JAN 15 2003

Summary For Basis of Approval

Reference Number: 99-0279

Drug Licensed name: Pneumococcal 7-valent polysaccharide Protein conjugate

Manufacturer: Wyeth-Lederle Vaccines

Drug Trade Name: Prevnar™

I. Indications for use:

Prevnar™ Is indicated for active immunization of infants and toddlers against invasive disease caused by *Streptococcus pneumoniae* due to capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F). The routine schedule is 2, 4, 6 and 12-15 months of age. For additional information on usage, see DOSAGE AND ADMINISTRATION (below and in the attached package insert).

II. Dosage form, route of administration and recommended dosage

Prevnar™ is manufactured as a liquid preparation. Each dose is formulated to contain 2 μg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 μg of serotype 6B (16 μg of saccharide); approximately 20 μg of the diphtheria CRM_{197} protein; and 0.125 mg of aluminum per 0.5 ml dose as aluminum phosphate adjuvant. The 0.5 ml dose is to be given intramuscularly. For infants, the immunization series of Prevnar™ consists of three doses of 0.5 ml each, at approximately 2-month intervals, followed by a fourth dose of 0.5 ml at 12-15 months of age. For previously unvaccinated older infants and children, who are beyond the age for routine infant schedule, the following schedule applies:

Age at first Dose	Total Number of Doses
7 – 11 months of age	3
12 – 23 months of age	2
≥ 24 months through 9 years of age	1

III. Manufacturing and Controls:

A. Manufacturing and Controls:

The production of Prevnar™ includes distinct manufacturing operations, including:

- Fermentation and purification of diphtheria CRM_{197} carrier protein
- Fermentation and purification of pneumococcal polysaccharides serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F

- Activation
- Conjugation
- Formulation
- Filling

Fermentation and purification of diphtheria CRM_{197} carrier protein: CRM_{197} is a nontoxic variant of diphtheria toxin isolated from *Corynebacterium diphtheriae* strain C7 (β197) grown in casamino acids and yeast-extract based medium. The production scheme is a [redacted] The fermentation broth [redacted] precipitated CRM_{197} [redacted] Column chromatography is used to purify CRM_{197}. The purified CRM_{197} is concentrated by ultrafiltration. [redacted]

Pneumococcal polysaccharide fermentation and purification: The production scheme is a [redacted] fermentation process in which the [redacted]

Polysaccharide Activation: [redacted]

[redacted]

Conjugation: The [redacted] activated saccharide mixture [redacted] The conjugation reaction is initiated by reductive amination. [redacted] Column chromatography [redacted] The conjugate is [redacted] to achieve the required final concentration and filtered.

[redacted]

Formulation and Filling: [redacted] Aluminum phosphate is added [redacted] The batch is downloaded into sterile containers. No preservative is added.

Release tests on the formulated bulk include saccharide and protein content, aluminum content, identity, sterility, and endotoxin.

The final containers are aseptically filled, stoppered, capped and inspected. Release tests on the final container include identity, sterility, and endotoxin.

B. Stability Studies:

The recommended storage temperature for the vaccine is 2° – 8 ° C. Formulated Prevnar was filled into final containers and stability was assessed over time at the recommended storage temperature using [redacted] assays. The stability assessment focused on [redacted]

The dating period for this product is 24 months from the date of manufacture when stored continuously at 2° – 8 ° C. The final formulated bulk may be stored for up to [redacted] and no more than [redacted] in final container when maintained at [redacted]

C. Validation:

Quality control records for the qualification and validation of all major equipment and critical processes at the Sanford and Pearl River facilities of Wyeth-Lederle Vaccines have been

inspected and found to be adequate for in-process, product release, stability studies, and regulatory purposes.

D. Labeling:
The container and package labeling as well as the package insert are in compliance with the appropriate sections, 610.60, 610.61, 610.62, 201.56, and 201.57, of 21 CFR. The package insert contains statements concerning use, contraindications, warnings, immunogenicity, experience, precautions, adverse reactions, dosage and administration, how supplied, and information on storage of the vaccine.

E. Establishment Inspection:
A pre-license inspection of the Wyeth-Lederle Vaccines production facility at Sanford, NC was conducted September 7-10, 1999. Complete respones to inspectional issues raised in the FDA form 483 for Sanford were received by the agency and all responses were considered satisfactory. A pre-license inspection of the Wyeth-Lederle Vaccines production facility at Pearl River, NY was conducted September 20-24, 1999. Complete respones to inspectional issues raised in the FDA form 483 for Pearl River were received by the agency and all responses were considered satisfactory.

F. Environmental Impact Analysis Report (EIAR):
A statement of compliance was submitted on February 26, 1999 indicating that the product license application for Prevnar is categorically excluded from the requirement for submitting an environmental assessment as per 21 CFR 25.31 (c).

IV. Pharmacology:

The mode of action is induction of serotype specific opsonic antibodies against the type specific capsular polysaccharides for types included in the vaccine.

The manufacturer's labeling is adequate with respect to pharmacology. For additional information see the clinical pharmacology section of the attached package insert.

V. Medical:

A. general Information
Streptococcus pneumoniae (pneumococcus) is a leading cause of serious illness in young children worldwide, and the most frequent bacterial cause of pneumonia, bacteremia, sinusitis, and acute otitis media. Each year in the United States pneumococci cause approximately 17,000 cases of invasive disease among children under 5 years of age, including 700 cases of meningitis and 200 deaths. Children who recover from pneumococcal meningitis often suffer persistent neurologic deficits, including hearing loss. The highest rates of invasive disease occur in children under 2 years of age, with the peak incidence among children age 6 to 11 months.

Pneumococcal polysaccharide vaccines, first licensed over 25 years ago, have proven ineffective in preventing invasive pneumococcal disease in infants and in children under 2 yrs of age. The inability of the immature human immune system to respond effectively to simple oligosaccharide and polysaccharide antigens appears related to lack of T-helper cell activity. Prevnar is the first licensed pneumococcal vaccine manufactured using protein-conjugation chemistry. In this regard, the conceptual approach taken in the manufacture of Prevnar is similar to that of the *Haemophilus influenzae* type B (Hib) conjugate vaccines, which have been dramatically successful in nearly eleminating invasive disease caused by *H. influenzae* type b.

Over 80 distinct pneumococcal serotypes have been identified based on antigenic differences in the capsular polysaccharides. The 7 serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) chosen for representation in Prevnar account for about 80-85% of invasive disease in small children. These vaccine serotypes are also responsible for about 80% invasive pneumococci that are not susceptible to penicillin.

B. Brief description of clinical studies:
The clinical section of the application contained study reports for 8 clinical trials and supporting data from 3 additional studies. Table 1 summarizes the studies included in the application.

All data supporting efficacy, and the bulk of the safety data in the application, derive from the Northern California Kaiser Permanente (NCKP) pivotal efficacy trial, Study 118-8.

Two other studies considered essential for licensure are:
- 118-12, the lot consistency study
- 118-16, the manufacturing-bridging study, which provided clinical evidence of ability to scale up production to the manufacturing scale

Additional safety and immunogenicity data, intended to support use of Prevnar in previously unvaccinated older children, were submitted from studies 118-16 and 118-18. These studies were completed and study reports submitted as amendments to the PLA after the November 5, 1999 advisory committee meeting.

Not included in the application are data from studies addressing safety and immunogenicity among children from some high-risk populations, such as children with sickle cell disease, HIV infection, Hodgkin's disease, and nephrotic syndrome. Also not included in the application are data from a trial of the effectiveness of 7VPnC in preventing otitis media, which was conducted in Finland.

Pivotal Efficacy Study 118-8: "Evaluation of the Safety, Immunogenicity and Efficacy of Heptavalent Pneumococcal Conjugate Vaccine and Safety of Meningococcal Group C Conjugate Vaccine in Infants at 2, 4, 6 and 12-15 Months of Age in Northern California Kaiser Permanente (NCKP) Medical Care Program"

This was a large, randomized, double-blinded, controlled, pivotal efficacy study conducted at multiple centers within the Northern California Kaiser Permanente health care system. The efficacy database included 37,816 infants randomized (1:1) to receive Prevnar or an investigational meningococcal group C conjugate vaccine (MnCC) at 2, 4, 6, and 12-15 months of age.

The primary objective of this study was to determine the protective efficacy of 7VPnC against invasive pneumococcal disease caused by vaccine serotypes.

