Vaccines and Related Biological Products Advisory Committee

Meeting Date: November 5, 1999

FDA Briefing Document for

Wyeth-Lederle Vaccine and Pediatrics Seven Valent Pneumococcal Conjugate Vaccine

Clinical Section

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Overview

Wyeth-Lederle Vaccines and Pediatrics submitted a Product License Application (PLA) to FDA/CBER on June 1, 1999, for Prenevar™, a 7-valent, polysaccharide-protein conjugate vaccine for prevention of disease caused by *Streptococcus pneumoniae*. FDA/CBER granted priority review status to the application, and committed to an expedited review, based on the severity of disease for which the vaccine would be indicated, i.e.,"invasive pneumococcal disease (meningitis and bacteremia)", and preliminary results indicating substantial evidence of efficacy. Preliminary efficacy data were presented to the committee at the November 19,1998 advisory committee meeting.

Regulatory approval was requested to market Prevenar for active immunization of infants and children beginning as early as 6 weeks of age for three indications:

- To help protect against invasive diseases caused by *Streptococcus pneumoniae* due to the capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, 23F)
- Reduction in the incidence of ear tube placement associated with frequent otitis media
- Reduction in the incidence of clinical pneumonia with abnormal chest x-ray

At the VRBPAC meeting of November 5, 1999, FDA/CBER will primarily address, and seek advice from the committee about, the safety and efficacy data intended to support an indication for prevention of invasive pneumococcal disease.

FDA/CBER has determined that indications for reduction in ear tube placement and clinical pneumonia will <u>not</u> be given priority review status. FDA/CBER will review data submitted to support the latter two indications within the standard review periods of 10 months, and data submitted to support these indications may be presented at a future VRBPAC meeting. Preliminary review comments based on Wyeth-Lederle's analysis of pneumonia and otitis media endpoints are attached to this document as an addendum.

A brief chronology of some key elements in the clinical development and review of Prevenar is presented below:

Chronology of Clinical Development

IND 5832 filed (7-valent)	November 1994
NCKP efficacy study initiated	October 1995
Safety, OM, pneumonia data of efficacy trial locked	April 30, 1999
Primary analysis of efficacy study	August 20, 1998
Otitis media analysis plan finalized	November 1998
Pneumonia analysis plan finalized	March 3, 1999
Efficacy trial unblinded, case ascertainment ends	April 20, 1999
Manufacturing-bridging study complete	May 17, 1999
PLA Submitted	June 1, 1999
FDA/CBER accepts PLA as complete	July 13, 1999
Advisory committee	November 5, 1999

The clinical section of the application contains study reports for 8 studies and supporting data from 3 additional clinical studies. An integrated clinical summary is also provided.

In the tables and summaries that follow, 7-valent pneumococcal conjugate vaccine is referred to as 7VPnC, meningococcal group C conjugate vaccine is referred to as MnCC.

Clinical Studies in the 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 among 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 only
	Toddlers	12-15	None	
D124-P501	Toddlers	12-17	MnCC	9-valent immunogenicity data for catch-up presented.
		18+	MnCC	

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.

Please note that an investigational meningococcal C vaccine was used in the control arm for some of the studies, including the large-scale efficacy trial. Only two infant studies (D118-12 and D118-16) compared the safety profile of 7VPnC against a 'no vaccine' control.

The questions used to provide the outline for this briefing document should be considered as draft questions. Actual questions at the time of the meeting may differ.

All efficacy data in the application derive from the Northern California Kaiser Permanente (NCKP) efficacy trial, Study 118-8. The study design and efficacy results are described below with question #1. Summaries of non-pivotal supporting studies are in Attachment B.

Draft Question #1

Do the data presented provide sufficient evidence of efficacy on which to base licensure of Prenevar for the requested indication:

For active immunization of infants and children beginning as early as 6 weeks of age to protect against invasive diseases caused by *Streptococcus pneumoniae* due to the capsular serotypes included in the vaccine (4, 6B, 9V, 14, 18C, 19F, 23F).

If not, what additional information should be obtained?

Study 118-08: 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

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

The study was initiated in October 1995; enrollment ceased August 24, 1998, after results of the planned interim analysis demonstrated substantial evidence of efficacy. Follow-up of infants 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. The 7VPnC vaccine was then offered to subjects in the control group.

Multiple secondary objectives were also specified:

- To assess the safety and tolerability of 7VPnC
- To assess the safety and tolerability of MnCC
- 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 immunogencity of 7VPnC following a primary series and 4th dose

Study Vaccines

7VPnC is a liquid formulation. Each 0.5 mL dose contains 15-26 ?g of CRM_{197} carrier protein, and a total pneumococcal saccharide content of 16 ?g. Serotype specific saccharide content for each component is:

- 2 ?g of polysaccharide for serotypes 4, 9V, 14, 19F, and 23F,
- 2 ?g of oligosaccharide for serotype 18C,
- 4 ?g of polysaccharide for serotype 6B

Each dose of 7VPnC also contains 0.5 mg of aluminum phosphate adjuvant. The formulation contains no thimerosal or other preservatives.

