26 per 1000 children and 0.09 per 1000 doses. If the fourth dose is included, the rate of HHE was 0.25 per 1000 children and 0.08 per 1000 doses.
The rate of HHE in the DTPwc vaccine in Sweden Trial I was 1.9 per 1,000 children. Total number of doses given to the DTPwc group was not provided.

There were a total of 33 cases of HHE in clinical studies of HCPDT, 29 of these occurred in Sweden Trial 2. Thirty-two cases occurred in the infant series and one case occurred following receipt of the fourth dose. The rate of HHE for the infant series was 1.38 per 1000 children and 0.47 per 1000 doses. The rate for all doses was 1.41 per 1000 children and 0.47 per 1000 doses.

The rate of HHE in the ---------- DTPwc group was 1.64 per 1000 children. Total number of doses given to the DTPwc group was not provided.

Seizures:

Sweden Trial I: There was a total of 10 seizures (0.4%), including suspected seizures, in Trial I in subjects who received CPDT. Two of these, both classified as suspected seizures (CAE), occurred within 3 days of vaccination. The rates of seizures, including suspected seizures, were not increased as compared to the DT group.
There were two additional seizure reported in the US studies, the USBS and the ongoing study ---------- (see below). In the USBS, the event was judged as possibly related to

vaccination and had an onset at 14 hours post-dose 2. In an ongoing study in the US, Study ----------, designed to assess the safety and immunogenicity of CPDT given at 2, 4, 5, and 15-16 months of age with routine recommended childhood vaccines, another seizure was reported post-dose 1. This event also occurred within the same day as vaccination, was afebrile, and was judged probably/likely related to vaccine. To date, 777 subjects in this trial have received their first dose although collection of safety data from these subjects was not complete at the time of the interim report (see below under post-marketing commitment section for further details of the study and the event). Thus in the two US studies designed in part to evaluate the safety of CPDT when given with routinely recommended vaccines the rate of seizures is 2/1098 children. Of note, the infant doses have not all been given in ---------- and data collection from the 777 subjects is incomplete.

There were 18 seizures, including suspected (0.09%), in the HCPDT group of Trial 2, four of these occurred within three days of vaccination. The rates were similar to that observed in the other vaccine groups. There were no other seizures reported in the other studies of HCPDT.

Other Severe Reactions in Clinical Trials with CPDT
There was one case of urticaria on the knee below the injection site with onset 3 hours following the 1st immunization in the CPDT group of the MAPT NIAID Cycle 1 Trial.

8.9 Summary, Conclusions, and Recommendations Regarding The Safety Data Submitted in Support of CPDT Vaccine
[Note, includes data obtained from trials with CPDT and HCPDT]

Summary of Local and Systemic Post-Vaccination Reactions Following Receipt of CPDT at 2, 4, 6 and 17-18 Months of Age.
Local and systemic reactions post-vaccination with CPDT from the three largest trials submitted to the PLA are summarized above. In the Sweden I trial, which included DT and DTPwc controls, the safety profile of CPDT for these reactions was similar to that of the DT control and CPDT was significantly less reactogenic than the DTPwc following all three doses. In the Phase 2 Lot Consistency study that included a DTPwc arm, CPDT was all significantly less reactogenic for local and systemic reaction as compared to the DTPwc vaccine. Rates of injection site reactions increased following the 4th dose of CPDT as compared those reported following the 3rd dose. Following receipt of the 4th dose, rates in clinically significant or severe redness and severe swelling were not significantly different from those observed in the DTPwc arm.
Injection site reactions following the fourth consecutive dose from all studies submitted to the application is summarized above. Data are available on a total 401 subjects. Approximately 20% had "severe redness" defined as $\geq$ 35 mm and 11% had severe swelling (same definition). Data were not consistently obtained on pain and tenderness associated with these reactions and neither were data on total limb swelling and or interference with activity. Increases in severity of injection site reactions have been noted to increase with consecutive doses of other licensed DTaP vaccines, particularly following receipt of the 4th and 5th doses.

Systemic post-vaccination reactions occurred at similar rates following receipt of CPDT vaccine and DT vaccine when these two vaccines were included in the same study. Fewer systemic reactions were noted in trials that compared CPDT vaccine to whole cell pertussis vaccines. Few data are available on use of CPDT with routinely recommended

vaccines given according to the US schedule. In a post-hoc analysis of subjects in the Sweden I trial, subjects who received IPV or IPV/Hib appeared to have a higher incidence of systemic reactions than those children who did not. While Hib vaccine was given in the USBS systemic reactions were not generally increased as compared to the Sweden I trial. However, these children received OPV instead of IPV, the current US standard. While some children received Hepatitis B concurrently with CPDT, the overall numbers who received it with all 3 doses was relatively small. No safety data are available for the use of MMR vaccine, Varicella vaccine and the recently licensed pneumococcal conjugate vaccine, Prevnar, when given concurrently with CPDT.

Post-marketing studies should be designed to better quantify and characterize injection site reactions following four consecutive dose of CPDT vaccine. Such a study should be adequately designed to assess the safety of CPDT when given with the currently recommended childhood vaccines.

CAE, SAE events and hospitalizations occurred at low rates in the Sweden I Trial in all vaccine groups. Rates in the CPDT were not significantly different from those observed in the DT control group or from those observed in the DTPwc group. There were some significant differences in severe reactions occurring within the 24-48 hours post vaccination between the CPDT and DTPwc group, with fever $\geq 40^{\circ}C$, generalized cyanosis, and marked local reactions with generalized symptoms occurring more frequently in the DTPwc group. HHE was significantly increased in the DTPwc arm when compared to the rate of HHE in the three other study groups combined, but not when compared to the CPDT group. Rates of seizures in the CPDT group were not increased as compared to the DT arm. Two seizures have been reported in the two studies designed to assess the safety of CPDT when given with routinely recommended childhood vaccines (USBS, ----------). No deaths were reported in any of the studies of CPDT submitted to the application.

In Sweden 2 Trial, rates of SIDS and sudden death occurred at similar rates in all vaccine groups. No DT control group was included in this study. Rates of convulsions or suspected convulsions occurring within 48 hours of vaccination and high fever within 24 hours ($> 40.5^{\circ}C$) occurred significantly less frequently in the HCPDT group than in the DTPwc group.

Rates of HHE were increased in all DTaP arms in the Sweden 2 Trial as compared to historical data and occurred at similar rates as in the DTPwc arm. The reasons for the high rates of HHE in all vaccine groups in this study remain unclear. Of concern is that a similarly high rate of HHE was also noted in other studies of HCPDT submitted to the PLA. The incidence of HHE in 8 studies of DTaP vaccine was compared in a publication by Heijbel et. al., *Dev. Biological Standard.*, in 1997. Rates of HHE were shown to be quite variable from 0/100,000 children to 167/100,000. In one study, a high rate was noted in a DT group. Nevertheless, in studies of HCPDT the rate has been consistently high rate. The follow-up study designed to measure gross developmental delay of children with HHE in the Sweden 2 Trial is consistent with the benign nature of HHE reported in other studies. However, but long term follow up and studies to detect subtle neurologic deficits have not been reported from most children who experience such episodes following vaccination.

A large postmarketing study should be conducted to assess the rates of HHE following receipt of CPDT and to assess whether rates of HHE following receipt of CPDT are

higher than those observed following receipt of other licensed DTaP vaccines. Additionally, rates of seizures should be further evaluated when CPDT is given with routinely recommended childhood vaccines. Ideally, such a study would include a provision for long-term follow-up of children who do experience an HHE episode or a seizure, with emphasis on neurologic function.

9.0 Compatibility of CPDT with Routine Concurrent Immunization

CPDT has been given concurrently with routinely recommended childhood vaccines in several clinical trials (see table below). Safety data with concurrent immunization were summarized above in the section of safety of the CPDT vaccine. The immune responses to oral poliovirus vaccine, Haemophilus influenza type b vaccine (Hib) and Hepatitis b vaccine were available from a subset of children enrolled in the US bridging study. There are no safety or immunogenicty data on concomitant use of CPDT with Prevnar, MMR, or Varicella vaccine and no immunogenicity data available on use of CPDT with IPV.

Table 61: Number of Children Who Received Routine Concurrent Immunizations with CPDT Studies.

	HIB	OPV	HEP B
Infant series			
Phase 2 Lot consistency		324	
NIAID MAPT cycle I	137*	137**	
NIAID MAPT cycle 2	75	75	
Phase 2 C	291	291	
Phase 2 B		34	
US bridging study	321	305	102[f]
Fourth dose			
Phase IB	34		
Phase 2C/PB9301	101	101	
Phase 2/2B		329	
NIAID cycle I		75	

*Introduced during the course of the trial and was administered to most infants, exact number not available.
** Given at 2, 4 months concurrently with dose 1 and 2
[f] Given at 0, 2, 6 months of age

Immunogenicity of concurrent administration:

Immunogenicity data on concurrently administered vaccines were available from the US Bridging Study and these are summarized below. Immunogenicity results were provided by CPDT vaccine group (i.e. lot CPDT----- or lot CPDT-----). There is no comparator group who did not receive CPDT with other routinely recommended vaccines.

9.1 Haemophilus influenza type B (HIB) – Infant Series

Concurrent immunizations in the USBS were to be given according to local practices. Thus, different HIB vaccines were allowed within the trial. However, the majority of children received PRP-T (ActHIB or OmniHIB) concurrently with CPDT (Lot CPDT----: N = 144; Lot CPDT-----: N = 138). Responses to HIB for children who received PRP-T and CPDT and from whom serum was available for HIB assays are provided below:

Table 62: Anti Hib-PRP GMCs (µg/mL) Post-Dose 3 With Administration of CPDT Lots ---- and ----

	Lot ---- (N = 126)	Lot ---- (N = 132)
GMC (µg/ml)	4.26	4.10
% ≥ 0.15 µg/ml	96.8	97
% ≥ 1.0 µg/ml	84.1	81.1

Fourth Dose:
There are no data on the immunogenicity of HIB vaccine, given as a fourth dose in toddlers who received three doses of CPDT and HIB vaccine as infants. In study ---------- a small number of toddlers were immunized with a combination vaccine CPDT/ActHIB (N = 26), or CPDT + ActHIB given separately either on the same day (N = 29) or ~30 days later (N = 26). These infants who were enrolled had received 3 doses of CPDT as infants as part of a Phase 2C study in Canada, but had not received concurrent immunizations with HIB vaccine as infants. All toddlers in ---------- had > 1 mcg/ml antibody to PRP post-HIB vaccination. Serology for the pertussis antigens was performed prior to assay validation in 1999.

9.2 Oral Poliovirus Vaccine

No data are available on responses to IPV given concurrently with CPDT in the infant series.
In the US Bridging Study, the majority of children received oral poliomyelitis virus vaccine (OPV) concurrently with CPDT at 2, 4, 6 months of age (Lot CPDT----: N = 152; Lot CPDT-----; N = 153). Responses were analyzed for these children from whom sera were available by calculating the percentage of subjects who demonstrated ≥ 1:4 (seroprotection) and ≥ 1:8 (seroconversion) neutralizing antibodies to each of the polio types. GMTs to each polio type were also calculated.

Table 63: Antibody Responses to IPV and GMTs (µg/mL) Post-Dose 3 With Administration of CPDT Lots ---- and ----

	Seroconversion Rates (% of subjects)			GMTs	
Test		Lot		Lot	
		---- (N=83)	---- (N = 95)	----	----
Polio 1	≥ 1:4	100	100	321	378
	≥ 1:8	100	100		
Polio 2	≥ 1:4	100	100	1814	1401
	≥ 1:8	100	100		
Polio 3	≥ 1:4	98.8	98.9	266	311
	≥ 1:8	97.6	98.9		

The sponsor provided some information in the form of summary tables from a study in which HCPDT was given with OPV or in combination with IPV (mIPV or vIPV), study ----------. These data indicate that following a 4th dose, all children who receive IPV

in combination with HCPDT had neutralizing antibody titer ≥ 1:32 for all three polio types, (n = ~81-85/group). The GMTs for types 1 and e were higher following receipt of one of the IPV preparations that following receipt of OPV. Tests of significance were not performed.