Table 1. Clinical Studies in the Prevnar Product License Application

Study Number	Population	Schedule (Months)	Control	Regulatory Objective/ Other Information
D92-P5	Infants	2, 4, 6	No 5VPnC	Saccharide model and dose selection
	Toddlers	15-18	None	PNU-IMUNE®23 Boost
D118-P2	Adults	18-60 yr	PNU-IMUNE®23	Safety, immunogenicity in adults
D118-P3	Infants	2, 4, 6, 12-15	MnCC	Safety and Immunogenicity Support MnCC as control for Phase 2 and 3
D118-P7	Infants	2, 4, 6, 12-15	MnCC	Pilot for Efficacy Study; Safety and Immun. Compatibility with Hep B
D118-P8	Infants	2, 4, 6, 12-15	MnCC	Efficacy: invasive disease, AOM, pneumonia; Large safety data base for adverse events; Safety when given with DTP or DTaP
D118-P9	Toddlers	15-24	7VPnC	2 Lots of 7VPnC;
D118-P12	Infants	2, 4, 6	No vaccine	Pilot Lot Consistency; Safety and reactogenicity given with DTaP; Catch-up data; Compatibility with HbOC, DTaP;
	Infants	7, 9	None	
	Toddlers	15-18	None	
D118-P15	Infants	2, 4, 6, 12-15	MnCC	Ongoing efficacy study, Navajo and Apache; Only catch-up immunogenicity data provided
	Toddlers	Various	MnCC	
D118-P16	Infants	2, 4, 6	No vaccine	Bridging from pilot to manufacturing; Safety and reactogenicity given with DTaP; Compatibility with HbOC, HepB, IPV;
D124-P2	Infants	2, 4, 6	7VPnC	Compatibility with MMR, immunogenicity data obtained with 9-valent formulation

	Toddlers	12-15	None	
D124-P501	Toddlers	12-17	MnCC	Immunogenicity data for catch-up obtained with 9-valent formulation
		18+	MnCC	

(Note: The abbreviation 7VPnC was used to designate Prevnar in study reports prior to licensure of the vaccine. MnCC refers to an investigational meningococcal group C conjugate vaccine, also manufactured by Wyeth-Lederle, which served as a control vaccine in some of the trials).

Multiple secondary objectives relevant to licensure of Prevnar were also specified:

- To assess the safety and tolerability of 7VPnC
- To determine the protective efficacy of 7VPnC among all enrolled subjects (intent-to-treat)
- To evaluate the effectiveness of 7VPnC on overall invasive pneumococcal disease, regardless of serotype
- To assess the effectiveness of 7VPnC on rates of acute otitis media and pneumonia as determined by computerized data sources
- To assess the immunogenicity of 7VPnC following a primary series and 4th dose

Children received recommended childhood immunizations concurrently. In the original protocol, DTP-HbOC (Tetramune) and OPV (Orimune) were given concurrently with study vaccine at 2, 4, and 6 months of age. Subjects could also receive one or more doses of hepatitis B vaccine (Recombivax HB) concurrently. At 12-15 months of age, DTP-HbOC or DTaP and HbOC (HibTITER), MMR, and varicella vaccine could be given concurrently.

Amendment # 2, implemented August 1996, allowed for the substitution of DTaP and HbOC for DTP-HbOC, and for the substitution of inactivated poliovirus vaccine (IPV) for OPV when immunizing infants for the primary series at 2, 4, and 6 months of age.

Data were collected through automated data entry and storage systems used in routine patient care at NCKP. Individual case report forms were not submitted with the PLA, but case summaries were extracted from chart review and submitted upon FDA request.

The study was initiated in October 1995. The safety database was locked on April 30, 1998, to clean the data and prepare a study report in anticipation of imminent accrual of sufficient cases to conduct the interim efficacy analysis. The database used in the primary analysis of efficacy was locked August 20, 1998, after sufficient cases had accrued to conduct the planned interim analysis. Results of the interim analysis met pre-determined criteria for efficacy (see below); therefore, new enrollment into the trial was stopped, and this analysis became the primary efficacy analysis. Follow-up of subjects for invasive pneumococcal disease and serious adverse events continued through
April 20, 1999, at which time vaccine assignments were unblinded to all study personnel and families of subjects. Prevnar was then offered to subjects in the control group.

Demographics

Demographic information was collected for a randomly selected subset of about 7500 subjects from whom local reaction and systemic event data were collected via telephone interview (Table 2). The subset was selected based on the last digit of the subject's medical record number.

Based on this subset, the two study vaccine groups appear to have been well balanced with respect to race/ethnicity.

Table 2 Efficacy Study 118-8 : Race/Ethnicity asReported at 48 Hour Interview1 After Dose 1

	Asian %	Black %	Hispanic %	White %	Multi-ethnic %	Other/ Unknown %	p-value[2]
7VPnC (N=3708)	13.4	7.7	19.6	39.3	19.4	0.6	0.123
MnCC (N=3693)	13.0	8.4	17.9	40.5	19.3	1.0	

Reproduced from Table 11, page 89, Volume 13 of PLA
1 Telephone interviews conducted October 16, 1995 – April 30, 1998
2 Chi-Square Test (sponsor's analysis

Efficacy

A case of invasive pneumococcal disease was defined as a positive culture of *S. pneumoniae* from a normally sterile body fluid (e.g., blood, CSF, joint fluid) obtained from a child presenting with an acute illness consistent with pneumococcal disease. Surveillance of cases was conducted weekly at each study site by review of all positive cultures for pneumococcus. Listings of children discharged from NCKP hospitals with diagnoses compatible with invasive pneumococcal disease were conducted monthly.

A subject was considered vaccinated per-protocol if the following criteria were met:

- first dose administered after 42 days of age
- minimum 35 days between primary series doses
- third dose given by 365 days of age
- 4th dose administered between 365 days (12 months) and 480 days (16 months), and ≥ 60 days between the 3rd and 4th doses
- subject did not have acquired or congenital immune deficiency; children who developed invasive disease were to be requested to undergo screening to rule out immune deficiency

Agreement had been reached between representatives of Wyeth-Lederle and FDA to provide for one interim analysis after 17 cases of invasive pneumococcal disease due to vaccine serotypes had accrued among children who were vaccinated per protocol. The test criterion at the interim analysis was specified as follows: If no more than 2 cases, out of a total of 17, were observed in the group vaccinated with Prevnar, the vaccine was to be considered efficacious and the trial was to be stopped for evidence of efficacy. Exact confidence limits were derived from exact binomial distributions.

Among fully vaccinated children, 17 cases of invasive pneumococcal disease were observed in the control group compared to 0 cases in the Prevnar group (Table 3). Thus, in the per protocol analysis, Prevnar was 100% efficacious (95% CI 75.4-100%). Among children who did not receive all the vaccine doses per schedule, the vaccine was still highly effective: 22 cases of invasive disease in the control group versus 0 cases in the Prevnar group.

Table 3 Efficacy Study 118-8: Vaccine Efficacy Against invasive Pneumococcal Disease - Primary Analysis

Invasive Pneumococcal Disease (Cases through August 20, 1998)	Number of Cases		Vaccine Efficacy Estimate (VE)	95% Confidence Limits* of VE
	7VPnC	MnCC		
Vaccine Serotypes				
Per-Protocol	0	17	100%	(75.4%, 100%)
Intent-to-Treat	0	22	100%	(81.7%, 100%)
All Serotypes				
Per-Protocol	2	20	90.0%	(58.3%, 98.9%)
Intent-to-Treat	3	27	88.9%	(63.8%, 97.9%)

Adapted from Tables 17 page 105 , Volume 13 of PLA, and Table 5, page 25 of June 8, 1999 submission to the PLA.

* Two-sided P-values were determined based on exact binomial distributions and confidence limits were also determined based on exact binomial distributions (Sponsor's analysis).

Extended follow-up of children for 8 months beyond the time of the primary analysis confirmed the high efficacy of Prevnar in preventing invasive disease (per protocol: 39 cases in control group vs. 1case in Prevnar group; intent-to-treat: 49 cases in control group vs. 3 in Prevnar group). Five cases of meningitis and two deaths attributable to vaccine serotype pneumococcus occurred in the control arm through the extended follow-up period.

Note: Complete data sets, including [redacted] data files, identity of all bacterial blood isolates, and full safety data, for the extended follow-up period were not available for FDA review at the time of licensure.

Theoretical concerns about replacement of the 7 vaccine serotypes by non-vaccine serotypes were considered and investigated in the NCKP trial. No increase in the frequency of cases due to non-vaccine serotypes was observed over the course of the trial. In total, 9 non-vaccine pneumococcal serotypes were isolated from cases of invasive disease, 3 in the Prevnar group and 6 in the control group; these accounted for 15% of all isolates.

Immunogenicity

Immunogenicity of Prevnar was assessed in a subset of 366 children (188 7VPnC and 178 MnCC) who received 3 doses of DTP-HbOC concurrently with study vaccines at 2, 4, and 6 months of age, and who had at least one serum sample drawn. Of these subjects, 180 met the eligibility criteria for the immunogenicity analysis following 3 doses.

After the 3rd dose, the lowest GMCs were observed for serotype 19F, and greatest for serotype 6B. For the 4th dose analysis, 68 subjects in the 7VPnC group met eligibility criteria and provided pre- and post- sera. Pre-dose 4 GMCs had declined to less than 0.50 μg/mL for 3 of the pneumococcal serotypes (4, 18C, and 23F). After dose 4, GMCs exceeded 2 μg/mL for all

serotypes. Response to the 4th dose was least robust for serotype 19F. (Refer to Table 2 in package insert).

A reasonable interpretation of the available immunogenicity data is that antibody levels achieved after 3 doses in the efficacy trial were associated with short term protection (until 12 months of age), while the antibody levels achieved after 4 doses were associated with longer term protection. An estimate of the duration of protection beyond 12 months of age following 3 doses of Prevnar is not possible due to the design of the study. Useful estimates of the duration of protection following a 4 dose series cannot be made from data available at the primary analysis. Wyeth-Lederle has agreed to continue follow-up of subjects participating in the efficacy trial in order to better estimate the duration of protection (see planned post- marketing studies, described below).