MnCC is also manufactured by Wyeth-Lederle Vaccines and Pediatrics. Each 0.5mL dose contains 10 ?g of group C oligosaccharides coupled to CRM_{197}. The vaccine contains 0.5 mg of aluminum phosphate adjuvant.

The two study vaccines vials were identical in appearance.

During the efficacy study, 11 different pilot lots of 7VPnC, and 12 different pilot lots of MnCC were used.

Licensed vaccines used in the study were: DTP-HbOC (Tetramune), OPV (Orimune), DTaP (Acel-imune), HbOC (HibTITER), MMR, Varicella, Hepatitis B (Recombivax HB), and IPV (IPOL).

Study Design

Randomization and Blinding

Healthy infants were randomly assigned to receive 7VPnC or MnCC, identified as A, B, C, or D in the following way: randomization was nested within each study site, block sizes were randomly chosen among 4, 6, 8, and 10, with treatment groups equally allocated. Treatment assignments (A, B, C, or D) were randomly permuted within each block. The group code assignment were entered by the study nurse into the child's study casebook and the injection log, but were not recorded on the subject's chart, computer records or in any other documents. Group assignment was known to the study nurse and dedicated nurse vaccinator at each site, to the NCKP statistician, and to the NCKP and Wyeth-Lederle clinical monitors. Group assignments were not to be disclosed to parents of children in the study, others involved with the child's care or involved in the trial, including pediatricians, study investigators, and telephone interviewers.

Schedule and Dose Administration

Subjects received 0.5 mL i.m. injections of either pneumococcal or meningococcal C conjugate vaccine at 2, 4, 6 and 12-15 months of age.

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 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.

At 12-15 months of age, DTP-HbOC or DTaP and HbOC (HibTITER), MMR, and varicella vaccine could be given concurrently.

Study vaccines were to be administered within the following time frames:

- Dose 1: 42-120 days after birth,
- Dose 2: 35-120 days after the first dose
- Dose 3: 35-120 days after the second dose
- Dose 4: 12 to 15 months of age, and at least 60 days after dose 3.

Case Surveillance

Surveillance for cases of invasive pneumococcal disease was conducted weekly at each study site by review of all positive cultures for pneumococcus from normally sterile body sites among children < 9 years of age, generated from the NCKP Regional Microbiology database. Listings of children discharged from NCKP hospitals with diagnoses compatible with invasive pneumococcal disease were conducted monthly.

Efficacy Endpoints

The primary outcome was efficacy in preventing cases of invasive disease among subjects vaccinated according to protocol caused by one of the 7 targeted pneumococcal serotypes during the per-protocol follow-up period.

Additional efficacy endpoints were:
- efficacy against invasive disease under intent-to-treat
- efficacy after one or two doses
- efficacy against individual serotypes and subsets of the 7 targeted serotype
- efficacy stratified by age at completion of the three-dose primary series
- effectiveness against acute otitis media (ascertained from clinical diagnosis in computerized data sources

Analysis

The final analysis plan for invasive disease at the time of unblinding differed from that proposed in the original protocol. The analysis plan had included group

sequential procedures for as many as 3 analyses at the 3 respective case accruals of 8, 20, and 40 cases, with stopping rules for case splits at each look. Agreement was reached in a meeting between representatives of Wyeth-Lederle and FDA on November 3, 1997, to modify the sequential analysis plan by eliminating the look at 8 cases, and instead to provide for one interim analysis when 17 cases of invasive pneumococcal disease due to vaccine serotypes 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 vaccinated group (7VPnC group), the vaccine was to be considered efficacious and the trial was to be stopped for evidence of efficacy. Exact confidence limits derived from exact binomial distributions.

118-8: Acceptable Case Splits for Stopping at Interim Analysis

Number of Cases		Vaccine Efficacy	95% Lower Conf. Limit	
Control	Vaccinated	Estimate	one-sided	two-sided
0	17	100	80.7	75.7
1	16	93.8	66.6	59.7
2	15	86.7	51.5	42.6

Adapted from Table 2, page 84, Volume 13 of PLA

Results

Enrollment was terminated on August 24, 1998. At that time, 37,868 infants had been randomized and received at least one immunization. A total of 18,927 and 18,941 subjects received the 7VPnC and MnCC vaccines, respectively.

118-8: Primary Efficacy Analysis
Number of Subjects and Follow-up Time

	7VPnC	MnCC	Total
Per-protocol	13,549	13,569	27,118
Follow-up time (child-year)	14,442	14,588	
Intent-to-treat	18,896	18,901	37,797
Follow-up time (child-year)	26,776	26,813	

Adapted from Table 16, page 104, Volume 13 of PLA.

Approximately 10,000 randomized subjects were not included in the per-protocol analysis. Children were excluded from the per protocol analysis for not having completed the primary series, failure to receive study vaccines in the designated time frames, receipt of immunoglobulin, receipt of incorrect vaccines, failure to meet entry criteria, invasive disease, and death. Loss of health plan membership did not result in exclusion from per protocol follow-up, unless a dosing violation occurred.

Demographics

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

The two study vaccine groups appear to be well balanced with respect to race/ethnicity.