9.3 Hepatitis B:
As noted above, concurrent immunizations were given according to local practices. Thus the schedule of Hepatitis B immunization and the manufacturer of the vaccine used was not pre-specified. Approximately 102 children received Hepatitis B vaccine at 0, 2, 6 months of age. Hepatitis B responses were provided for those children for whom serum was available. Since Hepatitis B serology was done only if sufficient serum was available after testing for all other antigens, the number of children included is low.

Table 64: USBS, Percent of Subjects Achieving 3 10 mIU/mL Hepatitis B Antibody Level and GMCs Post Dose 3 With Administration of CPDT Lots ---- and ----

Vaccine Group	Lot ---- (95% CI)	Lot ---- (95% CI)
Post-Dose 3	N=42	N=40
GMC	436.44 (240.4, 792.32)	873.4 (483.98, 1576.15)
% ≥ 10 mIU/ml	97.6 (87.4, 99.9)	97.5 (86.8, 99.9)

9.4 Summary, Conclusions, and Recommendations Regarding The Data Submitted in Support of CPDT Vaccine Administered with Concomitant Vaccines.
Comparator groups of children who received routinely recommended vaccine without CPDT are not available to assess the impact of administering CPDT on the immune response of these vaccines. Furthermore, the numbers of children with serum available for Hepatitis b responses and, to a lesser extent OPV was small. Thus, the available data are difficult to interpret. Nevertheless, responses are within the range of historical data obtained following immunization with these vaccines.

[

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10.0 Summary of Other Studies Submitted in Support of the CPDT Application.

Safety and Immunogenicity of the Connaught Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed (CPDT), in Calgary, Alberta; Surrey, Maple Ridge and Coquitlam, British Columbia, Canada – Lot Consistency Study - Primary series

Note: Safety and Immunogenicity have been summarized in sections on efficacy and safety. Trial design/conduct is summarized in further detail here.

Location: Canada

Study Date: November 1990-July 1991

Lot Number: ----------. The whole cell vaccine lot was ---------- and contained a reduced amount of diphtheria (15 Lf vs. 25 Lf) from the licensed vaccine available in Canada and a different preservative (0.6% 2-phenoxyethanol).

Study Objectives: Demonstrating consistency of manufacturing by comparing the immunogenicity and safety of three consecutively manufactured lots. The study also included a DTPwc arm to allow for a comparison of safety and immunogenicity of the three CPDT lots to a licensed DTPwc vaccine.

Population: Healthy 2 month old infants

Sample size: 432 (108/arm)

Design: Phase 2, randomized, double blind, multicenter trial.

Schedule: 2, 4 and 6 months

Concomitant Vaccines and Medications: All children received Polio Virus Live, Oral (Sabin) Trivalent at the same time as the 2 and 4-month immunizations.

Safety Monitoring: Infants were monitored for adverse reactions immediately following vaccination and by telephone at 2-6 hours, 8-12 hours, 24, 48, and 72 hours after immunization and day 7 prior to the next immunization and day 28 after the 6 month immunization.

Serologic monitoring: Sera were obtained at the time of the 1st and 3rd vaccinations and 28 days after the 3rd vaccination.

Study Conduct: 423 (97.9%) infants received three doses of trial vaccine and 7 month serology, and were included in the 7 month immunogenicity analysis.

Demographics: The proportion of males enrolled in the acellular vaccine groups is higher (54-60%) than the proportion enrolled in the whole cell vaccine group (44%).

Title: Safety and Immunogenicity of the Connaught Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed (CPDT), in Calgary, Alberta; Surrey, Maple Ridge and Coquitlam, British Columbia, Canada – Fourth Dose

Location: Canada

Study Date: February-July 1992

Lot Numbers: CPDT: ----------. DTPwc: ---------- (contained a reduced amount of diphtheria (15 Lf vs. 25 Lf) and a different preservative (0.6% 2-phenoxyethanol) from licensed product.

Study Objectives: To compare the safety and immunogenicity of the component pertussis vaccine combined with diphtheria and tetanus toxoids adsorbed and the diphtheria and tetanus toxoid and pertussis vaccine adsorbed as the booster immunization in children who had received the same formulation for the primary series.

Population: Healthy infants 18 months of age previously enrolled in the lot consistency study.

Sample size: 398

Design: Randomized double-blinded study.
Schedule: 18 month 4th dose
Concomitant Vaccines and Medications: OPV given concurrently. *H. influenzae* b conjugate vaccine given one month later.
Safety Monitoring: Infants were monitored for adverse reactions immediately following vaccination and by telephone at 2-6 hours, 8-12 hours, 24, 48, and 72 hours and days 7 and 28 post-vaccination.
Study Conduct: 25 infants who completed the primary series did not participate in the booster study. Reasons for non-participation are not provided. Serologic data were available on 391 (98%) of the 398 infants who did participate.
Demographics: The proportion of males enrolled in the acellular vaccine groups is higher (54-60%) than the proportion enrolled in the whole cell vaccine group (44%).

Title: NIAID Sponsored Phase 2 Trial (Cycle I): Comparison of Thirteen Acellular Vaccines.
The sponsor provided reprints from the publication "Report of the Nationwide Multicenter Acellular Pertussis Trial" ed. Decker, MD and Edwards KM, *Pediatrics*: 1995 S96. The following is a summary of information contained in this publication.
Location: 6 VTEU (NIAID) sites in the U.S.
Study Date: 1991-1992
Lot Number: 001
Study Objectives: To compare the safety and immunogenicity of 13 acellular pertussis vaccines and 2 DTPwc vaccines, including the commercially available Lederle DTPwc vaccine.
Population: Healthy infants. Age 6-12 weeks
Sample size: 2342 (115 received CPDT)
Design: Randomized, double blind, multicenter study. Only three acellular vaccines were available at the onset of the study; the remainder vaccines were introduced into the trial subsequently according to availability, so that the study consisted of several sequential phases.
Schedule: 2, 4, and 6 months
Concomitant Vaccines and Medications: OPV. During the course of the trial *H. influenzae* conjugate vaccines became available and VTEUs were instructed to administer them concurrently but at a separate anatomic site.
Safety Monitoring: Parent diary days 0-7 and 14. Parents were asked to record assessments 3 and 6 hours after immunization, and at bedtime for 7 days, and on the 14th day post-immunization. Long-term follow-up form was completed at the time the of booster immunization (~18 months of age). Rectal temperatures were obtained.
Study Conduct: 400 subjects (17%) excluded from immunogenicity analysis
Demographics: Age at enrollment and immunization comparable between groups.
Safety Results: All acellular pertussis vaccines (DTaP) were associated with a markedly lower incidence and severity of adverse events as compared to the commercially available Lederle DTPwc vaccine in regard to all monitored parameters except vomiting. Results were reported as percent of subjects experiencing reactions within the 1st three days post-immunization. Below is a summary of adverse events reported among the CPDT recipients and the DTPwc (Lederle) group.

Table 65: NIAID Cycle 1 Study – Local and System Adverse Events

	Vaccine	Dose 1 %			Dose 2 %			Dose 3 %		
		Mild	Mod.	Sev.	Mild	Mod	Sev.	Mild	Mod.	Sev.
Redness	CPDT	19.0	2.9	-	16.4	0.7	-	21.3	1.6	
	DTPwc	40.8	8.6	-	41.6	6.1	-	44.4	3.2	-
Swelling	CPDT	9.5	2.9	-	9.7	0.7	-	12.6	2.4	-
	DTPwc	23.2	16.5	-	24.6	9.5	-	30.1	5.6	-
Fever	CPDT	7.3	0	0	17.9	1.5	0.7	16.5	1.6	0
	DTPwc	24.3	3.0	0	28.8	3.9	1.4	27.8	7.3	2.6
Pain	CPDT	21.2	2.2	0	14.9	0.7	0	11.0	2.4	0
	DTPwc	30.8	17.6	9.7	30.7	12.6	6.1	26.9	12.0	3.8
Fussiness	CPDT	45.3	5.1	1.5	47.8	7.5	2.2	39.4	6.3	0
	DTPwc	46.0	16.8	3.8	44.1	16.5	7.0	41.2	12.6	4.7
Antipyretic	CPDT	39.4	-	-	38.8	-	-	32.3	-	-
	DTPwc	60.5	-	-	59.8	-	-	61.4	-	-
Drowsy	CPDT	29.9	-	-	16.4	-	-	12.6	-	-
	DTPwc	43.5	-	-	31.0	-	-	24.6	-	-
Anorexia	CPDT	10.9	-	-	7.5	-	-	3.9	-	-
	DTPwc	19.5	-	-	16.5	-	-	14.3	-	-
Vomiting	CPDT	6.6	-	-	3.7	-	-	4.7	-	-
	DTPwc	7.0	-	-	4.5	-	-	5.3	-	-

- Indicates not stated
Redness and Swelling: Mild = 1-20 mm, Mod. > 20 mm
Pain: Mod. = Cried or protested to touch; Severe = cried when leg moved
Fever: Mild = 100.1-101°F; Mod = 101.1-102°F; Severe: >102°F
Fussiness: Mod. = Prolonged crying and refused to play; Severe, persistent crying and could not be comforted.
Antipyretic use, drowsy, anorexia, vomiting: Yes/No

There were two unusual or serious adverse events reported in the CPDT group. One infant had urticaria on the knee below the injection site with onset 3 hours following the 1st immunization. This infant completed the study. A second infant was hospitalized for croup in between the 1st and 2nd immunization and completed the study. Long-term follow-up revealed that the rates of reported hospitalization, developmental delay, seizure, other neurologic problem, failure to thrive, prolonged cough, or other serious infection did not significantly differ among the studied vaccines. Safety data were available from 80 infants who received HIB vaccine (HBOC) concomitantly with the third dose of CPDT and were, retrospectively, compared to data from 35 infants who did not receive HBOC. There were no significant differences between the two groups in the incidence of fever >101°F, moderate fussiness or moderate local reactions.

Immunogenicity Results:
Assays were performed at FDA
The following results were obtained for CPDT recipients:

Table 66: NIAID Cycle I Study – Immunogenicity Results

Antigen	N	GMC		Seroconversion*
		Pre	Post	%
PT	115	1.3 (1.2, 1.5)	36 (32, 41)	94.8
FHA	115	3.6 (3.0, 4.3)	37 (32, 42)	78.3
PRN	115	5.5 (4.7, 6.3)	114 (93, 139)	86.1
FIM	115	8.7 (6.9, 11.0)	240 (204, 282)	83.5
D	13	0.037 (0.012)	0.378 (0.117-1.223)	76.9
T	13	6.88 (3.109-15.248)	5.0 (2.637-9.481)	100

* Proportion achieving a post-immunization value at least 4-fold greater than both the pre-immunization value and the minimum detectable level.
For diphtheria % ≥ 0.1 U; tetanus % ≥ 0.01 U.

Immunogenicity results revealed that DTaP vaccines produced significant increases in antibodies directed against included antigens. Post-vaccination GMCs differed significantly among DTaP vaccines; no DTaP vaccine was consistently most or least immunogenic with respect to all of its included antigens. Post-vaccination GMCs for anti-PT did not appear to correlate with the PT content of the vaccines.

Title: NIAID Multicenter Acellular Pertussis Trial (MAPT - 4th Dose)
Children enrolled in the MAPT primary series trial were offered a fourth dose of the same acellular pertussis vaccine they had received in the primary series. Children who received DTPwc in the primary series were randomized to receive one of the 12 acellular vaccines as their fourth dose. Results of this study were reported in a publication by Pichichero et al. (*Pediatrics* Vol. 100, No. 5, November, 1997). A reprint of the publication was submitted to the PLA in 12/1998, however a complete study report was not provided. Additional summary safety data were submitted to the PLA in 7/2000 and 9/2000.
Monitoring: Adverse events were collected by diary cards for the first three days, temperatures were measured rectally using digital thermometers. A nurse contacted each child's parents by telephone on the first and third days after vaccination. To be included in the serologic analyses, a child had to be vaccinated at 15 to 20 months of age and have sera drawn before and after immunization (20-91 days after vaccination).
Lot used: 001
Sample size: 94 (75 of these were primed with CPDT, and 19 were primed with DTPwc.