Safety

Specific local reactions and systemic events following vaccine injections were actively monitored in a subset of approximately 6000 infants who received DTP-HbOC concomitantly with the study vaccines early in the trial. Amendment #4, implemented April 1997, provided for monitoring of acute safety data via diary cards and telephone interviews in a subset (N=1500) of the population of children who received DTaP and HbOC concurrently with the primary series of study vaccine. At the time of implementation, 20,272 infants and children had already received at least one dose DTP-HbOC with study vaccines.

Injection site reactions were monitored for 48 hours following immunizations by use of diary cards. Fever was recorded on the day of immunization, and at bedtime for 2 days after, and at any other time within 14 days that the infant felt warmer than usual. Other systemic events were monitored for 14 days and recorded by parents on a diary card. At approximately 48-72 hours and 10-14 days after each dose, these data were collected by telephone interviews with parents.

Summary tables of local and systemic reaction rates are included in the package insert. In general, local reactions were more frequent and severe at sites inoculated with Prevnar than with DTaP or HbOC, but less than for DTP-HbOC. Fever $\geq$ 38 °C was reported more frequently in the groups that received Prevnar regardless of concurrent vaccines.

All subjects in the NCKP efficacy trial were followed for specified adverse events. Hospitalizations within 60 days of study vaccines, emergency room visits within 30 days, and outpatient clinic visits within 30 days of each vaccine dose were recorded. Rates of outpatient clinic visits for diagnoses of interest (i.e. seizures, allergic reactions, including hives, wheezing, shortness of breath and asthma) were also assessed and provided in the PLA.
Rates of hospitalizations for febrile seizures within 30 days and 60 days of a study vaccine dose were significantly greater in the 7VPnC group than in the MnCC group for the first 3 dose series and across all doses, when given concurrently with whole cell pertussis containing vaccine.

Rate of hospitalization for asthma within 60 days of a vaccine dose was significantly greater in the 7VPnC during the 3 first dose series when administered concurrently with acellular pertussis containing concomitant vaccines.

Rate of hospitalization for gastroenteritis within 14 days of a vaccine dose was significantly greater in the 7VPnC group, regardless of concomitant pertussis vaccine.

In the NCKP efficacy study, information about seizure events was collected through hospitalizations, emergency room visits, and clinic databases. Seizure events might also be detected among the actively monitored subset, as "convulsions" were listed among the solicited events. Seizures were also listed among the reasons for study termination.

FDA asked Wyeth-Lederle to provide an integrated summary of all seizure events, in which discrete events would be counted only once, and acute events would be distinguished from follow-up visits or an ongoing seizure disorder by means of chart review. Other potential sources of information, including spontaneous reports from clinic study nurses (not in the original PLA) were also reviewed. Using all data sources, the number of subjects that experienced acute seizure events occurring within 3, 14, and 30 days of a study vaccine dose were assessed (Table 4).

Table 4 118-08: Number of Subjects with Acute Seizure Events

Period after Receipt of Study Vaccine Dose	Number of Children Experiencing Acute Seizure Event	
	7VPnC	MnCC
Within 30 days	32	41
Within 14 days	21	21
Within 3 days	8	4

From October 18, 1999 submission to PLA.

Of the 8 recipients of 7VPnC with acute seizure events within 3 days of inoculation, 7 were described as febrile seizures, and 7 had received a whole cell pertussis containing vaccine concurrently with study vaccines. The comparison between vaccine groups of rates of seizures occurring within 3 days of a vaccine dose was not statistically significant. These reports of febrile seizures likely represent a fairly complete assessment of febrile seizure episodes in the study, as several ascertainment modalities were used. Based on 55,000 doses administered in the efficacy trial, the febrile seizure rate was approximately 1 per 7000 doses. This is substantially less frequent than the historical rate of 1 per 1750 reported for whole cell pertussis vaccines (AAP Redbook 2000), despite concurrent administration of Prevnar with DTwP for the greater part of the study.

The safety evaluation was complicated by the background of concurrent immunizations and by the use of an investigational vaccine in the control arm. Thus, FDA reviewers sought to assure that the safety of Prevnar was further evaluated by comparing rates of selected uncommon and rare adverse event rates to historical rates for events such as sudden infant death syndrome

(SIDS), diabetes mellitus, and selected autoimmune diseases. Rates of the specified adverse events and rates of SIDS did not exceed historical rates within the NCKP health care system.

Wyeth-Lederle has agreed to continue evaluation of post-vaccination seizures, asthma, gastroenteritis and selected uncommon events in a large post-marketing study (see below).

Lot Consistency Study (118-12): "A randomized double-blind trial of the safety and immunogenicity of three lots of heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) pneumococcal conjugate vaccine administered to healthy infants at 2, 4 and 6 months of age"

The primary objective of this study was to evaluate 3 independently produced pilot scale lots of 7VPnC for consistency of manufacture by comparing their safety and immunogenicity (Table 5). Assessment of compatibility of 7VPnC with HbOC and DTaP when co-administered with Prevnar was a secondary objective. This multi-center study was initiated in September 1996 and completed in March 1998.

Approximately 300 subjects were randomized to one of four treatment groups (75 per group). Subjects in three groups received one of three lots of 7VPnC at 2, 4, and 6 months of age, administered concurrently with HbOC, DTaP, and IPV/OPV. Subjects in the 4th group received only HbOC, DTaP and IPV/OPV. The study was double-blind with respect to vaccine lots; however, unvaccinated control subjects could be identified due to the difference in the number of injections.

Table 5 Study 118-12: Study Design

Vaccine group	**Vaccine lot** (lower left thigh @ 2, 4, 6 mos)	N	**Concurrent vaccines & schedule** (all groups)
1	Lot A 7-5018-011A	75	ACEL-IMUNE (right thigh) @ 2, 4, 6 mo HibTITER (upper left thigh) @ 2, 4, 6 mo OPV @ 2, 4, and 6 mo, or IPV right thigh or upper extremity @ 2 and 4 mo
2	Lot B 7-5018-010A	75	
3	Lot C 7-5018-008A	75	
4	Control group (no control vaccine or placebo administered)	75	

Post dose 3 antibody concentration (GMC) for each of the 7 vaccine serotypes was the primary immunogenicity endpoint (Table 6). Two-fold difference between GMCs in pairwise

comparisons between lots was the pre-specified primary immunogenicity criteria for determining consistency of antibody responses among lots.

Table 6. Study 118-12: Comparisons of GMCs for Three 7VPnC Pilot Lots,
Ratio of GMC between Lots (with 90% Confidence Interval)

Serotype	Lot A to Lot B	Lot A to Lot C	Lot B to Lot C
4	0.76 (0.59, 0.97)	1.15 (0.91, 1.47)	1.52 (1.19, 1.95)
6B	**1.32 (0.86, 2.02)**	**1.58 (1.04, 2.38)**	1.19 (0.78, 1.82)
9V	0.93 (0.72, 1.20)	0.77 (0.60, 0.99)	0.83 (0.64, 1.07)
14	1.42 (1.03, 1.95)	0.91 (0.66,1.25)	**0.64 (0.46, 0.88)**
18C	0.98 (0.76, 1.26)	0.74 (0.58, 0.95)	0.76 (0.59, 0.97)
19F	1.10 (0.83, 1.44)	1.00 (0.76, 1.30)	0.91 (0.69, 1.19)
23F	1.16 (0.81, 1.65)	1.19 (0.85, 1.68)	1.03 (0.73, 1.45)

Adapted from Table 9, page 37, Volume 27, Part IV of PLA

The 2-fold, 90% CI criterion for GMCs was breached for 3 comparisons (serotype 6B, Lot A to Lot B, serotype 6B, Lot A to Lot C, and serotype 14, Lot B to Lot C).

While the test criteria were not met for 3 of the 21 comparisons, the margins of error were small, and no clear pattern suggestive of a failed vaccine lot was evident. Serotype 6B from lot A accounted for 2 of the 3 failed criteria; however the failure resulted from a greater GMC than that of the other two lots for this serotype, which were similar to one another. Taken together with safety data from this trial, FDA/CBER accepts that the clinical data provided to demonstrate lot consistency are sufficient.

Compatibility of Prevnar with Hib and DTaP were also addressed in Study 118-12. Following the primary series, a slight enhancement of Hib GMCs was observed when HbOC was administered with Prevnar. Responses to pertussis fimbriae, pertactin, and FHA were modestly diminished with concurrent administration of Prevnar and DTaP. The clinical significance of these findings is unknown. (See section on Safety and Compatibility of Prevnar with Recommended Vaccines, below).

Manufacturing Bridging Study (118-16): "Bridging Study Comparing the Safety and Immunogenicity of a Full-Scale Manufacturing Lot of Heptavalent Pneumococcal Conjugate Vaccine to a Pilot Scale Lot in Healthy Infants Immunized at 2, 4 and 6 Months of Age"

Vaccine lots used in the pivotal efficacy study were produced in sub-manufacturing scale quantities. The primary objective of this study was to demonstrate comparability of initial manufacturing lots of 7VPnC to pilot scale lots used in the efficacy trial. "Bridging" of pilot to manufacturing scale was intended to demonstrate that vaccine produced on a scale intended for marketing is not inferior to vaccine used in the efficacy trial as assessed by measures of safety and immunogenicity. Compatibility of 7VPnC with simultaneously administered Hib, inactivated polio (IPV) and hepatitis B vaccines was also evaluated.