118-8: Race/Ethnicity As Reported at 48 Hour Interview[1] 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

The planned interim analysis following accrual of the 17th case of invasive pneumococcal disease due to vaccine serotype, which took place on August 20, 1998, is considered the primary efficacy analysis.

Primary efficacy analysis

A total of 17 vaccine-serotype invasive disease cases in fully vaccinated children accrued during the per-protocol follow-up period at the time of the interim analysis. All 17 cases were in the MnCC group.

Results of the intent-to-treat analysis were consistent with vaccine efficacy observed in the per-protocol analysis. No cases of invasive disease were observed among children either fully or partially immunized with 7VPnC.

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).

All invasive pneumococcal disease

Eight additional cases of invasive disease due to non-vaccine serotypes were observed at the time of the primary analysis. Three cases occurred in the 7VPnC group and five in the MnCC group. Vaccine efficacy for all serotypes in the intent-to-treat analysis was 88.9%, with a lower 95% confidence limit of 63.8%.

Serotype Distribution of Cases

The proportion of all invasive disease due to vaccine serotypes at the time of the primary analysis was 81.5% (22/27). The most common vaccine serotype was 19F. No invasive disease cases due to pneumococcal serotype 4 were observed.

Serotype Distribution of Cases of Invasive Pneumococcal Disease - Cases Accrued Through August 20, 1998

Vaccine Serotypes	Number of Cases (Percentage* due to Each Serotype)			
	Fully Vaccinated Children		All Randomized Children	
	7VPnC	MnCC	7VPnC	MnCC
19F	0	7 (35.0%)	0	8 (29.6%)
18C	0	4 (20.0%)	0	4 (14.8%)
6B	0	2 (10.0%)	0	3 (11.1%)
9V	0	2 (10.0%)	0	2 (7.4%)
14	0	1 (5.0%)	0	2 (7.4%)
23F	0	1 (5.0%)	0	3 (11.1%)
4	0	0 (0%)	0	0 (0%)
Total	0	17 (85.0%)	0	22 (81.5%)
Non Vaccine Serotypes				
38	1	1 (5.0%)	1	1 (3.7%)
3	0	1 (5.0%)	0	1 (3.7%)
19A	0	1 (5.0%)	0	1 (3.7%)
10F	1	0 (0%)	1	0 (0%)
18B	0	0 (0%)	0	1 (3.7%)
11A	0	0 (0%)	0	1 (3.7%)
23A	0	0 (0%)	1	0 (0%)
Total	2	3 (15.0%)	3	5 (18.5%)
All Serotypes Total	2	20	3	27

Adapted from Table 18, Clinical Study Report, Volume 13 of PLA.
* Percentage of the number of all invasive pneumococcal disease cases in MnCC group.

Vaccine Efficacy by Dose

At the time of the primary analysis, 10 cases of invasive disease had accrued between the 3rd and 4th doses, and 7 additional cases occurred after the 4th dose.

Analysis of Vaccine Efficacy Against Invasive Pneumococcal Disease by Dose- Cases Accrued Through August 20, 1998

Invasive Pneumococcal Disease	Number of Cases		Vaccine Efficacy Estimate (VE)	95% Lower CI* of VE
	7VPnC	MnCC		
Vaccine Serotypes				
? 2 doses	0	5	100%	-9.2%
3 doses	0	10	100%	55.3%
4 doses	0	7	100%	30.6%
All doses	**0**	**22**	**100%**	**81.7%**
All Serotypes				
? 2 doses	1	7	85.7%	-11.2%
3 doses	2	10	80.0%	6.1%
4 doses	0	10	100%	55.3%
All doses	**3**	**27**	**88.9%**	**63.8%**

Adapted from Table 20, Clinical Study Report, Volume 13 of PLA.
* Two-sided P-values were determined based on exact binomial distributions and confidence limits were also determined based on exact binomial distributions.

Invasive Disease Case Characteristics

Case narratives for each of the invasive disease cases were provided. Among the 22 vaccine serotype cases at the time of the primary analysis, no deaths were reported. Two infants < 6 months of age developed meningitis. One child among the fully vaccinated group was hospitalized; 3 infants in the partially vaccinated group were hospitalized. Pneumococcus was isolated from the blood of all cases; those with meningitis also had CSF isolates. One partially vaccinated infant, who was diagnosed with meningitis, had residual hearing loss; all other children recovered fully. Pneumococcal isolates with decreased susceptibility to penicillin accounted for 41% (9/22) of the pneumococcal isolates from cases of invasive disease.

Characteristics of Cases of Invasive Disease at Primary Analysis: MnCC Group (N=22)

	Fully Vaccinated	Partially Vaccinated	Total
Characteristic	**N=17**	**N=5**	**22**
Age ? 12 months	7	5	12
Age ? 12 months	10	0	10
Source of isolate			
Blood	17	5	22
Spinal fluid	0	(2)*	(2)
Antibiotic susceptibility of isolate			
Penicillin sensitive	10	3	13
Penicillin intermediate	4	1	5
Penicillin resistant	3	1	4
Hospitalized	1	3	4
Treated outpatient	16	2	18
Clinical Diagnoses			
Bacteremia	17	5	22
Meningitis	(0)	(2)	(2)
Septicemia/sepsis	(2)	(1)	(3)
Pneumonia	(1)	(1)	(2)
Periorbital cellulitis	(1)	(0)	(1)
Immunocompromised	0	0	0
Outcome			
Complete recovery/"Doing well"	17	4	21
Residual deficit	0	1 (hearing)	1
Deaths	0	0	0

Compiled from case narratives provided in July 7, 1999 submission to PLA

* () n of cases for non-unique characteristics

Follow-up analysis

Enrollment ceased on August 24, 1998. Partially vaccinated subjects completed the vaccine schedule, and follow-up of such subjects was added to the continuing surveillance of efficacy outcomes and safety. A summary and analysis of invasive disease cases accrued through April 20, 1999, were provided with the PLA.