Table 67: NIAID Cycle 1 - 4th Dose Study – Local and Systemic Adverse Events.

Reaction	Vaccine	Dose 4 - %		
		Mild	Mod.	Sev.
Redness	CPDT primed	21.3	5.3	2.7
	DTPwc (WCL) primed	9.1	9.1	0.0
Swelling	CPDT primed	12.0	1.3	5.3
	DTPwc (WCL) primed	18.2	0.0	0.0
Fever	CPDT primed	20.0	5.3	2.7
	DTPwc (WCL) primed	36.4	0	0
Pain	CPDT primed	20.0	8.0	1.3
	DTPwc (WCL) primed	27.3	9.1	0.0
Fussiness	CPDT primed	41.3	8.0	1.3
	DTPwc (WCL) primed	45.5	0.0	0.0
Antipyretic	CPDT primed	37.3	-	-
	DTPwc (WCL) primed	81.8	-	-
Drowsy	CPDT primed	5.3	-	-
	DTPwc (WCL) primed	0.0	-	-
Anorexia	CPDT primed	10.7	-	-
	DTPwc (WCL) primed	18.2	-	-
Vomiting	CPDT primed	2.7	-	-
	DTPwc (WCL) primed	0.0	-	-

- Indicates not stated
Redness and Swelling: Mild = 1-20 mm, Mod. =20-50mm, Sev. > 50 mm
Pain: Mod. = Cried or protested to touch; Severe = cried when leg moved
Fever: Mild = 100.1-101°F; Mod = 101.1-102°F; Severe: >102°F
Fussiness: Mod. = Prolonged crying and refused to play; Severe, persistent crying and could not be comforted.
Antipyretic use, drowsy, anorexia, vomiting: Yes/No

Table 68: NIAID Cycle 1 Trial – Comparison of Adverse Events Post-Dose 3 and 4.

	6 Months %			**18 Months %**		
	Mild	Mod.	Sev.	Mild	Mod	Sev.
Redness	21.3	1.6		21.3	5.3	2.7
Swelling	12.6	2.4	-	12.0	1.3	5.3
Fever	16.5	1.6	0	20.0	5.3	2.7
Pain	11.0	2.4	0	20.0	8.0	1.3
Fussiness	39.4	6.3	0	41.3	8.0	1.3
Antipyretic	32.3	-	-	37.3		
Drowsy	12.6	-	-	5.3	-	-
Anorexia	3.9	-	-	10.7	-	-
Vomiting	4.7	-	-	2.7	-	-

Table 69: NIAID Cycle 1 Trial – Immunogenicty Results Post 4th Dose

	Pre (95% CI)	Post (95% CI)
PT (N=44)	2.4 (1.9, 2.9)	43.3 (34.1, 54.9)
FHA (N=44)	2.9 (2.3, 3.7)	32.3 (25.6, 40.9)
PRN (N=44)	10.1 (7.8,13.1)	182.4 (133.5, 249.3)
FIM (N=43)	13.4 (9.5, 19.0)	308.2 (223.1, 425.8)
Tetanus (N=11)*	1.2 (0.6, 2.1)	21.3 (18.8, 24.1)
Diphtheria (N=11)*	1.6 (0.8, 3.5)	9.0 (7.2, 11.3)

*100% protected as defined by diphtheria ≥ 0.1 IU; tetanus ≥ 0.01 IU

Title: Safety and Immunogenicity of Two Connaught Component Pertussis Vaccines in Combination with Diphtheria and Tetanus Toxoids Adsorbed (HCPDT and CPDT) in children 2-6 months of age with a Booster Immunization at 18 months of age - Phase 2C

Location: Canada, USA

Study Date: 1992-1993

Lot Numbers: CPDT: --------
HCP4DT: ---------

Study Objectives: This study was designed to assess the safety of the HCPDT vaccine in 2000-2500 children prior to inclusion of this vaccine formulation in the Sweden 2 efficacy trial. The objective of the study was, therefore, to evaluate the safety and immunogenicity of the HCPDT vaccine ($CP_{20/20/5/3}DT$) in comparison with the CPDT vaccine ($CP_{10/5/5/3}DT$).

Population: Healthy 2 month old infants

Sample size: 2050 (291: CPDT Lot ----; 1759: HCP4DT)

Design: Double blind, randomized controlled trial at 9 sites (6 in Canada and 3 in the U.S). Subjects were randomly allocated in a 6:1 ratio to receive HCP4DT vs. CPDT.

Schedule: 2, 4 and 6 months

Concomitant Vaccines and Medications: OPV and Hib

Monitoring:

Safety: Parent diary at 48 hours and day 7. Telephone interview at 24 hours and 14 days post-immunization. All hospitalizations until 60 days after the 3rd dose were investigated by review of the hospital discharge summary.

Immunogenicity: Sera were collected from one site (Montreal) at the time of the first immunization and 28 days after the 3rd immunization.

Study Conduct: 93 subjects withdrew from study, 15 for adverse events.

Demographics: 53% of subjects were male in both vaccine groups. The mean age of participants at the time of the first dose was 9.3 months in both groups.

Safety Results:

Sixty-six immediate (within 15 minutes of vaccination) reactions post-vaccination were reported of which 86% were from one center. Most were reported after the 2nd dose (n = 36). None were listed as serious and the increased rate in the one center was felt to be due to increased reporting of flushing associated with the pressure required to restrain the limb.

Table 70: CPDT and HCPDT Bridging Study – Adverse Event Occurring with 48 Hours of Vaccination.

Reaction	Vaccine	2 Months			4 Months			6 Months		
		Any	CS	S	Any	CS	S	Any	CS	S
Any Local	CPDT	17	6	4	21	10	2	19	5	0
	HCPDT	16	4	2	25	8	0	20	6	0
Redness	CPDT	9	5	0	13	8	1	14	5	0
	HCPDT	7	2	0	17	5	0	16	4	0
Swelling	CPDT	6	3	0	10	8	0	8	4	0
	HCPDT	5	1	0	9	4	0	7	3	0
Tenderness	CPDT	9	3	0	12	2	1	5	1	0
	HCPDT	9	2	0	9	1	0	6	1	0
Any Systemic	CPDT	69	23	0	62	19	2	59	16	2
	HCPDT	68	21	0	63	20	2	60	17	2
Fever	CPD1T	25	5	4	19	4	0	22	4	0
	HCPDT	24	5	2	25	6	0	24	6	0
Fussiness	CPDT	42	14	0	41	12	1	39	12	2
	HCPDT	42	10	0	39	11	1	41	9	1
Crying	CPDT	24	7	1	21	6	0	19	6	1
	HCPDT	22	5	0	21	6	0	18	3	0
Decreased Activity	CPDT	19	6	0	18	5	0	12	3	0
	HCPDT	26	6	0	16	2	1	12	1	0
Anorexia	CPDT	16	2	3	18	3	0	17	2	0
	HCPDT	20	5	1	14	3	0	14	3	0
Vomiting	CPDT	5	0	0	6	1	0	6	2	0
	HCPDT	8	0	0	6	1	0	5	1	0
Diarrhea	CPDT	14	5	0	9	1	1	11	0	0
	HCPDT	15	3	0	11	3	0	10	3	0

Redness and Swelling: Mild (1-9mm), Moderate (10-34 mm), Severe 35 mm.
Tenderness: Mild = whimpered when site was touched, Moderate = cried when site was touched, Severe = cried when the limb was moved.
Fever (axillary): Mild = 37.3-37.8°C, Moderate =37.8-39.9°C, Severe = ≥40°C axillary
Fussiness: Mild = continuously fussy < 1 hour, Moderate = ≥ 1hour but < 3 hours, Severe = ≥ 3 hours.
Crying: Mild = < 1 hour, Moderate = ≥ 1 hour and < 3 hours, Severe ≥ 3 hours.
Decreased Activity: Mild = less interested in surroundings, Moderate = no interest in surroundings and sleeping through feeds, Severe sleeping most of the time.
Anorexia: Mild: less than normal for one or two feeds, Moderate = missing one or two feeds completely, severe = refuses most or all feeds.
Vomiting: Mild = 1-2 episodes without interfering with routine, Moderate = several episodes with inability to retain food, Severe = frequent vomiting and inability to have oral intake.
Diarrhea: Mild = more loose stools than usual, Moderate = frequent runny, Severe = multiple liquid stools.

There were a total of 34 serious adverse events reported in the study: Eight fevers of ≥ 40°C (2 CPDT, 6 Hybrid; Seven episodes of crying ≥ 3 hours: 3 CPDT, 4 Hybrid; Nine episodes of high-pitched/unusual crying (2 CPDT, 9 HCPDT); 2 **HHE** (both HCPDT); 2 SIDS (both HCPDT); 1 Infantile spasm (HCPDT); 3 invasive bacterial infections (all HCPDT).

Listed below are the case narratives for the 2 HHE cases and the two SIDS cases:

HHE
Case #1: CAL-2C-509. Male infant DOB ---------- received his first vaccination on 9/9/92 of HCPDT/OPV/Act-HIB at around 2 pm. That evening ~7 hours later the infant had an episode lasting ~10 minutes in duration in which he was limp and unresponsive to voice, was not pale or cyanotic. The infant also cried inconsolably the night of vaccination had a temperature to 39.2C, had vomiting and diarrhea lasting 1.5 days. The infant experienced severe pain at injection site and severe fussiness (lasting more than 3 hours) following vaccination. No further HCPDT immunizations were given.

Case 2: CAL-2C-644. Male infant DOB ---------- received his first dose HCPDT, OPV, ActHIB on 11/10/92 at ~ 2 pm. Approximately 32 hours later, the infant was pale and limp for ~ 10 minutes. The child recovered. The child experienced some mild diarrhea within 48 hours of vaccination. Additionally, the CRF states that the mother reported that the child had "jerking" episodes, which occurred as child was falling asleep or when alert in upright position. Upon further questioning, these were determined to have been present prior to vaccination and were not felt to be seizures.

SIDS
Case 1: US-2C-140. Male infant DOB ---------- received first dose of HCPDT, OPV, Hib, HepB on ----------. Post-vaccination course was uneventful except for some mild injection site tenderness at 24 hours and an "unusual crying" on day 14, which was not characterized as high, pitched in nature. He was also described as unusually fussy 48 hours post-vaccination which prompted a call to the physician. The child died on ---------- ---------- (20 days post-vaccination) of what was presumed to be SIDS at his day care center. An autopsy was performed. The lungs had areas of atelectasis and there were petechial hemorrhages. The child had died while sleeping on a waterbed and these finding were consistent with either a diagnosis of SIDS or suffocation.

Case 2: HFX-2C-002. Male infant DOB ---------- received first doses of HCPDT, OPV, ActHIB on ----------. The child was reported as being mildly fussy 24 hours post-vaccination and having mild diarrhea. The child died 6 days post-vaccination, having been found between 8-9 am in the morning cyanotic without respiration or pulse by his mother. An autopsy was performed and the death was judged to be related to SIDS.

There were a total of 64 hospitalizations during the course of the study (5 CPDT, 59 Hybrid). Within the first 30 days post-vaccination the following were reasons for hospitalization in the CPDT group: (1 croup, 1 viral meningitis); for the Hybrid group: 2 UTI/pyelonephritis, 6 cases of asthma +/- URI/bronchitis/otitis/pneumonia, 2 cases of bronchiolitis/pneumonia; 2 croup; 1 cranial synostosis; 2 cases of diarrhea/vomiting; 1 vomiting; 1 dehydration/flu; 1 fever; 1 congestive heart failure; 1 hyponatremia/dehydration; 1 infantile spasm; 2 otitis media; 1 perianal abscess; 1 case of pertussis; 1 surgery for cleft lip; 1 tracheal malacia.