The study was initiated February 12, 1998 and conducted at 7 sites through the Kaiser Permanente Vaccine Study Center. A protocol amendment provided for immunizations at 7 and 9 months of age those subjects randomized to the control group. Immunogenicity data generated

under the protocol amendment were not submitted with the application, but were provided as an amendment to the PLA on December 17, 1999, to support a schedule of immunizations of older children.

Two manufacturing lots were compared to the pilot lot for immunogenicity (Table 7). The manufacturing lots differed in type of aluminum phosphate used and type of vial. [redacted] was designated as the preferred lot for scale-up.

Table 7. 118-16: Study design and subject allocation

Vaccine lot (lower left thigh @ 2, 4, 6 months)	N Planned (evaluable)	**Concurrent vaccines & schedule** (All groups)
Pilot scale lot Adjuphos adjuvant; blow-molded vials	175 (150)	DTaP (right thigh) @ 2, 4, 6 mo HbOC (upper left thigh) @ 2, 4, 6 mo IPV (left upper deltoid) @ 2, 4 mo Hep B (upper right thigh) @ 2, 6 mo
Full-scale manufacturing lot "P" Adjuphos adjuvant; Blow-molded vials	175 (150)	
Full-scale manufacturing lot "N" Lederle AlPO4 adjuvant; single dose tubing vials	175 (150)	
Control group –no control vaccine or placebo	125 (100)	

A "no additional vaccine" control was included for safety comparisons; all children received recommended immunizations concurrently. Infants randomized to the Prevnar vaccine groups were followed until blood was drawn 1 month after the 3rd dose (7 months of age). Infants randomized to the control group participated until blood was drawn 1 month after the second catch-up immunization (10 months of age).

The study had 2 co-primary immunogenicity endpoints for each of the 7 vaccine serotypes: 1) GMCs and 2) response rates above defined threshold antibody concentrations (Table 8). Threshold values for each serotype were determined by the maximal difference in serum antibody concentrations between immunized and unimmunized children at the 7-month bleed observed in previous studies using lots of vaccine from clinical scale production (i.e., studies 118-12 and 118-8).

Table 8. 118-16: Threshold Serum Antibody Concentrations Used to Determine Percent Responders

Serotype	Threshold Concentration Level (μg/mL)
4	0.15
6B	0.25
9V	0.28
14	0.38
18C	0.21
19F	0.26
23F	0.18

Pre-defined criteria demonstrating acceptable bridging were: 1) ≤ 2-fold difference in GMTs between pilot and manufacturing lot, and 2) ≤ 10% difference in response rate between pilot and manufacturing lot at the defined threshold values for each serotype.

Successful bridging to the efficacy lots was demonstrated for lot "N" for all 7 serotypes (Table 9). The lower 90% CI for the ratio of GMCs exceeded 0.5 for all 7 serotypes. The lower 90% CI for the difference in % seroresponders at the defined threshold levels was not less than –10% for any serotype. Based on these immune response data, and taken together with the safety data from this study, FDA reviewers accepted that the clinical evidence provided to support bridging of pilot to manufacturing scale is sufficient.

Compatibility of Prevnar with concurrent Hib, IPV, and Hepatitis B vaccine was also addressed in study 118-16. Consistent with other studies, a statistically significant enhancing effect on Hib GMCs was demonstrated after the first 3 doses.

Seroconversion (1:10) to poliovirus type 1, at 88.96%, was diminished relative to control (lower 90% of difference, -13.29%), while types 2 and 3 showed no inhibition. The clinical significance of this finding is unclear. (See section on Safety and Compatibility of Prevnar with Recommended Vaccines, below).

Immune responses to Hepatitis B vaccine showed no immunologic incompatibility with Prevnar. These findings satisfactorily address concerns arising from Hep B responses from study 118-7 (see below), as study 118-16 enrolled more subjects, and the other concurrent vaccines received (DTaP and IPV) more accurately reflect current recommendations and practice.

C. Summaries of other supporting clinical trials:

Study 92-05: A randomized, controlled, blinded, multicenter trial of the safety and immunogenicity of 2 models of pentavalent (6B, 14, 18C, 19F, 23F) pneumococcal conjugate vaccine at 3 dose levels as a primary immunization series in infants at 2, 4, and 6 months of age with a booster dose of polysaccharide vaccine at 15-18 months of age

Table 9. 118-16: Comparisons of Proportions of Subjects Achieving Given Antibody Concentrations

% Subjects (95% CI) Achieving Given Antibody Level				Manuf. N Lot (Lederle Alum) versus Pilot Lot	
Serotype	Level (μg/mL)	Pilot Lot N=152	Manuf. N Lot (Lederle Alum) N=159	Difference	90% Lower Limit*
4	0.15	99.34 (96.3, 100)	99.37 (96.5, 100)	0.03	-3.81
6B	0.25	96.71 (92.4, 99.0)	97.48 (93.6, 99.4)	0.77	-4.21
9V	0.28	100 (97.6, 100)	95.60 (91.1, 98.3)	-4.40	-9.91
14	0.38	98.03 (94.3, 99.6)	94.34 (89.5, 97.4)	-3.69	-9.76
18C	0.21	100 (97.6, 100)	97.48 (93.6, 99.4)	-2.52	-7.52
19F	0.26	97.37 (93.3, 99.3)	96.23 (91.9, 98.7)	-1.14	-6.91
23F	0.18	96.71 (92.4, 99.0)	98.11 (94.5, 99.7)	1.40	-3.40

* Exact confidence limit using StatXact.
Adapted from Table 7, page 48, Volume 29, Part IV of PLA

This study of pentavalent pneumococcal conjugates was initiated in May 1993 and completed in January 1996. The purpose of this study was to determine the optimal formulation (oligosaccharide vs. polysaccharide) and saccharide dose level [redacted] 2, [redacted] μg) of a vaccine for use in infants. All 5 vaccine serotypes studied are among those chosen for inclusion in Prevnar.

A protocol amendment provided for a booster dose of PNU-IMUNE®23 to be given at 15-18 months of age to children who had received 3 doses at 2, 4, and 6 months of age. Another protocol amendment provided for a dose of 7-valent pneumococcal conjugate vaccine at 12-15 months of age to be given at one of the centers.

This is the only study in the PLA that provides safety and immunogenicity for a dose of pneumococcal polysaccharide vaccine following a vaccination series with pneumococcal conjugate vaccines.

Subjects were randomized equally to one of 6 treatment groups, or a 'no vaccine' control group (N=60/group). Investigational vaccines were inoculated into the left thigh at 2, 4, and 6 months of age. All subjects also received DTP-HbOC (Tetramune) in the right thigh.

Results of the immunogenicity assessments supported the manufacturer's choice of the polysaccharide model and the 2μg polysaccharide dose.

Antibody responses to a dose of polysaccharide vaccine at 15-18 months were robust for each of the 5 vaccine serotypes among the groups that received 3 doses of conjugate vaccine. In the control group, antibody responses were weak or not discernible following administration of a single dose of polysaccharide vaccine at 15-18 months of age.

Comparative antibody response data following a 4th dose of either 7-valent conjugate vaccine or polysaccharide vaccine were not provided in the PLA.

Also of note in this study, GMC's to Hib PRP post-dose 3 were significantly enhanced by co-administration of all 5VPnC formulations, and particularly so for the 2 μg dose group, which was chosen for subsequent development.

Study 118-02: A randomized, double-blind, controlled trial of the acute safety of heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) pneumococcal conjugate vaccine as a single injection in healthy adults

This early study was intended to demonstrate safety of 7VPnC in adults before initiation of studies in children and infants. The study was initiated in December 1994 and completed February 1995. It was the first clinical study conducted under U.S. IND using the 7VPnC.

Thirty adult subjects, 18 to 60 years of age, were enrolled at a single center, and randomized (1:1) to receive a single dose of either 7VPnC or 23-valent pneumococcal polysaccharide vaccine (PNU-IMUNE®23).

Local and systemic reactions were recorded for 3 days post-inoculations. Local reactions (erythema, induration, or tenderness) were reported for 93% of 7VPnC recipients, and 73% of PNU-IMUNE®23 recipients; more severe local reactions occurred with similar frequency (33%) in both groups. Any systemic reaction (decreased appetite, vomiting, headache, rash, muscle pain, joint pain, fever) was reported for 60% of 7VPnC recipients and 27% of PNU-IMUNE®23 recipients. Fever (≥ 38.0 °C) was reported for 1 subject in the 7VPnC group, and 2 subjects who received PNU-IMUNE®23.

Antibody responses to the 7 pneumococcal serotypes included in 7VPnC, as determined by IgG ELISA assays, did not differ significantly between groups in this small study, with the exception of serotype 23F, which was significantly greater in the conjugate vaccine group.

Study 118-03: A Randomized Double-Blind, Trial of the Safety and Immunogenicity of Heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine and Meningococcal Group C Conjugate Vaccine in Healthy Infants at 2, 4, and 6 Months of Age, followed by a Booster Dose at 12-15 months of Age of the Same Vaccines.