Results of follow-up cases are consistent with the primary analysis. One case of invasive disease due to vaccine serotype occurred among fully vaccinated subjects in the 7VPnC group, and 39 cases were observed in the MnCC group.

Efficacy Against Invasive Disease: Follow-up Analysis

Invasive Pneumococcal Disease (Cases through April 20, 1999)	Number of Cases		Vaccine Efficacy Estimate (VE)	95% Confidence Limits* of VE
	7VPnC	MnCC		
Vaccine Serotypes				
Per-Protocol	1	39	97.4%	(84.8%, 99.9%)
Intent-to-Treat	3	49	93.9%	(81.0%, 98.8%)
All Serotypes				
Per-Protocol	3	42	92.9%	(77.6%, 98.6%)
Intent-to-Treat	6	55	89.1%	(74.7%, 96.2%)

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 and confidence limits based on exact binomial distributions (Sponsor's analysis).

The single invasive disease case of vaccine serotype (19F) among the fully vaccinated 7PnC cohort presented no unusual characteristics (see Attachment A for case narrative). Two additional cases of invasive disease of vaccine serotype (6B, 19F) occurred among 7VPnC recipients in the intent-to-treat follow-up analysis (see Attachment A for case narratives).

All pneumococcal invasive disease

Nine cases of invasive disease due to non-vaccine serotypes had accrued at the time follow-up for invasive disease was terminated, 3 in the 7VPnC group and 6 in the MnCC group. Only 1 additional case of invasive disease due to non-vaccine serotypes accrued since the primary analysis. During the same interval an additional 30 cases due to vaccine serotypes accrued. Vaccine efficacy for all serotypes in the follow-up intent-to-treat analysis was 89.1%, with a lower 95% confidence limit of 74.7%.

Vaccine serotypes accounted for 85% of all cases of invasive disease at the time case accrual was terminated. Replacement of prevalent serotypes chosen for representation in the vaccine by non vaccine serotypes was not apparent during this study.

Invasive Disease Case Characteristics

Invasive disease characteristics for all cases of invasive disease regardless of serotype are presented below:

Characteristics of Cases of Invasive Disease: All Cases (N=61)

Characteristic	Vaccine Serotype N= 52		Non Vaccine Serotype N= 9		Total N=61	
	n	%	n	%	n	%
Age ? 12 months	18	33%	5	56%	23	38%
Age ? 12 months	34	67%	4	44%	38	62%
Source of invasive disease						
Blood	52	100%	8	89%	60	98%
Spinal fluid	(5)*	(9.6%)	(1)	(11%)	(6)	(10%)
Thyroglossal duct cyst	0	0	1	11%	1	2%
Antibiotic susceptibility of isolate						
Penicillin sensitive	33	63%	8	89%	41	67%
Penicillin intermediate	11	21%	0	0	11	18%
Penicillin resistant	8	15%	1	11%	9	15%
Hospitalized	13	25%	3	33%	16	26%
Treated outpatient	39	75%	6	67%	45	74%
Clinical Diagnoses						
Meningitis	(5)	(9.6%)	(1)	(11%)	(11)	(18%)
Pneumonia	(9)	(17%)	(2)	(22%)	(9)	(15%)
Immunocompromised	1	2%	1	11%	2	3%
Outcome						
Complete recovery	48	92%	8	89%	56	92%
Residual deficit	1	2%	0	0	1	2%
Death	3	5.8%	1	11%	4	7%

Compiled from case narratives included in July 7, 1999 submission to PLA
* () n and % of cases for non-unique characteristics

Of the 4 deaths among children with invasive disease, 2 could be attributed to invasive pneumococcal disease. The remaining 2 deaths can be attributed to underlying disease or immunocompromising conditions (see Attachment A for case narratives).

The study protocol provides for assessment of immunocompetence of all children with positive cultures for *S. pneumoniae* from a normally sterile body site. Assays for immunocompetence for the initial 22 cases included CBC, quantitative immunoglobulins (IgG, IgA, IgM), total hemolytic complement, and T-cell subsets for most cases. Results of tests of immunocompetence were provided upon FDA/CBER request, for the initial 22 cases in the intent-to-treat analysis (received August 31, 1999). Tests of immune status for the remainder of the 61 invasive disease cases have not been submitted to the PLA.