Immunogenicity Results:
Serologies were obtained from all infants enrolled in one center (Montreal) prior to the first dose and at 7 months of age. Sera were assayed at APL, (prior to the assay validation in 1999)

Table 71: Immunogenicity Result from CPDT and HCPDT Bridging Study

		CPDT			HCPDT	
Antibody	N	GMC (95% CI)	% >4X	N	GMC (95% CI)	% >4X
PT	42	105.1 (85.3, 129.4)	64.3	250	101.6 (94.1, 109.7)	68.0
FHA	42	82.5 (63.5, 107.0)*	85.7	250	163.9 (152.1, 176.5)	91.6
FIM	42	358.6 (283.1, 454.1)*	92.9	250	220.6 (191.0, 254.7)	87.6
PRN	42	71.1 (53.9, 93.8)	92.9	250	87.6 (78.0, 98.3)	87.6
			%>.01 U			%>.01 U
D♦	42	0.331 (0.221, 0.496)	100	250	0.375 (0.323, 0.435)	100
T♦♦	42	1.956 (1.566, 2.442)	100	250	1.793 (1.643, 1.956)	100

* $p < 0.001$; ♦ IU/mL; ♦♦ EU/mL

Comment
A significantly greater response as assessed by GMC was observed in the CPDT group for FIM and a significantly lower response for FHA. The lower FHA result in the CPDT group is not unexpected in light of the higher concentration of FHA in the HCPDT vaccine.

Title: Safety and Immunogenicity of Two Connaught Component Pertussis Vaccines in Combination with Diphtheria and Tetanus Toxoids Adsorbed (HCPDT and CPDT) in children 2-6 months of age with a Booster Immunization at 18 months of age - Phase 2C Booster (4.2.6)
Location: Canada
Study Date: 1995
Lot Number: CPDT: ----
HCP4DT:------
Study Objectives: To evaluate the safety and immunogenicity of the increased antigen Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids, Adsorbed ($CP_{20/20/5/3}DT$) in comparison to the original formulation, CPDT ($CP_{10/5/5/3}DT$), for the fourth dose given at 17 to 19 months of age in children who had been previously immunized with three doses of the same formulation at 2, 4, and 6 months of age.
Population: Healthy children 17 to 19 months of age who had completed the three immunizations and follow up of the initial 3 dose series. (Infants at 3/5 sites were given the option of participating in another booster study, which included a Hib vaccine in combination with the DTaP formulations.)
Sample size: 514 (HCPDT: 442; CPDT: 72)
Design: Double blind, randomized, multicenter trial
Schedule: 17-19 months of age
Concomitant Vaccines and Medications: OPV, Hib

Monitoring:
Safety: Immediate post-vaccination monitoring for 15 minutes. Telephone contact at 24 and 72 hours.
Immunogenicity: Sera were collected from participants at the Montreal site prior to and 28 days post-vaccination.
Study Conduct: 1170 infants were eligible for enrollment. Of these 545 elected to enroll in another booster study. Of the remaining 625 infants, 514 participated in this booster study. The most common reasons given for non-participation were that the subject had moved (n = 42) or had already been vaccinated. Safety data were available from all participants and serological data were collected from participants at the Montreal site and were available from 93% of these subjects.
Demographics: 54% of CPDT participants were female vs. 49% of HCPDT participants. The mean age at enrollment was 18.4 months.
Safety Results:

Table 72: CPDT and HCPDT Bridging Study – Safety Results Post Doses 3 and 4

Table 2.2. Summary of reaction rates within 24 hours after vaccination at 6 months and after Fourth Dose Vaccination in Phase 2C study

Adverse	Dose/	N*		Any N (%)†		Clinically Significant n (%)†		Severe n (%)†	
Event	Age M	CP5DT	HCPDT	CP5DT	HCPDT	CP5DT	HCPDT	CP5DT	HCPDT
Swelling	6	277	1679	3.6	4.4	0.4	1.1	0.0	0.1
	18	72	442	11.1	17.4	8.3	13.1	5.6	8.6
Redness	6	277	1679	7.9	11.5	2.5	2.9	0.4	0.1
	18	72	442	25.0	22.2	16.7	16.3	9.7	10.6
Tenderness	6	277	1679	4.0	3.6	0.7	0.5	0.0	0.1
	18	72	442	20.8	20.8	4.2	2.7	1.4	0.2
Fever ***	6	270	1647	18.5	17.6	4.1	3.5	0	0.1
	18	68	431	20.6	21.8	5.9	6.3	0	0
Less Active	6	277	1679	7.9	6.0	1.1	0.5	0	0
	18	72	442	9.7	13.1	0	1.1	0	0
Crying	6	277	1679	9.4	10.1	1.4	1.0	0	0
	18	72	442	15.3	15.6	2.8	1.1	0	0
Diarrhea	6	277	1679	6.1	5.2	0.4	0.5	0	0
	18	72	442	5.6	6.8	2.8	0.9	0	0
Eat Less	6	277	1679	11.9	8.6	0.7	1.5	0	0.1
	18	72	442	19.4	14.5	6.9	2.9	0	0
Fussiness	6	277	1678	28.2	27.0	5.4	3.6	1.1	0.4
	18	72	442	30.6	26.5	4.2	5.7	0	0.2
Vomit	6	277	1679	4.0	2.9	0.4	0.2	0	0
	18	72	442	1.4	2.3	0	0	0	0

* N = Number of evaluable subjects
† n (%) = number of events (reaction rates)

Redness and Swelling: Mild (1-9mm), Moderate (10-34 mm), Severe ≥ 35 mm.
Tenderness: Mild = whimpered when site was touched, Moderate = cried when site was touched, Severe = cried when the limb was moved.
Fever (axillary): Rectal or tympanic temperature was adjusted to axillary temperature for analysis purpose by decreasing the value by 0.5°C. Any fever was then defined as > 37.3°C, clinical significant fever > 37.8°C and severe fever > 40°C
Fussiness: Mild = continuously fussy < 1 hour, Moderate = ≥ 1hour but < 3 hours, Severe = ≥ 3 hours.

Crying: Mild = < 1 hour, Moderate = ≥ 1 hour and < 3 hours, Severe ≥ 3 hours.
Decreased Activity: Mild = less interested in surroundings, Moderate = no interest in surroundings and sleeping through feeds, Severe sleeping most of the time.
Anorexia: Mild: less than normal for one or two feeds, Moderate = missing one or two feeds completely, severe = refuses most or all feeds.
Vomiting: Mild = 1-2 episodes without interfering with routine, Moderate = several episodes with inability to retain food, Severe = frequent vomiting and inability to have oral intake.
Diarrhea: Mild = more loose stools than usual, Moderate = frequent runny, Severe = multiple liquid stools.

Serious Adverse Events:
There was one episode of HHE occurring in a recipient of the HCPDT vaccine, OPV and ActHIB. The episode began approximately 90 minutes following immunization and lasted 8-9 hours. The child was described as staring with "glazed eyes", limp, unresponsive. The child was put to bed after 2-3 hours and whimpered several times throughout the night. The child awoke in the morning was irritable but otherwise normal. She had 30 mm of injection site redness and swelling at the site of injection associated with mild tenderness. Three days post-vaccination the child became ill with vomiting and diarrhea for 5 to 6 days without fever. The child had completed the primary series with HCPDT. A week following the first dose, the CRF indicates that the child began having episodes of high-pitched crying ~ 6 times per day each lasting 10-15 minutes and apparently unprovoked. She had no adverse events following receipt of the second dose and had an ear infection and one episode of mild diarrhea within 14 days of receipt of the third dose.

Immunogenicity Results:
Only five subjects at the Montreal site received CPDT and had post-booster dose sera collected and only 49 sera were available from subjects who received the HCPDT formulation. Sera were tested prior to assay validation in 1999. Thus, immunogenicity results and comparisons are of limited value.

Title: Safety and Immunogenicity of the Connaught 4-Component Pertussis Vaccine in 16 to 20 Month Old Children - Phase IB. (4.2.8)
Location: USA
Investigator(s): JA Englund, WP Glezen, A Parades
Study Date: 1990
Lot Number: CPDT ----
Study Objectives: To evaluate the safety and immunogenicity of the CPDT Vaccine in 18-month-old children who had previously received a primary series of three doses of whole cell DTP and who had no severe reactions to the primary series.
Population: Healthy children, 16-20 months of age
Sample size: 41 (28 CPDT, 13 DPTwc, licensed product manufactured by AP-Swiftwater, PA)
Design: Double blind, randomized, controlled trial. Random allocation to acellular and whole-cell pertussis vaccines in a 2:1 ratio
Schedule: One vaccination at 16-20 months
Concomitant Vaccines and Medications: No information provided regarding vaccinations. Antipyretics given as needed.
Monitoring:
Safety: Diary cards for the first 10 days including rectal temperature measurements, and telephone contact on days 1, 3, 10 following vaccination.

Immunogenicity: Sera were collected prior to enrollment and 28 days post-vaccination.
Study Conduct: Sera from 80% of participants were available for both pre- and post-immunization evaluation.
Demographics: Not provided
Safety Results: The DTPwc group experienced significantly more pain (92% vs. 14%), especially severe pain (46% vs., 0%); redness (6% vs. 3%), fever (69% vs. 29%), irritability (85% vs. 46%), increased crying (38% vs. 4%) and took more antipyretic medications (54% vs. 29%) than the CPDT group ($p<0.05$ for all reactions noted). Two subjects in the CPDT group had swelling $\geq$ 2cm vs. none in the DTPwc group. There were no significant differences noted in the incidence of swelling, drowsiness, appetite and vomiting between the two groups.
Immunogenicity Results: Serologic assays were performed at APL prior to assay validation in 1999. Post-vaccination IgG GMCs to all vaccine antigens were significantly increased over pre-vaccination levels in both groups, however no significant differences in GMCs were noted between groups for any of the antigens. All children achieved diphtheria and tetanus anti-toxoid antibody levels of $\geq$ 0.1 IU/ml.

Title: Safety and Dose Response of the Connaught Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids - Phase ID (4.2.9).
Location: Canada
Investigators: B. Law, B. Eastwood, S. Halperin
Study Date: 1991
Lot Number(s): CPDT ----; DCPDT ------ (Pertussis antigen content PT: 20µg, FHA: 10µg, FIM: 6µg, 69kD: 3µg – note this formulation contains one half the content of FHA as the Hybrid formulation); DTPwc: ---------- (contains the same diphtheria content, 15 Lf, as the component vaccines).
Study Objectives: The purpose of the study was to evaluate the safety and dose response of the acellular pertussis vaccines in 18-month-old children. Dose response was evaluated by comparing two component vaccines with different antigen content. A third whole cell arm was also included for comparison.
Population: Healthy 17-18 month old children who had previously completed their 2, 4, 6 month DTP.
Sample size: 91 (CPDT: 30, DCP4DT: 31, DTPwc: 30)
Design: Double-blinded, multicenter, randomized trial.
Schedule: One dose at 17-18 months of age.
Concomitant Vaccines and Medications: No information provided regarding concomitant vaccinations. Antipyretics given as needed.
Monitoring:
Safety: Telephone contact at 2-6 hours, 8-12 hours, 24, 48 and 72 hours and 7-10 days and 28 days post-vaccination.
Immunogenicity: Serum was collected prior to immunization and 28 days post-immunization from all children.
Study Conduct: Safety and immunogenicity results were available for all study participants.
Demographics: 45% males
Safety Results: Overall adverse reactions, any local reaction, any clinically significant local reaction and any clinically significant general reaction were reported significantly more frequently in the DTPwc group. Specifically, tenderness and severe redness occurred significantly more frequently in the DTPwc group. Among systemic reactions, fever, irritability, drowsiness, listlessness and decreased feeding were reported

significantly more frequently in the DTPwc group. There were no significant differences in AEs between the two component vaccine groups.
Immunogenicity Results: Serologic assays were performed at ---- prior to assay validation in 1999. Post-vaccination GMCs to PT by EIA, FHA, PRN, FIM were comparable in both the acellular vaccine groups. CHO cell neutralizing antibodies were significantly higher in the CPDT group than in the DCP4DT group (35.9 vs. 15.0; p=0.04). All children achieved diphtheria and tetanus anti-toxoid antibody levels of ≥ 0.1 IU/ml.