The objectives of the study were to determine the safety and immunogenicity of 7VPnC among infants, and to assess the safety of meningococcal group C conjugate vaccine (MnCC) as a control for 7VPnC. Safety data obtained following administration of MnCC served to support its continued use as a control in subsequent Phase 2 and 3 studies. The study was conducted from February 1995 through June 1997, at 4 study sites. The original protocol was amended to allow for open-label study of a 4th dose. Potential interference with concurrent DTP, HbOC, and MMR was also assessed.

A total of 212 healthy infants were randomized 1:1 to receive 7VPnC or MnCC at 2, 4, and 6 months of age in the left thigh. Each infant also received DTP-HbOC in the right thigh, and OPV with the primary series.

As a 4th dose, 7VPnC subjects were again randomized 1:1 to receive either HbOC, or MMR.

After the 3rd dose, GMCs ranged from 0.98 μg/mL for serotype 9V, to 3.48 μg/mL for serotype 14. Antibody levels declined substantially after the primary series for some serotypes; pre dose 4 GMCs were lowest for serotypes 4 (0.20 μg/mL) and 18C (0.22 μg/mL). After the 4th dose, GMCs for each serotype exceeded 2.0 μg/mL.

Study 118-07: A Randomized, Double-Blind Trial of the Safety and Immunogenicity of Heptavalent Pneumococcal Conjugate Vaccine and Meningococcal Group C Conjugate Vaccine in Healthy Infants at 2, 4 and 6 Months of Age with a Booster Dose Administered at 12-15 Months of Age

This Phase 2 study was conducted within the Northern California Kaiser Permanente health care system, a population similar to that of the subsequent efficacy study. The study, initiated in June 1995, and completed July 1997, served as a pilot study for the large-scale safety and efficacy trial of 7VPnC. The stated primary objective was to gain experience with respect to the safety and immunogenicity of MnCC and 7VPnC.

Protocol amendment 1 provided for a 4th dose to be administered at 15-18 months of age with or without DTaP and HbOC. Amendment 2 allowed for assessing duration of post-dose 4 antibody levels at 24 months of age; however, data addressing duration of antibody were not included in the PLA.

Contributions of this study to the PLA are: 1) reactogenicity data for 7VPnC given against a background of DTP-HbOC in the primary series, and DTaP as a 4th dose, and 2) assessment of potential for immune interference between 7VPnC and recommended vaccines administered concurrently.

A total of 302 healthy 2 month old infants were randomized (2:1) to receive 7VPnC or MnCC at 2, 4, and 6 months of age. All subjects also received DTaP, HbOC and OPV concurrently. One-half of the subjects in each cohort were also randomized to receive Hepatitis B vaccine in the right thigh at 2, 4, and 6 months of age.

Potential of Prevnar to interfere with responses to diphtheria, tetanus, pertussis, and polio antigens, while examined in this study, is best addressed in studies 118-12 and 118-16, as the current standard of care is to administer DTaP and IPV with doses of the primary series.

Concurrent immunization with Hepatitis B did not adversely affect responses to pneumococcal vaccine serotypes, however, some interference with Hepatitis B vaccine responses was apparent with 92.6% (95% CI 84.6%, 97.2%) achieving seroconversion at 10 mIU/mL hepatitis B antibody. Compatibility of Prevnar with Hepatitis B vaccine was also assessed in study 118-16.

No statistically significant differences in any solicited systemic reaction were demonstrated. However, vaccine reactogenicity is also better addressed by other, larger studies in the PLA. One infant experienced a hyporesponsive episode on the day of the 1st dose of 7VPnC; the event was considered probably related to 7VPnC and no additional doses were administered. No deaths or seizures were reported during the study period.

Study 118-09: A Randomized, Double-Blind Trial Comparing the Safety and Immunogenicity of Two Lots of Heptavalent (4, 6B, 9V, 14, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine in Toddlers 15-24 Months of Age

This was a single-center, randomized and double-blind study, initiated in May 1995, and completed November 1995. The original objectives of the study were to assess safety and immunogenicity among toddlers following a single dose of 7VPnC from two pilot lots. The role of the study in the PLA is to support a catch-up schedule for children age 12-24 months.

Sixty healthy toddlers, age 12-24 months were randomized to receive a single dose of 7VPnC from one of two pilot lots. Subjects were actively monitored for local and systemic reactions.

Safety and immunogenicity results were presented by age at enrollment, either 12-17, or 18-23 months. Immunogenicity results for the two lots were similar.

Safety and immunogenicity data from this study supporting use of Prevnar in previously unvaccinated older children are included in the package insert. No serious or unusual adverse events were reported.

Study 124-2: Safety and Immunogenicity of a Booster Dose of Nine Valent (1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F) Pneumococcal Conjugate Vaccine Administered Concurrently with MMR in Toddlers 12-15 Months of Age.

The original study compared safety and immunogenicity of 7VPnC and a 9-valent pneumococcal conjugate vaccine (9VPnC), also based on CRM_{197}. The 9VPnC vaccine is a lyophilized formulation that contains pneumococcal conjugates for all serotypes represented in the liquid 7VPnC formulation, plus serotypes 1 and 5.

A full study report was not provided in the PLA. Data were included in the PLA intended to support concurrent immunizations of MMR with a 4th dose of Prevnar.

A total of 184 subjects were randomized 1:1 to receive 7VPnC or 9VPnC at 2, 4, and 6 months of age. An amendment to the study provided for a 4th dose of 9VPnC to be given to children of both groups at 12-15 months of age, administered concurrently with MMWR. No other vaccines were administered concurrently with the 4th dose. A total of 75 subjects were analyzed for immunogenicity to MMR determined by ELISA methods. Seroconversion was defined as a change from seronegative to seropositive or a 4-fold rise in antibody titer.

FDA/CBER did not view these data as sufficient to support concurrent immunization with Prevnar and MMR at the 4th dose.

Study 118-18: A Phase II Open-Label Study to Determine the Safety, Tolerability, and Immunogenicity of a Heptavalent Pneumococcal Capsular Polysaccharide-CRM_{197} Conjugate Vaccine in Children Between 1 and 9 Years of Age (Table 10).

The purpose of this study was to provide additional safety and immunogenicity data for 7VPnC among children over 1 year of age who received 1 or 2 doses of vaccine. The study was open-label and uncontrolled. It was initiated in May 1999 and completed in October 1999. Children who had received MnCC control vaccine in the completed efficacy study 118-8 were eligible to participate, but were analyzed separately (group M).

Table 10. Study 118-18: Ages, Doses and Planned Enrollment

	Age	Number of Doses	Number of Subjects
Group A	≥ 12 and < 18 mos	2	50
Group B	≥ 18 and < 24 mos	2	50
Group C	≥ 24 and < 36 mos	1	50
Group D	≥ 36 mos and < 60 mos	1	50
Group E	≥ 5 yrs and < 10 yrs	1	100
Group M	≥ 12 mos and < 24 mos	2	100
	≥ 24 mos and < 36 mos	1	

The allowable interval between vaccine doses was 42-72 days.

Vaccine reactions were recorded on diary cards for 7 days and data collected from parents by telephone on days 3 and 7. Physician visits within one week, and prescription medications within one week were collected. In addition, hospitalizations, ER and outpatient visits were collected for the entire study period.

Blood for antibody assessments was collected pre-immunization and 1 month following the last immunization.

Vaccine reaction data and ELISA GMCs data were included among the tables in the vaccine label to support use of Prevnar in previously unvaccinated older children.

D. Safety and Compatibility with Recommended Vaccines

The contribution of each study to the safety database is summarized in Table 11.

Table 11. Safety Database: Number of Children Who Received Prevnar in PLA Studies and the Number of Doses Administered

Infant Studies	Age (mos)	Primary Series		4th Dose	
		Subjects	Doses	Subjects	Doses
118-3	2, 4, 6, 12-15	106	303	58	58
118-7	2, 4, 6, 12-15	202	570	138	138
118-8 Enrollment as of 4/30/98 Data cut-off for safety	2, 4, 6, 12-15	17,066	46,305	9,047	9,047
118-12	2, 4, 6	256	740	--	--
118-16	2, 4, 6	538	1538	--	--
	TOTAL	18,168	49,456	9,243	9,243
		(20,029)	(54,817)	(11,136)	(11,136)
Older Infants (>6 Month) and Children					
118-9	15-24 (1 dose)	60	60	--	--
118-12	7, 9, 15-18	54	105	24	24
Adult Studies					
118-2	18-65 yrs	15	15	--	--

Adapted from Table 2, page 15, of Integrated Clinical Summary, Volume 33 part IV of PLA

Overall, the safety of Prevnar was evaluated in a total of six clinical studies in which 18,282 infants and children received a total of 58,888 doses of vaccine at 2, 4, 6, and 12-15 months of age. In addition, safety was evaluated in 560 children from 4 ancillary studies, 520 of whom received their first immunization at 7 months to 9 years of age. Local and systemic reactions were actively monitored in each study. Typically, injection site reactions were monitored for 48-72 hours following immunizations by use of diary cards. Fever was recorded on the day of immunization, and at bedtime for 2 days post-immunization, and at any other time within 14 days that the infant felt warmer than usual. Other systemic events were monitored for 14 days and recorded by parents on a diary card.