Two cases of invasive disease in the follow-up analysis occurred among children who were clearly immunocompromised; both subsequently died. A child with severe combined immunodeficiency in the MnCC group was included in the intent-to-treat analysis of all vaccine serotypes. A child with leukemia in the 7VPnC group was omitted from the follow-up intent-to-treat analysis. It was stated that this child did not meet the case definition because of the immunocompromised status of the child, but the case was listed for completeness. FDA requested that the case be analyzed under intent-to-treat.

Review comments regarding efficacy of invasive disease

Case ascertainment

In FDA/CBER's review of efficacy for invasive disease, assurance was sought that no cases of invasive disease had been missed. FDA requested all bacterial culture results for subjects during the study period. Culture results through the study period ending August 20, 1998 were received with the PLA submission (culture data for subjects in the follow-up analysis have not been received).

The summary of all non-pneumococcal culture results revealed no imbalance across treatment groups. All positive cultures were identified.

118-8: All Non Pneumococcal Blood Culture Results For Study Subjects at the Primary Analysis (August 1998)

Vaccine Group	Negative	Non-pneumo Positive
7VPnC	2722	104
MnCC	2613	103

Adapted from Table in PLA submission of July 28, 1999.

Thus, for subjects who remained in the NCKP health plan throughout the study, the likelihood that cases of invasive disease were missed appears low.

Meningococcal isolates through April 20, 1999, were provided. Six blood isolates of meningococcus were identified, 3 in each vaccine group. None of the isolates was serotype C.

Follow-up

As of April 30, 1998, the cumulative follow-up times for the 7VPnC and MnCC groups were nearly identical at 10,047 and 10,098 child-years, respectively. Given that the estimate of vaccine efficacy (VE) is a function of the ratio of follow-up times between the two groups, precise knowledge of follow-up time is preferred. In this trial, lack of precision of the ratio of follow-up exists because the follow-up data available on April 30, 1998 was used to project the ratio of follow-up on August 20, 1998, the date of the primary analysis.

Responding to FDA inquiries, Wyeth-Lederle performed an analysis (received August 31, 1999), in which variations in follow-up times were assumed in order to assess effects on confidence limits around the efficacy estimate. It was demonstrated that if the proportion of follow-up in the 7VPnC group were differentially reduced by as much as 33%, the lower bound of the 95% confidence interval for efficacy in the primary analysis remained above 71%. Thus, any difference in projected follow-up to actual follow-up is likely to be inconsequential. The sponsor is in the process of determining actual follow-up times at the time of the primary analysis.

Calculation of the confidence interval for the point estimate is further complicated because included in the total follow-up time is follow-up time attributed to subjects who left the Kaiser health plan between their 3rd and 4th doses or after their 4th dose, but before the study's end. While early termination from the health plan could decrease the probability that extra cases would be ascertained, it would not be expected to introduce a systematic bias in the relative group proportions of "missed case" ascertainment. The sponsor determined that the relative group proportions of follow-up time accrued to subjects leaving the health plan were similar (7.1%, 7VPnC vs. 6.6 %, MnCC). Adjustments to the accumulated child-years which is reduced by the loss-to-follow-up fraction, may be appropriate for calculation of confidence intervals, even though the risk reduction point estimate will not vary.

Protocol violations and reasons for exclusion from the per protocol analysis were provided as supplemental to the PLA. Most common reasons for exclusions and truncation of follow-up times are shown below. The number of subjects appears to be well balanced between study groups by reason for exclusion.

118-8: Per Protocol Follow-up Exclusions by Reason

	7VPnC	MnCC
Number of subjects randomized	17,066	17,080
Number excluded from per protocol	3696	3723
Reasons for exclusion		
Dose 3 not given by data cut-off	2859	2877
Dose 3 not given by age 1 year	629	607
Dose 1 given <42 days, or > 120 days	35	35
Interval between doses 1 and 2 < 35 days	15	19
Interval between dose 2 and 3 < 35 days	32	36
Received incorrect vaccine	29	48
Follow-up time truncated	1300	1289
Dose 4 not given by 16 months of age	1213	1171
Age at dose 4 < 12 months	41	69

Excerpted from Tables 6 and 7 of September 29, 1999 submission to PLA

Results of the intent-to-treat analysis provide additional support for the efficacy estimate of the per protocol analysis. Follow-up time in the intent-to-treat analysis accrues from the time of enrollment for each subject and continues through April 30, 1998. The intent-to-treat follow-up period is unaffected by protocol violations. The lower bound of the 95% confidence interval for invasive disease due to vaccine serotype in the intent-to-treat analysis was above 80%.

Draft Question #2: Do the data provide adequate evidence of safety for Prenevar?

If not, what additional information should be obtained?

Safety Data Base

Safety of the 7VPnC vaccine was assessed in a total of seven clinical studies. In five of these studies (118-3, 118-7, 118-8, 118-12, 118-16), safety was evaluated in infants. Safety of a 4th dose of vaccine administered at 12-15 months was evaluated in three studies (118-3, 118-7, 118-8). Study (118-9) examined safety of a single dose in toddlers. Study 118-2 provides the only safety data for adults in the application.

Safety Database: Number of Children Who Received 7VPnC Vaccine 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

Important contributions of the individual studies to the safety evaluation are discussed below.