11.0 Summary of Non-Pivotal Trials Submitted in Support of the CPDT License Application:
Study reports and/or summaries were submitted to the PLA by the sponsor for the studies listed below. These studies were designated as not being pivotal for licensure. Serum samples for immunogenicity, when obtained, were assayed prior to the assay validation of 1999. Additionally, sample sizes were too small to allow for meaningful interpretations. Brief summaries of the study designs and results are provided.

Title: Safety and Immunogenicity of the Connaught 4-Component Pertussis Vaccine in adults - Phase IA (4.3.1)
This study was a Phase 1 study performed in healthy adult volunteers, ages 21-59, in the USA in 1990. The objective of the study was to evaluate the safety of the acellular components of CPDT (i.e. without DT) in a double blind, placebo controlled. Thirty-one subjects were enrolled, 16 received CP and 15 placebo. Subjects were monitored for 28 days post-vaccination for safety. Safety laboratory tests were obtained 6 hours, days 1, 2, 3 or 4 and 7 post-vaccination. Serum samples for antibody studies were obtained prior to Immunization and on days 10 and 28 post-vaccination.
Results: Local reactions were noted during two distinct time periods, days 0-3 (10/15) and days 5-8 (6/15). Of the vaccine recipients who had late local reaction, 5/6 had had mild or moderate tenderness early in the post-vaccination period. Early local reactions consisted primarily of pain (10/15), 2/15 noted redness at the site of immunization and 2/15 experienced axillary tenderness. Late local reactions were swelling (6/15) and axillary tenderness (4/15 - although table 2 indicates 2/15 had axillary tenderness) and in 1/15 palpable axillary adenopathy. Local reactions occurred at a statistically significantly higher rate than in the placebo recipients. No participant experienced at T>100.5°C and other systemic complaints e.g. headache and myalgia were evenly distributed among vaccine and placebo recipients. Safety laboratory tests including fasting glucose measurements were unremarkable.
Serology: GMC IgG titers to the four pertussis antigens ant the CHO cell assay were significantly higher in the vaccine group at both 10 and 28 days, though no significant differences in IgM antibodies were noted between the two groups. IgA anti-bodies to LPF, 69kD and aggutinogens were significantly increased in the vaccine group.

Title: Safety of the Connaught Component Pertussis Vaccine Adsorbed in Infants Immunized at 17 and 18 months of Age - Phase 1A (4.3.2)
This was a Phase 1 randomized, double-blinded study designed to compare the safety safety and immunogenicity of two acellular pertussis vaccines, CP3 (10µg PT, 5µg FHA, 5µg FIM) and CP4 study (10µg PT, 5µg FHA, 5µg FIM, 3µg 69kD) in 17-18 month old infants who had previously been immunized with DTPwc. The study was conducted in Canada in 1990, 68 subjects were enrolled (35 CP3 and 33 CP4). No concurrent immunizations were given. Subjects were monitored for safety at 2-6, 8-12, 24, 48 and

72 hours and at 7 and 28 days post-vaccination. Immunogenicity was assessed prior to vaccination and 28 days post-vaccination.
Results: There were no significant differences in reactogenicity between the two groups. The following rates of adverse reactions were observed in the CP3 and CP4 groups, respectively: tenderness: 5.7 vs. 12.1; redness: 0% vs. 6.1%; swelling: 0% both groups; hardness: 2.9% vs. 3.0%; fever 5.7% vs. 9.1%; eat less: 20% vs. 12,1%; drowsiness: 14.3% vs. 30%; irritable: 31.4 vs. 27.4; vomiting: 8.6% vs. 3.0%; pallor 11.4% vs. 9.1%; diarrhea 14.2% vs. 6.1;
Serologic assays were performed at ----. Significant antibody rises were demonstrated against every antigen contained in the acellular pertussis vaccines. Although the CP3 did not contain 69kD, a significant rise in anti-69kD was detected post-vaccination with CP3 (2.1 vs. 6.4; $p<0.00001$). There were no significant differences in antibody response to pertussis antigens between the CP3 and CP4 vaccine groups with the exception to anti-69kD GMCs that were significantly higher in the CP4 group (6.4 vs. 432; $p<0.00001$).

Title: Safety of the Connaught Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed (CPDT) in Infants Immunized at 17 to 18 Months of Age - Phase 1B (4.3.3)
This was a Phase 1 randomized, double-blinded study designed to compare the safety and immunogenicity of two acellular pertussis vaccines combined with diphtheria and tetanus toxoids, CP3DT (10µg PT, 5µg FHA, 5µg FIM), Diphtheria Toxoid 15Lf, Tetanus Toxoid 5Lf and CPDT study (10µg PT, 5µg FHA, 5µg FIM, 3µg 69kD, Diphtheria Toxoid 15Lf, Tetanus Toxoid 5Lf) in 17-18 month old infants who had previously been immunized with DTPwc. The study was conducted in Canada in 1990. Sixty-nine subjects were enrolled (35 CP3 and 34 CP4). No concurrent immunizations were given. Subjects were monitored for safety at 2-6, 8-12, 24, 48 and 72 hours and at 7 and 28 days post-vaccination. Immunogenicity was assessed prior to vaccination and 28 days post-vaccination.
Results: The two acellular vaccines had comparable safety profiles. The following rates of adverse reactions were observed in the for CP3DT and CPDT groups, respectively: tenderness: 25.0 vs. 11.8; redness: 5.6% vs. 17.6%; swelling: 5.6 vs.2.9; hardness: 2.8% vs. 2.9%; fever 13.9% vs. 20.6%; eat less: 5.6 vs. 15.9%; drowsiness: 16.7% vs. 5/9%; irritable: 19.4% vs. 23.5%; vomiting: 8.3% vs. 2.9%; listlessness 0% vs. 2.9%; pallor 5.6% vs. 2.9%; diarrhea 8.3% vs. 8.8%.

Immunogenicity Results: Serologic assays were performed at ----. Significant antibody rises were demonstrated against every antigen contained in the Component Pertussis Vaccines. Although the CP3DT did not contain 69kD, a significant rise in anti-PRN was detected post-vaccination with CP3 (6.8 vs. 36.7; $p<0.00001$). There were no significant differences in antibody response to pertussis antigens between the CP3DT and CPDT vaccine groups with the exception to anti-PRN GMCs that were significantly higher in the CPDT group (36.7 vs. 368; $p<0.00001$).

Title: Safety of the Connaught Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed (CPDT) and Hybrid CPDT - Phase 1E (4.3.4)
This was a Phase 1 open label study to evaluate the safety and immunogenicity of the hybrid acellular pertussis vaccine combined with diphtheria and tetanus toxoids (HCPDT -20µg PT, 20µg FHA, 5µg FIM, 3µg 69kD), in 17-18 month old infants who had previously been immunized with DTPwc. The study was conducted in Canada in 1991.

35 subjects were enrolled. No concurrent immunizations were given. Subjects were monitored for safety at 2-6, 8-12, 24, 48 and 72 hours and at 7 and 28 days post-vaccination. Immunogenicity was assessed prior to vaccination and 28 days post-vaccination.

Results:
Safety: Local adverse reactions were reported in 42.8% of participants. Tenderness was reported in 28.6%, redness in 17.1%, swelling in 8.6%. All local reactions were mild except for two reports of moderate erythema (25 mm and <35 mm) and one report of moderate swelling. Systemic reactions were reported in 48.6% of subjects, with irritability reported in 48.6% and fever in 5.7%, drowsiness in 31.4%, pallor in 11.4%, vomiting in 5.7%, and diarrhea in 25.7%.
Immunogenicity: Significant antibody rises were demonstrated against every antigen contained in the Component Pertussis Vaccines. The post-vaccination GMCs were PT: 43.7, FHA 64.1, Agglutinogen: 1468, and PRN: 47.6.

Title: Safety of the Connaught Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed (CPDT). Phase 2B (4.3.5) and Phase 2B booster (4.3.6)
This was a Phase 2 randomized, double-blinded study designed to compare the safety and immunogenicity of CPDT (Lot----), the hybrid vaccine (Lot ----), and a DTPwc, (similar to the licensed vaccine but contains 15 Lf of diphtheria toxoid) in healthy 2 month old children. The study was conducted in Canada in 1991-2. Vaccine was given a 2, 4, and 6 months of age. OPV vaccine was given concurrently at 2 and 4 months of age. One hundred subjects were enrolled (34 CPDT, 33 HCPDT, 33 DTPwc), 54% male. Subjects were monitored for safety at 2-6, 8-12, 24, 48 and 72 hours and at 7 post-each vaccination, prior to each injection, and 28 days post third dose. Immunogenicity was assessed prior to vaccination and 28 days post-vaccination. Students enrolled in this study, subsequently received a booster dose of the same vaccine they had received in the primary series at 17-18 months of age. A total of 86 (28 CPDT, 28 hybrid, 30 DTPwc) participated in the booster phase of the study.

Results:
Safety:

Table 73: Phase 2B Study – Adverse Events Occurring within 72 Hours Post-Vaccination

			2 Months		4 Months		6 Months			18 Months	
	Vaccine	N	Any	Sev.	Any	Sev.	Any	Sev.	N	Any	Sev
Swelling	CPDT	34	2.9	2.9	6.1	0	12.1	0	28	21.4	7.1
	HCPDT	33	0	0	18.2	0	6.1	0	28	28.6	21.4
	DTP	33	36.4	9.1	48.4	0	26.7	3.3	30	50	20
Redness	CPDT	34	0	0	18.2	0	39.4	0	28	53.6	17.9
	HCPDT	33	6.1	0	24.2	0	18.2	0	28	46.4	17.9
	DTP	33	36.4	3	54.8	0	56.7	0	30	53.3	23.3
Tender	CPDT	34	11.8	0	9.1	0	9.1	0	28	50	0
	HCPDT	33	9.1	0	12.1	0	6.1	6.7	28	42.9	3.6
	DTP	33	48.5	6.1	51.6	9.7	40	0	30	93.3	6.7

Systemic reactions were reported more frequently in the DTPwc group than in either of the DTaP groups. The number of subjects enrolled in this study was small but not increases in systemic reaction rates were seen over time.

Immunogenicity Results:

Table 74: Phase 2B Study - Immunogenicity Results Post-Dose 3

	CPDT		HCP4DT		DTPwc	
	Pre	Post	Pre	Post	Pre	Post
PT	4.36	58.44	4.35	133	5.03	10.4
CHO	8.1	32.7	5.72	82.35	7.46	3.96
FHA	2.57	45.2	3.05	94.9	5.3	8.93
69 kD	1.74	40.6	1.09	37.05	1.49	6.82
FIM	12.14	111.4	10.9	203.7	10.49	393.9

Table 75: Phase 2B Study – Immunogenicity Results Pre and Post-Dose 4

	CPDT		**HCP4DT**		**DTPwc**	
	Pre	Post	Pre	Post	Pre	Post
PT	35.9	107	45.5	199	30.8	69.4
CHO	5.0	149	9.3	315	1.5	7.8
FHA	17.9	91.8	22.7	170	8.3	61.3
69 kD	17.4	282	18.4	398	3.4	23.7
FIM	29.8	316	30.2	470	47.5	727

Title: Connaught Acellular DTP Safety Study in Seine Maritime, France - 2C (4.3.7)
A study brief summary of this study was submitted to the PLA.
This was a double blind, randomized Phase 2 study conducted in France in 1992-3 to assess the safety of CPDT (Lot ----) and the hybrid vaccine (Lot ----) in infants. A total of 583 infants were enrolled (83 CPDT, 500 hybrid). Vaccine was given at 2, 3, and 4 months of age. A combination IPV and *H. influenzae b* conjugate vaccine was administered concurrently. Children were monitored by use of a parent diary card for 14 days post-injection and by phone calls on days 1, 2, and 14 days post-vaccination and 60 days after the 3rd vaccination.