In each of the infant studies, Prevnar was administered with recommended childhood vaccines, however, the schedule of recommended vaccines changed during the clinical development of Prevnar. Whole cell pertussis containing vaccine (DTwP) was replaced by acellular pertussis (DTaP) for all doses, and oral polio vaccine (OPV) was replaced by inactivated polio vaccine (IPV). Therefore, much of the safety data was collected in combination with vaccine regimens no longer in use.

Vaccine reactogenicity data from studies 118-16 and 118-12 are most relevant to current practice; safety comparisons in these 2 studies were made to a control group that received only recommended vaccines, and were therefore most easily interpretable. Systemic reaction data from study 118-16 following the primary series were included in the vaccine label, in addition to data from the NCKP efficacy study.

Febrile reactions reported in studies which used concomitant vaccines consistent with recommendations current at the time of licensure are summarized in Table 12. A clear pattern of increasing fever with use of Prevnar is evident. It should be noted that use of Hepatitis B and IPV varied in the 3 studies summarized. Also, use of antipyretics was inconsistent across studies, though differences between treatment groups were noted (data not shown).

Local and systemic reaction data for older, previously unvaccinated children (control subjects during the primary series) from both 118-12 and 118-16 are included among the safety data addressing vaccination of older children in the vaccine label, along with safety data from the uncontrolled, open-label study 118-18. In general, the frequency of local reactions (pain and induration) increased with age of the child at the time of first vaccine dose. Among 5 to 9 year olds, induration > 2.4 cm was reported for 9.3%, and pain interfering with limb movement was reported by 39.4%. Reports of fever appeared to decrease in frequency among the age groups studied.

E. Compatibility with Recommended Childhood Vaccines

The impact of Prevnar on immune responses to antigens in recommended childhood vaccines administered concurrently was examined in various studies, and are summarized below.

HIB

In studies 118-12 and 118-16, Hib-PRP responses were assessed among groups receiving either 7VPnC or control (no additional vaccine) administered concurrently with DTaP + HbOC (Table 13). In study 118-12, data for the 3 pilot 7VPnC lot groups were pooled. In study 118-16, data from the preferred manufacturing lot data are presented. No evidence of interference of 7VPnC with concurrent HbOC was observed; a slight enhancing effect was apparent in the GMCs.

Table 12. Studies 118-8, 118-12, 188-16: Fever Rates Reported within 48-72 Hours Post-Vaccination by Dose, Comparisons Across 3 Studies When Prevnar Administered Concurrently with DTaP and HbOC (+/- Hep B, IPV/OPV)

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC%	MnCC%	p-value	7VPnC%	MnCC%	p-value	7VPnC%	MnCC%	p-value
Study 118-8[a]	N=710	N=710		N=556	N=507		N=460	N=414	
Fever ≥38°C	15.1	9.4	0.001	23.9	10.9	0.001	19.1	11.8	0.003
Fever >39°C	0.9	0.3		2.5	0.8	0.029	1.7	0.7	0.180
	7VPnC	Control		7VPnC	Control		7VPnC	Control	
Study 118-16[b]	N=498	N=108		N=452	N=99		N=445	N=89	
Fever ≥38°C	21.9	10.2	0.005	33.6	17.2	0.001	28.1	23.6	0.44
Fever >39°C	0.8	0.9	1.00	3.8	0.0	0.053	2.2	0.0	0.38
Study 118-12[c]	N=256	N=86		N=245	N=82		N=239	N=80	
Fever ≥38°C	4.9	8.6	0.271	19.3	12.8	0.230	16.3	12.0	0.457
Fever >39°C	0.8	0.0	1.000	1.8	1.3	1.000	0.9	0.0	1.000

[a] Adapted from Tables 64, 65, and 66 of Clinical Study report, Volume 13, Part IV of PLA. 59%, 56%, and 5% received IPV or OPV at doses 1, 2, and 3 respectively. 84%, 48% and 59% received hep B vaccine; Approximately 75% of subjects received prophylactic or therapeutic antipyretics within 48 hours of each dose. Chi-Square test or Fisher's exact test (Sponsor's analysis).

[b] Adapted from Table 30 of Integrated Clinical Summary, Volume 33, Part IV of PLA. Approximately 72% of subjects received prophylactic or therapeutic antipyretics within 48 hours of each dose. Control group received concomitant vaccines only in the same schedule as the Prevnar group (DTaP, HbOC at dose 1, 2, 3; IPV at doses 1 and 2; Hep B at doses 1 and 3. Pilot lot and 2 Manufacturing lots data pooled. P-value for comparison of pooled data to control (Sponsor's analysis).

[c] Adapted from Table 27, page 55, Volume 27, Part IV of PLA. P-value based on Fisher's exact test (Sponsor's analysis). Antipyretic use was reported by 27-39% of Prevnar recipients. Oral poliovirus vaccine or IPV was given at 2 and 4 months of age. Hepatitis B vaccine was administered at least two weeks prior to, or after the study vaccinations.

Table 13. Studies 118-12 and 118-16: Hib-PRP GMCs Post Dose 3 Concurrent Administration of DTaP + HbOC and 7VPnC

Study	7VPnC		Control: No 7VPnC		p-value
	N	GMC (95% CI)	N	GMC (95% CI)	
118-12	214	6.21 (5.17, 7.44)	67	4.36 (3.07, 6.19)	0.067[1]
118-16	159	11.93 (9.61, 14.81)	83	7.79 (5.72, 10.61)	0.017[2]

Adapted from Table 10, page 58, Volume 25, and Table 9a, page 54, Volume 29, Part IV of PLA.

[1] p-value based on ANCOVA model (sponsor's analysis)

[2] Preferred manufacturing lot N vs. control . p-value based on ANOVA (sponsor's analysis)

No significant differences between 7VPnC and control recipients in the proportions of subjects who attained 0.15 μg/mL and 1.0 μg/mL serum antibody concentration were observed (Table 14).

Hib-PRP responses following concurrent and separate administration of 7VPnC and HbOC with the 4th dose were assessed in study 118-07 (Table 15). In both studies, the first 3 doses of 7VPnC were administered with DTP-HbOC. In study 118-07, DTaP and HbOC were administered concurrently with 7VPnC, or one month after. The Hib-PRP GMCs was significantly greater in the control group, however the GMCs were relatively high in both groups, and proportions responding at ≥ 1.0 μg/mL exceeded 97%.

No data were included in the PLA for responses to HbOC among subjects who received DTaP + HbOC concurrently with study vaccine for all 4 doses.

Also, no data were included in the PLA addressing concurrent administration of Prevnar with Hib conjugate vaccines based on carriers other than CRM_{197}.

Hepatitis B

In the pilot efficacy study, 118-7, the antibody response to Hepatitis B vaccine after 3 doses when administered with 7VPnC was inferior to that of the control vaccine group, and the 95% confidence interval for the percent responders was less than 90% (Table 16).

In the manufacturing bridging study, 118-16 (Table 16), antibody responses to Hepatitis B vaccine were at least as good as in the control group, and the response rate at ≥10 mIU/mL was clearly acceptable (lower bound of 95% CI exceeds 90%).

Table 14. Studies 118-12 and 118-16: Comparisons of Hib-PRP Seroconversion Rates Between 7VPnC Recipients and Control Post Dose 3

		% Children Achieving Antibody Level (95% CI)			Difference in Proportion Concurrent – Control Lower 90% Confidence Limit
Study	**Serum Antibody Conc.**	**With Concurrent 7VPnC***	**Without Concurrent 7VPnC**	**P-Value**	
118-12		N = 214	N = 67		
	≥ 0.15 µg/mL	99.5 (97.4, 100.0)	97.0 (89.6, 99.7)	0.142	-1.8
	≥ 1 µg/mL	88.3 (83.2, 92.3)	88.1 (77.8, 94.8)	1.000	-8.0
118-16		N=159	N=83		
	≥ 0.15 µg/mL	100 (97.7,100)	98.8 (93.4, 100)	-	-2.51
	≥ 1 µg/mL	96.86 (92.8, 99.0)	92.77 (84.9, 97.4)	-	-2.35

Adapted from Table 9b of 118-16 clinical study report and Table 22 statistical report for study 118-12.

Exact 90% confidence intervals calculated using StatXact.

Table 15. 118-07: Hib-PRP Responses Post Dose 4 Concurrent Administration of DTP, HbOC and 7VPnC

Study Group	N	GMC (µg/mL)		% ≥ 0.15µg/mL	% ≥ 1.0 µg/mL
7VPnC + DTaP + HbOC	47	22.73	p=0.009[1]	100	97.9
DTaP + HbOC only	26	47.86		100	100

Adapted from Table 26, page 72, Volume 11, part IV of PLA

[1] Fishers exact (Sponsor's analysis)

Concerns raised by results from Study 118-7 about interference of Hepatitis B responses by Prevnar were satisfactorily addressed by results from study 118-16, which enrolled more subjects, and used other concomitant vaccines more relevant to current practice (DTaP and IPV). Hepatitis B responses for the 7VPnC pilot lot control and for another manufacturing scale lot (Lot P) were similar to results for the preferred Lot N (data not shown).