118-8 NCKP Efficacy Trial

Safety data from the NCKP efficacy study accumulated through April 30, 1998, were reported in the application. Follow-up of subjects continued until April 20, 1999. Updated safety data consisting of line listings of ER visits, hospitalizations, and "out of plan adverse events" occurring from April 30, 1998, through December 31, 1998, were submitted as a planned update to the application on July 7, 1999.

Safety Variables

Specific local reactions and systemic events following vaccine injections were actively monitored by the parent/guardian in a subset of 6000 infants who received DTP-HbOC concomitantly with the study vaccine. Infants were randomly selected for active monitoring of vaccine reactions if the last digit of their medical record number was 2, 4, 6, or 8. The same cohort of infants was monitored after each dose.

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 of parents.

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.

Local Reactions

Rates of local reactions at DTP-HbOC injection sites (right leg) and 7VPnC or MnCC injections (left leg) were compared pairwise within the same child using the sign test. Local reactions occurring within 48 hours of an injection were reported with greater frequency and severity for DTP-HbOC injection sites than 7VPnC injection sites for each dose of the primary series.

Local reaction rates for 7VPnC and MnCC injection sites were also compared between treatment groups. Rates of induration and tenderness were greater in the 7VPnC group, compared to the MnCC group for each dose of the primary series. Clinically significant induration (> 2.4 cm) and tenderness (interferes with leg movement) were also more frequent at 7VPnC inoculation sites than at MnCC injection sites after doses 2 and 3.

Frequency of local reactions due to 7VPnC did not increase appreciably with sequential doses of the primary series.

Study 118-8: Local Reactions within 48 hours of Inoculations Among Infants Receiving DTP-HbOC, OPV, Hepatitis B, and 7VPnC or MnCC Vaccine

	7VPnC N=2890 %	DTP-HbOC N=2890 %	p-Value[1]	MnCC N=2877 %	DTP-HbOC N=2877 %	p-Value[1]	p-Value[2] 7VPnC vs. MnCC
Dose 1							
Erythema	12.4	21.9	0.0001	11.2	22.4	0.0001	0.124
? 2.4cm	1.2	4.6	0.0001	1.4	3.9	0.0001	0.416
Induration	10.9	22.4	0.0001	9.0	23.8	0.0001	**0.013**
? 2.4cm	2.6	7.2	0.0001	2.1	7.5	0.0001	0.307
Tenderness	28.0	36.4	0.0001	24.7	34.0	0.0001	**0.001**
Interferes with Leg Movement	7.9	10.7	0.0001	6.7	9.2	0.0001	0.062
Dose 2	N=2725	N=2725		N=2678	N=2678		
Erythema	14.3	25.1	0.0001	11.5	27.9	0.0001	**0.003**
? 2.4cm	1.0	2.9	0.0001	0.8	3.4	0.0001	0.364
Induration	12.3	23.0	0.0001	7.1	24.2	0.0001	**0.001**
? 2.4cm	2.4	5.6	0.0001	1.1	5.4	0.0001	**0.001**
Tenderness	25.2	30.5	0.0001	18.3	26.4	0.0001	**0.001**
Interferes with Leg Movement	7.4	8.4	0.015	4.4	5.8	0.0003	**0.001**
Dose 3	N=2538	N=2538		N=2532	N=2532		
Erythema	15.2	26.5	0.0001	12.7	26.8	0.0001	**0.011**
? 2.4cm	2.0	4.4	0.0001	1.3	4.1	0.0001	**0.028**
Induration	12.8	23.3	0.0001	9.7	23.2	0.0001	**0.001**
? 2.4cm	2.9	6.7	0.0001	1.5	6.1	0.0001	**0.002**
Tenderness	25.6	32.8	0.0001	18.2	28.5	0.0001	**0.001**
Interferes with Leg Movement	7.8	10.0	0.0001	4.7	7.2	0.0001	**0.001**

Adapted from Tables 48, 49, and 50 of Study Report, volume 13, Part IV of PLA.

[1] P-value, calculated using the sign test, assesses the difference between 7VPnC injection sites and DTP-HbOC/HepB injection sites in the 7VPnC recipients, and between MnCC injection sites and DTP-HbOC/HepB injection sites in the MnCC recipients.

[2] P-value, calculated using the Chi-Square test, assesses the difference between 7VPnC and MnCC injection sites in all subjects for which data were available.

N may vary for local reactions and dose number depending on available data.

After the 4th dose, local reactions at DTP-HbOC injection sites were significantly more common that reactions at 7VPnC injection sites. Rates of tenderness, and tenderness interfering with leg movement, were reported significantly more often among 7VPnC recipients (36% and 18%) than among MnCC control subjects (28% and 13%) (table not shown).

In the subset of subjects who received DTaP concurrently with study vaccines, HbOC and study vaccine were administered in the same leg (left), and DTaP +/- Hep B was administered in the opposite leg. The worse reaction of each leg was recorded. Comparisons of local reactions when 7VPnC or MnCC were administered concurrently with DTaP are shown below. Rates of erythema, induration, and tenderness interfering with movement were significantly greater for 7VPnC than for DTaP after the first dose, but not subsequent doses.

Rates of local reactions at 7VPnC injection sites do not appear to increase with sequential doses of the primary series.