Results:

Table 76: Phase 2C Study – France; Summary of Post-Vaccination AEs

	Dose 1		**Dose 2**		**Dose 3**	
Reaction	CPDT	HCPDT	CPDT	HCPDT	CPDT	HCPDT
F≥38	1.2	4.81	13.6	11.65	7.5	12.85
Antipyretic use	19.8	16.2	32.1	23.25	18.75	21.08
Redness	15.7	17.6	29.6	29.66	26.25	28.31
Swelling	20.5	21.4	35.8	33.27	27.5	31.12
Tenderness	4.8	8.6	8.6	7.23	6.25	6.63
Fussiness	35	37.6	30.9	31.93	23.8	27.71
Crying	27.7	25.0	23.5	24.1	18.8	17.07
Decreased activity	20.5	21.0	19.8	15.86	10.0	13.05
Decreased eating	20.5	21.2	29.6	19.68	20.0	17.27
Vomiting	3.6	10.0	11.1	10.24	3.75	8.23
Diarrhea	10.8	12.0	13.6	15.66	6.25	13.65
Medical visit	25.3	23.4	32.1	26.51	27.5	25.3

Reaction rates were comparable for both vaccine groups.
There were 63 hospitalizations during the study period, none were judged to be vaccine related. There were 7 hospitalizations in the CPDT group and 59 in the HCPDT group. These included bronchiolitis (17 cases in 16 infants), 5 bronchitis, 1 CMV pneumonia, 3 asthma, 3 UTI, 1 tonsillitis, 4 otitis, 13 cases of gastroenteritis, 8 hospitalizations for

surgery, 1 fever, 3 “routine” check up, 3 gastroesophageal reflux one associated with dyspnea, 1 bone fracture.
Fifteen serious adverse events, which did not result in hospitalizations, were noted during the trial. There were eight cases of 8 persistent crying for 3 hours or more (4 HCPDT and 4 CPDT), 3 unusual high-pitched crying (1 HCPDT and 2 CPDT), 1 **HHE** (HCPDT), 1 prolonged and discontinuous crying of 4hr 15min duration (HCPDT). Two events were judged to be unrelated to vaccine1 persistent crying in CPDT group 13 days after vaccination, 1 fainting episode 4 weeks after HCPDT vaccination.

Title: U.S. Multicenter Evaluation of Acellular DTP Vaccines in Use in the Swedish Field Trial (NIAID Cycle 2 - 4.3.8)
The sponsor indicated on 8/22/2000 that they considered this study to be pivotal in support of their license application. However, a complete study report has not been submitted to the PLA and the only information available to the FDA is in the form of a reproduction of a poster presented at Society for Pediactric Research. Thus, FDA does not have adequate information to evaluate the study and the limited amount of information that has been provided to the PLA is listed below.
The study was a Phase 2 randomized, double blind study conducted in 299 (75 CPDT, 75 HCPDT, 74 DTPwc, Lederle, 75 DTPwc ----) Infants and given at 2, 4, and 6 months of age. The study was conducted in the US.
Results:
The abstract indicates that the two whole cell vaccines were more reactogenic than the acellular pertussis vaccines with regards to fussiness, redness, swelling and pain after dose 1, with regards to fever after dose 2 and redness after dose 3. The following GMCs were provided for CPDT and HCPDT, respectively: PT: 42.7, 37.5; FHA: 34, 83.2; FIM: 310, 181; PRN: 51.4, 43.3.

Title: Safety of the Connaught Component Pertussis Vaccine Combined with Diphtheria and Tetanus Toxoids Adsorbed in Children Immunized at 4 to 6 Years of Age - Phase IC
This study was officially submitted to the PLA as a pivotal study in support of a fifth dose of CPDT at 4-6 years of age. However, following discussions with FDA the sponsor withdrew their application for licensure for a fifth dose. This study is, therefore, being viewed as not pivotal for the current application.

This study was a Phase 1, open label, study of CPDT (Lot ----) given to 4-6 year old children who had previously received DTPwc at 2, 4, 6 and 18 months of age. Twenty-two subjects were enrolled. Safety was monitored by a telephone interview at 2-6 hours, 8-12, 24, and 48 hours. Telephone contact or home visits occurred on day 7 and 28. Serum for immunogenicity analysis was obtained pre-vaccination and 28 days post-vaccination.

Results:
Safety: Local reactions were reported in 71.4% of subjects; 9.5% reported redness; 9% reported swelling; and 71.4% reported tenderness. The two children who reported swelling had significant involvement (25 mm and 70 mm). Systemic reactions were reported in 38.1%. Two subjects (9.5%) reported fever, 19% irritability, 23.8% drowsiness, 14.3% anorexia; 4.8% diarrhea. Antipyretic was used in 33.3%.
Immunogenicity: Pre-immunization sera were available from 21 children and post-immunization sera from 17 children. Significant antibody rises were demonstrated

against every antigen (anti-PT 5.8 to 171 EIA; anti-FHA 3.0 to 125; anti-agglutinogen 46.9 to 1336; anti-PRN 8.3 to 161).

Title: Safety and Immunogenicity of Two Connaught Component Pertussis Vaccines Combined with Diphtheria and Tetanus Toxoids Adsorbed ($CP_{20/20/5/3}$ DT and $CP_{10/5/5/3}$ DT).) Alone or in Combination with *Haemophilus influenzae* B Conjugate Vaccine in Children 17-19 Months of Age.

This was a Phase 2 study conducted in Canada in 1993. The study was designed to compare the safety and immunogenicity of CPDT or HCPDT and *H. influenzae* type b conjugated vaccine (PRP-T) given: 1) at the same visit as a single injection; 2) as separate injections at a single visit; or 3) as separate injections and separate visits in 17-19 month old children previously immunized with CPDT or the hybrid vaccine at 2, 4, and 6 months of age. Children who had participated in the Phase 2C (see above) study were eligible to enroll and received the same acellular pertussis vaccine formulation as they received in the primary series and were randomized to one of three regimens listed above.

The study was a partially, blinded randomized controlled trial. Five hundred and forty five subjects enrolled. Sera were collected prior to immunization and one month post-vaccination and assays for antibodies to vaccine antigens were performed at APL. The study summary does not clearly state at what time interval the separate injections given on separate days were given and when sera for these subjects were collected. Additionally, it is not stated if subjects who were randomized to receive separate injections on separate days always received them in the same order. The method of measuring and comparing local reactions that occurred between subjects who received separate injections to those who received a single injection is not clearly outlined.

Results: A total of 77 subjects who received CPDT during the primary series enrolled, and 468 who had received HCPDT. For the CPDT group, 21 received separate vaccinations on the same day, 29 received the combination vaccine CPDT/PRP-T, and 21 received CPDT and PRP-T. There was only one serious adverse event, generalized hives in a subject who received HCPDT and PRP-T given on separate days, although it is unclear after which immunization the reaction occurred. There were no significant differences in the responses to the pertussis antigens among the CPDT vaccine groups. For these subjects, the GMCs to PRP-T were higher in the group that received the combination product, but this group had higher pre-vaccination GMCs.

Conclusion: The results of this study are difficult to interpret because the numbers of children enrolled in each study group was small and the study summary provides insufficient information to allow adequate evaluation of the safety data. No serious adverse events were reported among recipients of the CPDT vaccine.

Safety and immunogenicity of Connaught component pertussis vaccine in combination with diphtheria and tetanus toxoids Adsorbed (HCPDT) alone or in combination with one of two inactivated poliomyelitis virus vaccine or oral poliomyelitis vaccine in children 17-19 months of age.
A summary of this study was submitted to the PLA. None of the vaccines studied in this trial were CPDT and the study was only reviewed for the occurrence of serious adverse events. A total of 425 subjects were enrolled in this study and no serious adverse events were reported.

Safety and immunogenicity of Connaught component pertussis vaccine in combination with diphtheria and tetanus toxoids Adsorbed and inactivated poliomyelitis virus vaccine (HCPDT-IPV) as compared with Connaught whole cell pertussis vaccine in combination with diphtheria and tetanus toxoids adsorbed and inactivated poliomyelitis virus vaccine (DTP-IPV) in children 4-6 years of age.
The sponsor is not seeking an indication for fifth dose with this application and none of the subjects in this study received CPDT. One hundred sixty five subjects were enrolled, there were no serious adverse events reported.

12.0 Post-Marketing Evaluation of CPDT

Prior to licensure, APL made commitments to conduct additional post-marketing studies to address specific concerns expressed by FDA reviewers and advisory committee members.

Study P3T06 - Safety, immunogenicity and lot comparability of CPDT adsorbed vaccine when administered with other recommended vaccines at 2,4, 6 and 15-16 months of age.

Study P3T06 was initiated in May 2001 to address concerns expressed by VRBPAC committee members that insufficient data had been obtained to assess the safety and immunogenicity of CPDT when given with routinely administered and recommended childhood vaccines and that additional data to assess the safety of the fourth dose of CPDT should be collected in clinical trials. Prior to licensure, APL was to submit an interim safety report after 50% of subjects had been enrolled and received their first dose in study P3T06. The final study report is to be submitted post-licensure at the completion of the study.

P3T06 is a 2 staged, randomized, multicenter study to assess safety, immunogenicity, and lot comparability of CPDT. The study also includes a arm that receives Pentacel. The lot consistency study for CPDT is blinded but the comparison to Pentacel is open-label in design.

Stage I:

Approximately 2000 subjects randomized to 4 groups (3 lots CPDT, 1 Pentacel group). CPDT is to be given with IPV (IPOL), Hib (ActHib), PncC7 (Prevnar), and Hepatitis B (Recombivax) vaccines (Groups 1-3) and Pentacel will be given Prevnar and Recombivax.

Primary Hypothesis for Stage I

The anti-pertussis (PT, FHA, FIM 2 & 3, PRN), anti-diphtheria toxoid and anti-tetanus toxoid GMC responses for subjects will be equivalent in recipients of three lots of CPDT Vaccine Adsorbed co-administered with other recommended vaccines upon completion of a primary series.

Secondary Hypothesis for Stage I

The anti-pertussis, D, and T antibody responses elicited by the primary series of Pentacel (HCPDT-mIPV//PRP-T) administered concurrently with Pnc7 and HepB will be non-inferior to responses (pooled from 3 lots) elicited by CPDT vaccine administered concurrently with Hib, IPV, Pnc7, hepB as assessed by the difference of the seroconversion and seroprotection rates.

Observational Objectives For Stage I

To present the immune responses of CPDT vaccine in Groups 1-3 pooled and Pentacel (Group 4) and the concomitant vaccines when CPDT and Pentacel are administered with other recommended licensed vaccines for the primary series.

For CPDT:

IPOL, ActHIB, Prevnar will be given with CPDT at 2, 4, 6 months.

Recombivax will be given at 2 and 6 months to subjects who have received a birth dose of HepB vaccine.

For Pentacel:

Prevnar at 2, 4, 6 months

Recombivax will be given at 2 and 6 months to subjects who have received a birth dose of HepB vaccine.

[Endpoints: for all antigens endpoint 1 = GMCs; in addition: PRP: ≥ 0.15 mcg/ml; ≥ 10 mcg/ml; D & T: ≥ 0.01 IU/ml and 0.1 IU/ml; PT, FHA, PRN, FIM ≥ 4 fold (post/pre); Polio 1, 2, 3 ≥ 1:8 dilution; HbsAg ≥0.01 mIU/ml; Pneumococcal ≥ 0.15/ml]

To present the safety profiles of all Stage I Groups (Groups 1-4).
To present the % of infants with PRN Ab less than 5, 10, 20 and 50 EU/ml after the 3rd dose in the infant series. Data and analyses assessing the antibody responses to the other pertussis antigens in infants who did not respond to pertactin will also be presented.

Table 77: Study P3T06, Stage I Vaccine Groups

Groups	Vaccines
1	CPDT Lot 1, IPV, Hib, and PncC7
2	CPDT Lot 2, IPV, Hib, and PncC 7
3	CPDT Lot 3, IPV, Hib, and PncC7
4	Pentacel and Pnc7

Serum will be obtained at 2 and 7 months of age from all subjects enrolled in Groups 1-4.

Stage II:
Is designed to determine the effect of co-administration of CPDT with Hib, PncC7, MMR and Varicella. Additionally, the immune responses to Pentacel will be compared to the concurrent immunization with CPDT and PRP-T given separately at different injection sites.