Table 16. Studies 118-7 and 118-16: Percent of Subjects Achieving Defined Antibody

Levels to Hep B Vaccine When Administered Concurrently with 7VPnC, Post Dose 3

Study	N	% ≥10 mIU/mL	(95% CI)
118-7			
7VPnC	81	92.6%	(84.6%, 97.2%)
MnCC	41	100%	(93%, --)
118-16			
7VPnC (Manuf Lot N)	156	99.4	(96.4%, 100%)
Control (No 7VPnC)	80	96.2	(89.1%, 99.2%)

Adapted from Table 34 page 59 and Table 53 page 71, Volume 12, and Table 10, page 56, Volume 29

Part IV of PLA

IPV

Responses to IPV (IPOL®) following concurrent immunization with 7VPnC and IPV in the primary series were evaluated in a single study, 118-16 (Table 17). IPV was administered at 2 and 4 months of age. Serum neutralizing antibody titers were determined at 7 months.

For poliovirus type 1, the lower limit of the 90% confidence interval for the difference between group in percent responders at an antibody titer 1:10 was 13.3%. This difference exceeded 10% difference criteria for equivalence for this serotype. Results of the comparison between pilot lot and control were similar. No interference of 7VPnC with polio type 2 and 3 was observed.

Table 17. Study 118-16: Percent of Subjects Achieving Defined Levels to IPV Administered Concurrently with 7VPnC

		% Subjects (95% CI)[1] Achieving Given Antibody Level		Manufacturing . Lot Versus Control	
		Manufacturing Lot N=156	Control Group N = 80	Difference	90% Lower Limit[2]
Polio 1	≥ 1:10	88.96 (82.9, 93.5)	93.59 (85.6, 97.9)	-4.63	**-13.29**
Polio 2	≥ 1:10	94.16 (89.1, 97.3)	93.59 (85.6, 97.9)	0.57	-6.31
Polio 3	≥ 1:10	83.77 (76.9, 89.3)	80.77 (70.2, 88.9)	3.00	-6.61

Adapted from Table 10, page 56, Volume 29, Part IV of PLA

[1] Exact 95% confidence intervals calculated using StatXact (sponsor's analysis).

[2] Exact 90% confidence intervals calculated using StatXact (sponsor's analysis).

The clinical significance of this apparent interference of 7VPnC with the poliovirus type 1 response is not clear. Responses assessed at 7 months may not represent peak responses following immunization at 2 and 4 months. The responder cut-off at 1:10 differs from the customary responder criteria of 1:8. Response rates for polio type 1 exceed response rates for polio type III in both groups, yet polio type 3 responses met the difference criteria. No other studies in the PLA address concurrent immunization of 7VPnC and IPV. Neither FDA reviewers nor advisory committee members judged this apparent vaccine interference to be an issue prohibitive to Prevnar licensure. Ongoing studies of Prevnar conducted [redacted] will provide additional information about potential interference with IPV antigens.

DTaP

Compatibility of 7VPnC with DTaP responses in the primary series was examined in study 118-12 (Table 18). The control group received concurrent vaccines only. The 3 pilot lots were similar with respect to immunogenicity to the pneumococcal serotypes and safety. Therefore, data from the 3 pilot lots of 7VPnC were combined for comparisons to control in the tables below.

After the 3rd dose, GMCs for diphtheria toxoid and all pertussis antigens were similar in an ANCOVA analysis, whether or not 7VPnC was administered concurrently; a 2-fold difference in GMCs could also be ruled out with 90% confidence. GMCs for tetanus toxoid were significantly higher in the control group (data not shown).

The proportions of subjects exceeding clinically relevant antibody levels were similar in the two groups for both diphtheria and tetanus toxoids. The percent responders were also consistent with what would be expected historically.

For the 4 pertussis antigens in Wyeth-Lederle's DTaP vaccine (ACEL-IMUNE), seroconversion at 2-fold and 4-fold rise in antibody titers was assessed. Only the antibody response to the pertussis fimbriae was statistically lower in the 7VPnC vs. control group, with 44.7% of the children in the 7VPnC group and 62.5 % in the control group achieving $\geq$ 4-fold rises (P=0.015, Pearson's Chi square test).

A 10% difference in seroresponse rates could not be ruled out with 90% confidence for any of the pertussis antigens. For seroresponders defined by a 4-fold rise, the lower 90% confidence limit of the differences were: fimbriae
-31%, pertactin, -24%, FHA, -16%. Based on a 2-fold rise in antibody titer, a 10% difference in response rates to pertussis toxin could not be ruled out with 90% confidence.

Responses to DTaP administered before, or concurrently with, 7VPnC at the 4th dose were examined in study 118-7 (Table 19). Whole cell pertussis vaccine (DTP-HbOC, Tetramune) had been administered with the 3 doses of the infant series in this study.

Table 18. Study 118-12: Comparisons of Seroconversion Rates to Antigens in DTaP Between 7VPnC Recipients and Control, Post Dose 3

Antigen	% Children Achieving Antibody Level (95% CI[2])			Difference in Proportion (Concurrent – Control) and 90% CI*
	With Concurrent 7VPnC N[1] = 214	Without Concurrent 7VPnC N[1] = 67	P-Value[2]	
Diphtheria				
≥ 0.01 IU /mL	100 (98.2, 100.0)	100 (94.5, 100.0)	1.000	0 (-3.5, 6.1)
≥ 0. 1 IU /mL	100 (98.2, 100.0)	97.0 (89.4, 99.7)	0.056	3.0 (-1.1, 10.7)
Tetanus				
≥ 0.01 IU /mL	100 (98.2, 100.0)	100 (94.5, 100.0)	1.000	0 (-3.5, 6.1)
≥ 0. 1 IU /mL	100 (98.2, 100.0)	100 (94.5, 100.0)	1.000	0 (-3.5, 6.1)
Pertussis Toxin				
≥ 2 fold rise	82.2 (76.3, 87.2)	83.3 (72.1, 91.4)	1.000	-1.1 (-11.9, 9.8)
≥ 4 fold rise	74.0 (67.5, 79.9)	69.7 (57.1, 80.5)	0.526	4.3 (-6.6, 16.4)
Fimbriae				
≥ 2 fold rise	62.6 (55.6, 69.3)	75.0 (62.6, 85.0)	0.073	-12.4 (-24.7, -0.6)
≥ 4 fold rise	44.7 (37.7, 51.8)	62.5 (49.5, 74.3)	0.015	-17.8 (-30.8, -6.0)
Pertactin				
≥ 2 fold rise	79.9 (73.8, 85.2)	87.9 (77.5, 94.7)	0.199	-8.0 (-18.1, 2.6)
≥ 4 fold rise	65.6 (58.6, 72.0)	77.3 (65.3, 86.7)	0.095	-11.7 (-23.6, -0.2)
FHA				
≥ 2 fold rise	78.4 (72.1, 83.8)	78.8 (66.9, 87.9)	1.000	-0.4 (-11.9, 10.8)
≥ 4 fold rise	66.4 (59.4, 72.8)	69.7 (57.1, 80.5)	0.654	-3.3 (-15.9, 8.3)

Reproduced from Table 22, page 50, Volume 27, Part IV of PLA

[1] Maximum number of samples available; actual varies slightly with antigen.

[2] Exact P-values determined using Pearson's Chi-square; Exact confidence intervals computed using StatXact.

Significantly inferior GMCs for diphtheria, pertussis toxoid, and FHA were observed when 7VPnC was administered concurrently with DTaP at the 4th dose. Ratios of GMCs with confidence intervals were not provided with these study results.

Significant differences in % seroresponders at defined levels were not observed for any DTaP antigen. However, confidence intervals for the difference in % responders were not provided in the PLA.

Table 19. Study 118-7: Immunogenicity of DTaP With or Without Concurrent Administration of 7VPnC Following a 4th Dose

Antigen	GMC µg/mL		p-value[1]	Defined Levels	% Achieving Defined Levels		p-value[2]
	7VPnC	No 7VPnC			7VPnC	No 7VPnC	
	N=47	N=26			N=47	N=26	
Diphtheria	2.00	3.15	0.026	≥0.01 IU/mL	100	100	--
				≥0.1 IU/mL	100	100	--
Tetanus	14.37	18.80	0.146	≥0.01 IU/mL	100	100	--
				≥0.1 IU/mL	100	100	--
PT	68.59	121.15	0.015	≥4-fold rise	68.1	73.1	0.792
FHA	28.97	48.20	0.040	≥4-fold rise	68.1	84.6	0.167
Pertactin	84.44	83.02	0.950	≥4-fold rise	83.0	96.2	0.145
Fim 2	5.21	3.79	0.477	≥4-fold rise	63.8	50.0	0.322

Adapted from Tables 25 and 26, Volume 11 of PLA.

[1] p-value assesses differences between treatment groups using the t-test

[2] p-value assesses differences between treatment groups using Fisher's exact (PT, pertactin) or Kruskal-Wallis (FHA, Fim 2).

After the 4th dose, no significant differences in % responders were observed relative to control; however, the differences appear substantial for FHA and pertactin. Given the small sample size it is unlikely that a 10% difference could be ruled out.