Rates of erythema and induration at 7VPnC injection sites were significantly greater than rates for MnCC injection sites after doses 1 and 2.

Study 118-8: Local Reactions Within 48 Hours of Injection Among Infants Receiving DTaP, and 7VPnC or MnCC Vaccine with the Primary Series

	7VPnC N=693 %	DTaP N=693 %	p-Value[1]	MnCC N=691 %	DTaP N=691 %	p-Value[1]	p-Value[2] 7VPnC vs. MnCC
Dose 1							
Erythema	10.0	6.7	**0.0006**	6.5	5.6	0.3449	**0.026**
? 2.4cm	1.3	0.4	0.0313	0.6	0.9	0.5000	0.164
Induration	9.8	6.6	**0.0021**	4.2	4.3	?.999	**0.001**
? 2.4cm	1.6	0.9	0.1250	0.1	0.3	?.999	0.004
Tenderness	17.9	16.0	0.0533	17.9	18.9	0.2649	0.970
Interferes with Leg Movement	3.1	1.8	**0.0039**	2.5	2.5	?.999	0.505
Dose 2	N=526	N=526		N=489	N=489		
Erythema	11.6	10.5	0.5118	0.5118	10.8	0.0113	**0.030**
? 2.4cm	0.6	0.6	?.999	?.999	1.4	0.5078	0.717[3]
Induration	12.0	10.5	0.3123	0.3123	7.4	0.0801	**0.001**
? 2.4cm	1.3	1.7	0.6250	0.6250	1.0	0.2500	0.180[3]
Tenderness	19.4	17.3	0.0801	0.0801	15.6	0.6776	0.069
Interferes with Leg Movement	4.1	3.3	0.2188	0.2188	2.5	?.999	0.168
Dose 3	N=422	N=422		N=377	N=377		
Erythema	13.8	11.4	0.1433	9.3	8.2	0.5572	**0.049**
? 2.4cm	1.4	1.0	0.6250	2.4	1.9	0.7266	0.308
Induration	10.4	10.4	?.999	6.9	8.3	0.4731	0.066
? 2.4cm	2.4	1.9	0.6875	0.8	2.1	0.1250	0.082
Tenderness	14.7	13.1	0.2649	12.3	12.0	?.999	0.280
Interferes with Leg Movement	2.9	1.9	0.2188	1.6	0.5	0.1250	0.240

Adapted from Tables 48, 49, and 50 of Study Report, volume 13, Part IV of PLA.

[1] P-value, calculated using the sign test, assesses the difference between 7VPnC injection sites and DTaP injection sites in 7VPnC recipients, and between MnCC injection sites and DTaP injection sites in the MnCC recipients.

[2] P-value, calculated using the Chi-Square test, assesses the difference between 7VPnC and MnCC injection sites in all subjects for which data were available (Sponsor's analysis).

[3] P-value, calculated using Fisher's exact test (Sponsor's analysis)

Total N may vary depending on available data.

Local reactions following the 4th dose of 7VPnC or MnCC when given concurrently with DTaP were assessed in the NCKP efficacy trial. Subjects could have received either DTP-HbOC or DTaP and HbOC with the primary series, thus complicating the assessments. Erythema and induration were reported more frequently for 7VPnC injection sites than for DTaP in pairwise comparisons within subjects, and more frequently than for MnCC injection sites in control subjects.

118-8: Local Reactions within 48 Hours of Injection Among Children Vaccinated with DTaP vs. 7VPnC or MnCC Vaccine
Dose 4

	7VPnC N=165 %	DTaP N=165 %	p-Value[1]	MnCC N=178 %	DTaP N=178 %	p-Value[1]	p-Value[2] 7VPnC vs. MnCC
Erythema	10.9	3.6	**0.0042**	4.5	4.0	>.9999	**0.043**
? 2.4cm	3.6	0.6	0.1250	0.0	0.0		**0.005**[3]
Induration	12.1	5.5	**0.0127**	4.5	3.4	0.6875	**0.005**
? 2.4cm	5.5	1.8	0.0703	0.0	0.0		? **0.001**[3]
Tenderness	23.3	18.4	0.0963	15.4	14.9	>.9999	0.052
Interferes with Leg Movement	9.2	8.0	0.7539	1.7	1.7		**0.002**

Adapted from Table 55 of Clinical Study Report, Volume 13, Part IV of PLA
[1] P-value, calculated using the sign test, assesses the difference between 7VPnC injection sites and DTaP/HepB injection sites in the 7VPnC recipients, and between MnCC injection sites and DTaP/HepB injection sites in the MnCC recipients.
[2] P-value, calculated using the Chi-Square test, assesses the difference between 7VPnC and MnCC injection sites in all subjects for which data were available.
[3] P-value calculated with Fisher's Exact Test.
Subjects may have received mixed pertussis vaccine regimens concurrently in the primary series.

Supporting studies 118-12 and 118-16

Local reactions following concurrent administration of 7VPnC and DTaP with the primary series were also assessed in supporting studies 118-12 and 118-16. In both studies, local reactions for 7VPnC and HbOC in the left leg were compared pairwise within subjects to reactions in the right leg, inoculation site of DTaP +/- Hep B. Erythema, induration and tenderness were more common in the leg receiving 7VPnC. Severe reactions were uncommon.