Primary Hypothesis for Stage II
The anti-pertussis (PT, FHA, FIM 2 & 3, PRN), anti-diphtheria toxoid and anti-tetanus toxoid antibody responses elicited by the booster dose of CPDT Vaccine Adsorbed concurrently with Hib, Pnc7, MMR, and varicella vaccines will be non-inferior to those elicited by CPDT concurrently administered with Hib vaccine, as assessed by the difference of seroconversion and seroprotection rates (anti-petussis, D, T responses of Group 2 are non-inferior to Group 1).
Primary Hypothesis for Stage II
The anti-PRP response elicited by Hib vaccine when co-administered with CPDT will be non-inferior to that obtained by Hib vaccine co-administered with other recommended vaccines (Pnc7, MMR, Varicella) as assessed by the difference in seroprotection rates (≥ 1.0 mcg/ml) (Group 1 non-inferior to Group 3).
The serotype specific anti-pneumococcal Ab responses elicited by Pnc7 when coadministered with the booster dose of CPDT Vaccine Adsorbed, Hib, MMR and varicella vaccines will be non-inferior to that obtained by Pnc7 co-administered with Hib, MMR and varicella vaccines, as assessed by the difference of the seroresponse rates (anti-Pnc7 responses of Group 2 are non-inferior to Grp 3).
The anti-MMR and varicella antibody responses elicited by MMR and varicella vaccines when co-administered with the booster dose of CPDT, Pnc7 and Hib vaccines will be non-inferior to that obtained by the MMR and varicella vaccines when given with Pnc7 and Hib as assessed by seroresponse rates (Group 2 non-inferior to Group 3).
Observational Endpoints for Stage II
To present the immune responses of CPDT when co-administered with Hib in Grp 1 and those of Pentacel in Grp 4.

[Endpoints: for all antigens endpoint 1 = GMCs; in addition: PRP: ≥ 10 mcg/ml; D & T: 0.1 IU/ml; PT, FHA, PRN, FIM ≥ 4 fold (post/pre);]
To present the safety profile of all Stage II Groups (Group 1-4) including the frequency of local reactions of > 50 mm erythema, > 50 mm swelling and limb swelling related to the injection site of the booster dose of CPDT and Pentacel.
To present the antibody responses as expressed in GMCs, rates of seroprotection/seroconversion and RCFD for all vaccines administered at 15 to 16 months of age. Anti-pertussis Ab responses pre and post 4th dose will also be presented by a stratification of the 7 months PRN antibody level (5, 10, 20 EU/mL).

Table 78: Study P3T06, Stage II Vaccine Groups

Groups	Months of Age	Vaccines
1	12	MMR, Varivax, Prevnar
	15 to 16	CPDT Lot 1, ActHib
2	15 to 16	CPDT Lot 1, ActHib, MMR, Varivax, Prevnar
3	15 to 16	ActHib, MMR, Varivax, Prevnar
	16 to 17	CPDT Lot 1
4	12	MMR, Varivax, Prevnar
	15 to 16	Pentacel

Serum samples will be obtained from at least 425 subjects per group in Stage II immediately before the booster dose of CPDT and Pentacel (at 15-16 months of age) and 28 to 48 days later. Only the immune responses of vaccines administered at 15 to 16 months of age will be assayed and compared.

Interim Safety Results Following Receipt of 1st dose by 50% of Subjects Submitted 1/24/2002

An interim study report was submitted after 1,027 subjects had been enrolled. This report is preliminary and the sponsor states that there was no process established to verify that all the data at the clinical sites entered into the database are fully verified at this time. Also, lot administration of DAPTACEL (CPDT) remains blinded and so lot comparison data are not provided. A full clinical and statistical report will be written at study completion.

Fifty percent enrollment for this study was achieved as of 12/7/2001 when 1,027 subjects had been enrolled and all had at least immediate reaction data available.
Location: USA
Investigator(s): 30 sites participating – each with one or more investigator.
Study Date: May 2001 -
Vaccines: CPDT, Pentacel, ActHib, IPOL, Prevnar, MMR, Varivax
Lot Number: CPDT Lot 1: ----------, Lot 2-------- (Lot 2), Lot ----------: Lot 3; Pentacel: Quadracel Lot ---------- and ActHIB Lot ----------
Study Objectives: see above
Population: Healthy infant 2 months of age (≥ 42 days to </= 84 days of age.
Sample size: For interim report, 1027 (777 CPDT [76%]; 250 Pentacel group [24%])
Design: Open label, randomized, controlled trial. Random allocation to CPDT vs Pentacel was 3:1. Subjects were randomly allocated to one of the 3 CPDT lots or Pentacel group.
Schedule: 2, 4, 6, 15-16 months.

Concomitant Vaccines and Medications: See above tables for Stage 1 and 2 groups.
Monitoring:
Safety: Immediately for 30 minutes post-vaccination. Diary cards for the first 7 days including rectal temperature measurements. SAEs throughout the trial and a f/u post-card or phone call 6 months after the last dose. Serology to be collected pre-dose 1, at 7 months, pre-fourth dose and 28 days post-4th dose.

Study Conduct: Interim report as noted above.

Table 79: Study P3T06 - Demographics

Demographic	Category	Statistics	Pooled DAPTACEL Lots (n=777)	Pentacel (n=250)
Gender	Male	% (n)	47.4 (368)	50.4 (126)
	Female	% (n)	52.6 (409)	49.6 (124)
Age	Months	Mean	2.1	2.1
		StdDev	0.4	0.3
		Median	2	2
Race	Caucasian	% (n)	81.2 (631)	79.2 (198)
	Black	% (n)	5.8 (45)	6.8 (17)
	Hispanic	% (n)	4.0 (31)	4.4 (11)
	Asian	% (n)	0.5 (4)	0.8 (2)
	Other	% (n)	8.5 (66)	8.8 (22)

Safety Results:
Immediate Reactions (within 30 minutes of vaccination):
There were 3 reactions reported, all in the CPDT group. One was fussiness for 20 minutes and two had mild redness at the injection site (size of reaction not provided). One reaction was post-dose one, 2 were post dose 2 but neither the table nor the text specifies which dose the specific 3 reactions occurred after (i.e. was fussiness post-dose 1 etc.).
Unsolicited Adverse Events (Section 2.2.2)
The report notes that this category of events includes answers to two open ended questions on the diary card as well as any solicited local or systemic reactions that were noted to be severe. The sponsor has only reported those reactions that were assessed as being related in line listing format and has provided all reactions but intabular format. These tables list adverse events using the MEDRA coding system, i.e. by body system in table format.
There were a total of 143 subjects in the CPDT group with unsolicited AEs at 2 months, i.e post-dose 1 (the sponsor notes that is 18.4% of the total of 777). Elsewhere it is noted that only 515 subjects returned diary cards in the CPDT groups for this visit, thus it is not clear what the correct denominator and percentage should be (i.e. if no data are available, these subjects should not be included in rate computations). Sixty-five of these were categorized as severe. Of these six were listed as gastrointestinal disorders, 55 were listed under "general disorder and administration site conditions, 1 as an infection or infestation, 2 as metabolism and nutrition disorders. Post-dose 2 there were a total of 66 unsolicited reactions of which 14 were listed as severe. In the severe category there were 2 GI disorders, 12 general disorders and administration site conditions. Post-dose 3 there were a total of 22 unsolicited reactions, 2 of which were listed as severe, 1 general disorders and administration site conditions, vaccination and has not list the day of onset post-vaccination. From the line listing data the severe

reactions judged possibly related to vaccine were irritability and anorexia in the same child, both of which were ongoing at the time of the report, one report of fussiness, the outcome of which is recorded as resolved with sequelae, one irritability from which the child had recovered, 1 crying which had resolved, 1 vomiting which had resolved, 1 fussiness which had resolved.

Serious Adverse Events (SAE, Section 2.2.3)

Serious adverse events were defined as per CFR. At the time of this report, 9 subjects had reported an SAE. The table below represents temporal relationship to vaccine for SAEs.

Table 80: Trial P3T06 – Interim Safety Report; Temporal Relationship of SAEs to Vaccination

	Pooled DAPTACEL Lots			Pentacel Lots		
	2 Months N = 777*	4 Months N = 350*	6 Months N = 86*	2 Months N= 250*	Months N = 117*	6 Months N = 35*
Days 0-3	2	0	0	0	0	0
Days 4-7	0	0	0	0	0	0
Days 8-60	5	0	0	1	0	1

*N = number enrolled, not number with diary card information

One SAE was considered to be vaccine related:

<u>Subject 1362:</u> Seizure and apnea judged probably/likely associated with vaccine. A 52 day old female child received CPDT, ActHib, Recombivax HB, Prevnar, and IPOL on 8/21/2001, time not recorded. At 20:32 that day, the mother reported left leg tenderness. Tylenol was given (unknown dose) at 22:30. At 23:23 the child started twitching over her entire body. The child's head twitched back and forth for ~15 seconds and she developed apnea, and required being startled to resume breathing. There was no change in skin color. Only her right eye was open and she appeared to be staring into space for ~30 seconds. She then slept for ~1 hr 45 minutes during which she was difficult to arouse. After that, she had a normal arousal level. She was seen in the ER at 00:30 ---------- and admitted. At the time of admission she had a normal exam including normal tone and temperature (36.5). The child remained normal during 15 hours of observation and was discharged. She had a normal EEG. The subject was withdrawn from the study but received subsequent vaccines given as single injections without incident. The investigator assessed the event as an afebrile seizure probably/likely related to vaccines.

Eight of the SAEs were considered unrelated to vaccine. These included:

Subject 0070 – Suspected pertussis A 3 month old male who was admitted to the hospital one month after receipt of his first dose of CPDT, ActHib, Prevnar, IPOL and a dose of Recombivax HB (presumably 2nd dose of HepB vaccine). The subject had severe coughing associated with cyanosis and vomiting and was diagnosed with suspected pertussis, treated for 14 days with erythromycin.

Subject 0002 – Cleft lip repair. A 2-½ month old patient with cleft lip and palate at birth was hospitalized 2 weeks after receipt of 1st dose of CPDT, ActHib, Prevnar, IPOL and receipt of Recombivax HB.

Subject 0833 – Viral infection. A 3-month-old male hospitalized one month after receipt of his first dose of CPDT, ActHib, Prevnar, IPOL and a dose of Recombivax HB (presumably 2nd dose of HepB vaccine). Hospitalized with fever, CXR with bronchovascular markings, negative blood and urine cultures. Patient was treated with IV Ceftriaxone. The illness had resolved 3 days after hospitalization.

Subject 0912 – Pneumonia. A 10-week-old female was admitted 3 days after receipt of her first dose of CPDT, ActHib, Prevnar, IPOL and a dose of Recombivax HB (presumably 2nd dose of HepB vaccine) because of low grade fever, cough, difficulty breathing which had started the day after vaccination. CXR revealed interstitial infiltrates at the base, possibly early pneumonia. She was diagnosed with pneumonia and treated with IV fluids and albuterol. The pneumonia had resolved the day after hospitalization.
Subject 0382 – Meningitis. A 9 month old female with a history of GE reflux was hospitalized 13 days after receipt of her first dose of CPDT, ActHib, Prevnar, IPOL and a dose of Recombivax HB (presumably 2nd dose of HepB vaccine) was hospitalized with a one day history of vomiting, diarrhea, and fever. CSF the following day revealed 4000 WBC and 4000 RBC, cultures were negative but antibiotics had already been initiated (Ceftriazone and ampicillin) the day before. Eight days later the meningitis was reported as being resolved.
Subject 1254 – Croup and dehydration. A 3 month old female was hospitalized ~ 1month after receipt of her first dose of CPDT, ActHib, Prevnar, IPOL and a dose of Recombivax HB (presumably 2nd dose of HepB vaccine) with a 2 day history of cough, wheezing, and sudden onset vomiting, fever and a croup-like cough. She was treated with IV fluids and racemic epinephrine. The illness resolved 2 days after hospitalization.
Subject 1257 – Fever. A 7 week old female was hospitalized for a fever of 103.7 2 weeks after receipt of her first dose of CPDT, ActHib, Prevnar, IPOL and a dose of Recombivax HB (presumably 2nd dose of HepB vaccine). Her CXR and cultures were negative and the fever resolved after a single IM dose of Ceftriaxone and antipyretics.
Subject 0919 – Emesis and dehydration. A 6 month old female was hospitalized ~ months after receipt of her 1st dose of Pentacel, Prevnar and a dose Recombivax for fever, congestion, irritability, anorexia, vomiting. Her temperature was 37.7 C (?method). She was treated with IV fluids for infectious gastroenteritis that had resolved three days later. Information is not provided as to whether the subject had received a second dose of Pentacel and concurrent vaccinations and if so, what was the temporal relationship of this event to vaccination.