Post-dose 4 data following an infant series of DTP-HbOC may not be highly relevant to current practice, which uses DTaP for all doses. No data were presented in the PLA addressing pertussis responses following 4 consecutive doses of DTaP administered concurrently with 7VPnC.

It should be noted that the predetermined acceptance criteria at the time the study was designed for demonstration of non-interference was lack of statistical significance for the difference between groups. The more stringent criteria of demonstrating that the 90% CI of the difference does not exceed
–10% has been applied more recently to new combination vaccines.

MMR

Responses to measles, mumps and rubella following concurrent administration with 7VPnC was examined in study 118-3 (Table 20). Responses were compared using ELISA assays rather than the traditional neutralization tests

Subjects received 4 doses of 7VPnC or MnCC. Concurrently with the 4th dose, subjects were randomized to receive MMR or HbOC. Proportions seroconverting in the MnCC group are provided here for comparison; no statistical comparisons of responses by treatment groups are presented in the PLA.

Table 20. Study 118-3: Percent of Subjects Seroconverting to MMR when Administered Concurrently with 7VPnC

Antigen	7VPnC		MnCC	
	N	% Seroconverters[1] (95%CI)	N	% Seroconverters[1] (95%CI)
Measles	27	93% (76%, 99%)	28	100% (88%, 100%
Mumps	27	82% (62%, 94%)	28	82% (63%, 94%)
Rubella	27	89% (71%, 98%)	28	89% (72%, 98%)

Reproduced from Table 30b, Statistical Report, Volume 8, Part IV of PLA.

[1] Antibodies measured by ELISA using Biowhittaker assay kits and reported in Predicted Index Value (PIV). Results with PIV ≥ 1 are considered seropositive.

Although comparative responses between study arms appear similar, response rates to mumps and rubella are low by historical standards, sample sizes are small and confidence intervals are wide (as low as 62% for mumps).

FDA reviewers determined that the data presented were insufficient to determine whether or not Prevnar is likely to interfere with responses to MMR. The sponsor agreed to conduct an additional study to better describe the compatibility of the 4th dose of Prevnar with MMR (see below).

F. Post Marketing Evaluation of Prevnar

Prior to licensure, Wyeth-Lederle made commitments to conduct additional studies post-marketing and to provide information addressing specific concerns expressed by FDA reviewers and advisory committee members.

Wyeth-Lederle has chosen to conduct these studies at [redacted] In addition to extended safety and efficacy follow-up of subjects enrolled in the efficacy trial, additional studies will be conducted. These studies are comprised of 5 components:

1. Safety

The objective of this component of the post-marketing studies is to expand the safety database to capture more serious and rare adverse events among children who receive Prevnar at 2, 4, 6, and 12-15 months of age. Surveillance will continue until approximately 60,000 children have been evaluated 120 days after receiving at least 3 doses. Because Prevnar was proposed for universal immunization, these additional safety data were viewed as essential to better identify and describe uncommon or rare adverse events, that could not be detected or well described in the pre-licensure trials.

Subjects are to be immunized as part of routine care. [redacted] databases for emergency services, hospitalizations, outpatient will be utilized to capture specific events. California state mortality rates and SIDS rates will be provided for comparisons.

Adverse events to be ascertained for specified observation periods include:

- For 14 days post-vaccination, febrile illness resulting in medical utilization, seizures, allergic reactions, and asthma.
- For 30 days post-vaccination, specific adverse events observed more frequently in the efficacy study (i.e., gastroenteritis, febrile seizure, asthma, croup, breath holding).
- For the length of the study, selected diagnoses/outcomes, some possibly related to dysfunctional immune responses, including aplastic anemia, asthma, autoimmune hemolytic anemia, diabetes mellitus, neutropenia, autoimmune disease not otherwise specified, thrombocytopenia, and death (including SIDS).
- Extended follow-up of original efficacy study cohort for diabetes mellitus and developmental delay, including autism.

The chosen sample size can detect 2-fold increases in febrile illness rates, and 3 to 4-fold increases in febrile seizure rates. Numerous comparisons and analyses are planned. As the study proceeds, additional comparisons and analyses may be conducted, as appropriate.

Vaccine lot numbers will be monitored during the trial to assess lot-related differences in adverse events. Annual reports will be provided to FDA/CBER.

2. Non-inferiority study of immunogenicity of MMR administered concurrently with Prevnar, compared to MMR alone

The primary objective of this component is to demonstrate that immune responses to MMR when administered with Prevnar are not inferior to responses to MMR when administered alone. A secondary objective is to compare immune responses to other routine vaccines, with priority given to varicella vaccine.

Six hundred children approximately 12 months of age will be randomized to receive either MMR with Prevnar, or MMR (Prevnar administered 6 weeks later) in addition to DTaP, Hib, IPV and varicella vaccine. Blood will be obtained for measles, mumps, and rubella serology prior to vaccination and 6 weeks post immunizations. If sufficient blood is available, antibody titers/levels for varicella, poliovirus 1, 2, and 3, pertussis antigens, and Hib will also be assessed.

[redacted]

3. Local and systemic reactogenicity of Prevnar administered simultaneously with the 4th dose of DTaP (in a 4-dose DTaP series)

Little information was available at the time of licensure addressing safety of Prevnar when administered with DTaP with each dose in a 4-dose DTaP series. Because DTaP has been recommended for a 4-dose series, these additional safety data were viewed as necessary to accurately describe the safety profile of Prevnar with current use.

A total of 280 children 12-15 months of age who have received 3 doses of Prevnar with DTaP will be enrolled at the time of the 4th dose. The submitted protocol calls for active monitoring of local and systemic vaccine reactions by parents for 72 hours post-vaccination. This information is to be collected by telephone interview. Incidence rates and 95% confidence intervals will be provided for local and systemic reactions, including fever and antipyretic use.

4. Local and systemic reactogenicity of Prevnar administered in catch-up populations (i.e., 7-11 months of age, 12 months - 2 years of age, 2-5 years, and 5-9 years)

Available safety data supporting catch-up schedules at the time of licensure were limited to less than 100 subjects for some age groups (see vaccine label). The objective of this component of the post-licensure study is to expand the safety database to better describe the local and systemic reactogenicity for the older age groups.

A total of 1200 children, 300 per age groups cited above, will be enrolled. Local and systemic reactions, including fever and antipyretic use, are to be reported for the period 72 hours post-vaccination. Incidence rates with 95% confidence intervals will be provided.

5. Ongoing surveillance of invasive pneumococcal disease in [redacted] population

Objectives of this component of the post-marketing studies are to:
(1) monitor the original participants in the efficacy study for invasive disease due to *S. pneumoniae* and to determine the serotypes causing disease;
(2) compare incidence of invasive disease due to vaccine serotypes and non-vaccine serotypes after the introduction of routine immunization with Prevnar to assess for emergence of new prevalent serotypes.

Using the [redacted] microbiology laboratory database, cases of invasive disease will be identified and characterized for a 5-year period following licensure. Reports will be prepared annually.

G. Compatibility with recommended childhood vaccines

The PLA review identified some vaccine combinations of Prevnar with other recommended vaccines for which data did not provide convincing evidence for lack of immune interference, or were unavailable.

Hib conjugate vaccines not based on CRM_{197}: Some vaccine advisory committee members remarked that it would be desirable to demonstrate compatibility with Hib conjugate vaccines using different carrier proteins. Wyeth-Lederle indicated that some data will be available from a [redacted]

Also, the MMR non-inferiority study, described above, may provide some data utilizing PRP-T.

Polio virus type 1: Wyeth-Lederle indicated that immunogenicity data will be available from a randomized, controlled study conducted in [redacted] vaccine on a 3, 4, and 5-month schedule. It is also possible that additional data may be available from the planned Phase 4 MMR non-inferiority study, described above.

Pertussis: Some data may be available from the [redacted] Data may be available from the planned Phase 4 MMR non-inferiority study, described above.

FDA/CBER recognize that, it may not be feasible to conduct randomized, controlled studies to address these deficiencies in post-marketing studies in the U.S.

H. Vaccine Label

The vaccine indication is limited to prevention of invasive disease among children immunized at 2, 4, 6, and 12-15 months of age, thus reflecting how the bulk of the safety, immunogenicity and efficacy data were obtained. The label provides an informative description of the pivotal large safety and efficacy study conducted at NCKP. Sufficient information is provided in the label regarding vaccine reactogenicity such that clinicians will be able to appreciate the risks of fever and other systemic and local reactions.

FDA reviewers recognized that Prevnar could be useful in some older children with risk factors for invasive pneumococcal disease. After evaluating additional safety and immunogenicity data for older, previously unimmunized children submitted by Wyeth-Lederle late in the review cycle from study 118-18, it was deemed appropriate to include these data in the label. Additionally, dosage and administration guidelines for children through age 9 years were accepted for inclusion in the label.

As additional safety data from the post-marketing study and from the Vaccine Adverse Event Reporting System (VAERS) become available, the vaccine label will be revised to more accurately describe the safety profile of Prevnar.

VI. Advisory Committee Considerations:

Data regarding the safety and immunogenicity of Prevar ™ were presented and discussed with the Vaccines and Biological Products Advisory Committee meeting of November 5, 1999. The Committee recommended approval of the license application.

VII. Approved Package Insert:

The labeling for Prevnar is appropriate for the product and indication. The package insert is attached.

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