Solicited Adverse Events (Section 2.2.4)
Of subjects who received one or more doses of DAPTACEL or Pentacel, only the solicited reactions of those that had completed and returned the diary card are captured below.
Local Reactions:

Table 81: Study P3T06 - Limb Locations for Individual Vaccines

Vaccine	DAPTACEL Group	Pentacel Group
DAPTACEL or Pentacel	Left upper thigh	Left upper thigh
ActHib	Left lower thigh	
IPOL	Left arm (subQ)	
Prevnar	Right lower thigh	Right lower thigh
Recombivax HB	Right Upper thigh	Right upper thigh

Table 82: Study P3T06 - Solicited Local Reactions, Interim Report

	DAPTACEL Group			Pentacel Group		
	2 Months N = 777	4 Months N = 350	6 Months N = 86	2 Months N= 250	Months N = 117	6 Months N = 35
Diary Cards	515	196	37	178	70	20
	%	%	%	%	%	%
Any d 0-3	58.1	52	56.8	62.4	62.9	50
Any d 4-7	2.9	4.6	2.7	4.5	7.1	10
Redness						
Any	25.6	33.7	37.8	31.5	34.3	35
Moderate*	0	0	0	0	0	0
Severe**	0	0	0	0	0	0
Swelling						
Any	14.8	17.9	16.2	15.7	30	25
Moderate*	0	0	0	0	0	0
Severe**	0	0	0	0	0	0
Tenderness						
Any	47.4	35.2	37.8	48.9	45.7	40
Mild♦	28	25.5	27	29.2	37.1	25
Moderate♦♦	15.5	8.2	5.4	14.6	4.3	10
Severe♦♦♦	3.9	1.5	5.4	5.1	4.3	5

*Moderate redness and swelling = 25-49 mm; **Severe redness and swelling >50 mm. ♦Mild = subject whimpers when site it touched, no crying; ♦♦Moderate = subject cries when site it touched; ♦♦♦ Severe = subject cries when leg or arm is moved.

Table 83: Study P3T06 - Solicited Systemic Reactions, Interim Report

	DAPTACEL Group			Pentacel Group		
	2 Months N = 777	4 Months N = 350	6 Months N = 86	2 Months N= 250	Months N = 117	6 Months N = 35
Diary Cards	516	195	37	179	70	20
	%	%	%	%	%	%
AE, Any d 0-3	91.9	84.6	75.7	89.9	87.1	80
AE, Any d 4-7	43.8	41.5	29.7	49.7	31.4	50
Fever						
Any	15	23.5	24.1	10.9	18.4	40
Mild >38◦C	15	23.5	24.1	10.9	18.4	40
Mod >39.5	0	0	0	0	0	0
Sev. >40.5	0	0	0	0	0	0
Fussiness						
Any	77.9	73.8	62.2	77.7	70	55
Mild <1 hr	41.9	41.5	37.8	41.9	45.7	35
Mod. 1-3 hr	30.6	24.6	18.9	30.2	17.1	15
Sev. >3 hr	5.4	7.7	5.4	5.6	7.1	5
Crying						
Any	62.6	56.4	51.4	62.6	51.4	35
Mild < 1 hr	43.4	40.5	32.4	41.3	40	30
Mod. 1-3 hr	16.7	12.8	16.2	18.4	11.4	0
Sev. >3hr	2.5	3.1	2.7	2.8	0	5
Less Active*						
Any	50.8	34.9	29.7	43	41.4	20
Mild	25.6	19.5	16.2	20.7	24.3	10
Moderate	24	13.8	13.5	19	17.1	10
Severe	1.2	1.5	0	3.4	0	0
Anorexia**						
Any	29.7	23.1	27	28.5	25.7	30
Mild	21.7	16.4	21.6	18.4	20	15
Moderate	7.4	5.6	2.7	10.1	5.7	10
Severe	1.6	1	0	0.6	0	0
Diarrhea***						
Any	21.9	19	10.8	21.8	20	15
Mild	18.8	15.9	10.8	17.9	15.7	10
Moderate	2.3	2.6	0	2.8	2.9	5
Severe	0.8	0.5	0	1.1	1.4	0
Rash	4.7	3.6	2.7	3.9	5.7	5

*Less active: mild: daily activity not affected, subject interactive; moderate: interferes with and limits daily activity, less interactive; severe: disabling.

**Anorexia: mild: refuses 1 feed; moderate: refuses 2 feeds; severe: refuses≥ 3 feeds.

*** Diarrhea: mild: 1-3 stools; moderate: 4-5 stools; Severe: > 5 stools.

Comments and Requests for Information regarding Interim Safety Report for P3T06:
As noted by the sponsor, these results are part of an interim report and all the data had not been fully verified at the time of submission. A number of discrepancies are noted. Some concerns will need to be addressed by the sponsor in the final study report, including full follow-up information on serious and severe adverse events. The manner

in which unsolicited AEs are reported should be clarified. Currently, this category includes a number of specific solicited AE leading to duplicative report for some events. Additionally, the data are present in both tabular format and as line listing but neither format includes all the relevant data that would be required to assess and interpret the data. The categorization of fever remains problematic. The definitions for grades of fever were discussed during review of the protocol and CBER relayed concerns that mild fever should not be defined as a fever of < 39.5°C and moderate as <40.5°C. Nevertheless, these definitions are included in the final protocol. For the CSR, CBER requests that fever gradations be defined more appropriately (see below).
While 777 subjects were enrolled and received a first dose, only 516 diary cards were returned. The sponsor should clarify whether this is largely due to the fact that they had not yet been collected or whether this is due to noncompliance on the part of parents or guardians of study participants.

Of concern is that a 2nd afebrile seizure has been reported among US children enrolled in clinical trials and receiving concomitant routinely recommended childhood vaccines. The only other study in which all routinely recommended vaccines were given with CPDT (except for Prevnar which was not licensed at the time that study was conducted) was the USBS in which an afebrile seizure was reported post-dose 2 within 24 hours of vaccination. Both seizures, the one in P3T06 and the one in USBS were judged to be possibly or probably/likely related to vaccine. The seizures were not only temporally related to vaccination but no other cause for the seizures was detected and neither subject went on to develop a seizure disorder. Thus, as noted above, to date (i.e. with interim data from P3T06) in the two US studies designed to assess safety of CPDT given with routinely administered concomitant vaccines the rate of seizures is 2/1098.
Comments for the sponsor:

- For immediate reactions we note that neither the text (page 15) nor the table (section 6, table 2) specifies which immediate reactions occurred following each dose. For instance, there was one episode of fussiness within the 30 minutes post-immunization but it is not clear if this occurred after the first or second dose. Please ensure that the final report will specify which reactions occurred by dose, by vaccine, and by lot.
- For the final study report we request that you define grades of fever as follows (using rectal temperature equivalents): None = < 38°C, Mild = ≥ 38°- ≤ 38.5°C, Moderate = > 38.5°C - ≤ 40°C, and Severe = ≥ 40°C.
- The report included in the unsolicited reactions category the following information: responses to two open ended questions on the diary card (listed on page 16), the indication for a medication, and severed solicited local and systemic events graded. Therefore, the unsolicited AE database contains several categories of reactions, some of which are duplicates of entries in the solicited adverse event data. For the final CSR, the unsolicited AE will be presented separately from the solicited AE.
    - Please clarify whether duplicate entries for adverse events will be eliminated in the final study report (e.g. severe solicited events will not be entered in the unsolicited event categories). Such an approach will facilitate review of the data.
    - The second open-ended question asks whether the child had any seizures (convulsions), fainting, or any change in his mental status since the immunization. As these appear to be quite specific questions, please explain why answers to this question are being referred to as unsolicited.

  - Telephone calls at 30 and 60 days post vaccination were to query for certain types of AEs occurring post-vaccination. How will these events be categorized and reported in the CSR? Similar information is to be queried for at the time of the next vaccination and also 6 months post dose 4. Please also clarify how you intend to enter and report adverse events reported at these times.
  - The report has line listings (listing 6, section 7) for unsolicited reactions occurring post-vaccination with the specific diagnoses but not the dose post-vaccination and the assessed relationship to vaccine. Table nine lists all reactions and their assessed relationship by dose but reactions are listed by body system categorizations and do not include information regarding the resolution of the events. Thus it is very difficult to assimilate the information on unsolicited reactions that would be needed to adequately interpret the data. This task would be likely be simplified if solicited reactions were not included in your reports of unsolicited reactions. Please consider revising the tables so that information on particular events can be readily assimilated.
  - We note that Table B, page 17 list 31 severe unsolicited reactions post-dose 1 whereas Table 8, page 43 list 65. Similar discrepancies are noted for reactions following other doses. Please clarify these discrepancies.

- We note that for serious adverse events, we requested that you collect them through out the duration of the trial and for 6 months post-dose 4. In Table C of section 2.2.3 of this report, SAE reporting is limited to 60 days post-vaccination. Please verify that you are planning to collect all SAEs throughout the duration of the study as specified above.
- Table C in section 2.2.3 indicates that there were a total of 9 SAEs, 7 in the CPDT groups and 2 in the Pentacel group. The case narratives in section 5 indicate that eight of these were in the CPDT groups (all but subject 0919). Please clarify this discrepancy.
- Subject 1362 experienced an afebrile seizure and apnea judged probably/like related to vaccines. The case narrative indicates that the child recovered and was withdrawn from the study and received all subsequent vaccines as single vaccines without incident. Please proved the information regarding the schedule of subsequent vaccinations and specify which DTaP vaccines were subsequently given. Please also describe whether any reactions were record with any subsequent vaccination. Please provide the duration of available follow up for this child. We encourage you to continue to follow this child for safety throughout the duration of the study and to provide long term follow up on the child's health and development when available.
- We note that one subject, subject 0912, was hospitalized and diagnosed with pneumonia three day post-vaccination with clinical symptoms beginning the day after vaccination. The report states that the subject's pneumonia resolved the day following hospitalization following treatment with IV fluids and albuterol. Please provide any additional information you have on this subject such as longer term follow up and/or any additional test results that might confirm the diagnosis of pneumonia (e.g. WBC count, culture results, serology for viral pathogens etc).
- Subject 0912 was diagnosed with meningitis based on clinical symptoms and an elevated CSF WBC. Antibiotics were started prior to CSF cultures being

obtained. The meningitis is said to have resolved 8 days after admission. Please provide the basis on which meningitis was deemed to have resolved (i.e. clinical symptoms or repeat CSF examination), the CSF WBC differential, and information as to whether blood cultures were obtained. If they were obtained, were they obtained prior to initiation of antibiotics and what were the results. Please provide information on cultures or serologic tests that were performed and the results of these tests.

- Subject 1257 was hospitalized at 7 weeks of age for fever, 2 weeks after receipt of her first dose of CPDT. Please provide her age at the time of receipt of CPDT and clarify if she met the inclusion/exclusion criteria for age.
- Subject 0919 was admitted to the hospital for infectious gastroenteritis approximately four months after receipt of her 1st dose of Pentacel and other concurrent vaccination. Please describe what the basis was for the diagnosis of infectious gastroenteritis (i.e. culture, epidemiological data) and also clarify whether the patient had received her 2nd and 3rd doses of vaccines and if so, what the temporal relationship to was between the hospitalization and receipt of these subsequent doses of vaccine. If no other doses were received after the 1st dose, please explain why no further doses were given.

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THESE

12 PAGES

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TO BE

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