118-16: Local Reactions W\ithin 72 hours of Injection
Within Subject Comparison of Leg Vaccinated with 7VPnC and HbOC Vaccine vs. Leg Vaccinated with DTaP and HepB

Local Reaction	Dose 1: All 7VPnC Lots (N=487)			Dose 2: All 7VPnC Lots (N=440)			Dose 3: All 7VPnC Lots (N=440)		
	7VPnC Site %	DTaP Site %	p-value[1]	7VPnC site %	DTaP Site %	p-value[1]	7VPnC site %	DTaP site %	p-value[1]
Erythema	10.9	6.2	**0.0002**	11.6	8.6	0.053	4.3	10.9	**0.049**
>2.4 cm	0.6	0.6	>.9999	0.7	0.5	>.999	0.9	0.2	0.250
Induration	9.9	5.6	**0.0015**	10.5	6.8	**0.036**	10.0	6.6	**0.028**
>2.4 cm	1.2	1.0	>.9999	0.9	0.2	0.375	1.1	0.2	0.125
Tenderness	22.3	17.2	**0.0001**	17.0	13.3	**0.029**	15.8	13.2	**0.043**
Interferes w/ Movement	2.9	2.9	>.9999	3.5	1.8	0.065	1.8	2.1	>.999

Adapted from Tables 17, 18, and 19, pages 68, 69, and 71, Volume 29, Part IV of PLA
Controls received DTaP and HbOC at age 2, 4, and 6 months. All groups received Hepatitis B at age 2 and 6 months. IPV was administered in the arm at ages 2 and 4 months.
[1] P-value, calculated using the sign test, assesses the difference between 7VPnC injection sites and DTaP/HepB injection sites in recipients of a 7VPnC lot.

118-12: Comparisons of Local Reactions within 72 hours Injections, HbOC with 7VPnC Versus DTaP, Within Subject Comparisons

Local Reaction	Dose 1			Dose 2			Dose 3		
	HbOC+ 7VPnC L thigh N=256 %	DTaP R thigh N=256 %	P-value*	HbOC+ 7VPnC L thigh N=245 %	DTaP R thigh N=245 %	P-value*	HbOC+ 7VPnC L thigh N=239 %	DTaP R thigh N=239 %	P-value*
Erythema	11.2	4.4	**0.001**	12.9	5.6	**0.002**	16.7	6.9	**0.001**
> 2.4 cm	1.6	0.8	0.414	0.4	0	1.000	1.7	0.9	0.414
Induration	10.7	3.6	**0.001**	17.2	7.3	**0.001**	14.2	7.4	**0.003**
> 2.4 cm	2.0	0	0.063	2.1	0	0.063	0.9	0.4	0.564
Tenderness	19.8	13.1	**0.001**	15.2	7.6	**0.001**	13.2	8.1	**0.005**
Interferes w/ Movement	2.4	2.4	1.000	2.5	1.3	0.083	3.0	1.3	**0.046**
Any Reaction	27.9	16.4	**0.001**	28.2	15.1	**0.001**	28.4	15.7	**0.001**
Any Signific. Reaction	5.2	3.2	0.166	4.7	1.3	**0.005**	5.6	2.2	**0.021**

Adapted from Table 33, page 61, Volume27, Part IV of PLA.
The number of children with available reaction data may be smaller and vary from reaction to reaction.
Combined data of three 7VPnC lot groups.
* P-value based on McNemar test for within-subject comparison. In the cases where the frequencies in one or both groups are zero, Wilcoxon signed rank test was used.

In study 118-12, it was also possible to separate out rates of local reactions due to 7VPnC + HbOC vs. HbOC alone, as subjects in the control group did not receive 7VPnC. Rates of local reactions in legs inoculated with both 7VPnC and HbOC were significantly greater than in control subjects. Induration and tenderness were reported more frequently after each dose of the primary series for 7VPnC recipients. Severe reactions were uncommon.

118-12: Comparisons of Local Reactions –HbOC + 7VPnC vs. HbOC Alone

Local Reactions at Left Thigh	Dose 1			Dose 2			Dose 3		
	HbOC with 7VPnC N=256 %	HbOC N=86 %	P-value*	HbOC with 7VPnC N=245 %	HbOC N=82 %	P-value*	HbOC with 7VPnC N=239 %	HbOC N=80 %	P-value*
Erythema	11.2	1.2	**0.003**	12.9	1.3	**0.002**	16.7	5.2	**0.012**
>2.4 cm	1.6	0	0.576	0.4	0	1.000	1.7	0	0.575
Induration	10.7	3.6	**0.048**	17.2	2.6	**<0.001**	14.2	5.2	**0.041**
>2.4 cm	2.0	0	0.337	2.1	0	0.336	0.9	1.3	1.000
Tenderness	19.8	10.6	0.068	15.2	10.1	0.348	13.2	3.9	**0.021**
Interfering Limb Movement	2.4	2.4	1.000	2.5	0	0.343	3.0	0	0.200
Any Reactions	27.9	11.9	**0.003**	28.2	10.1	**<0.001**	28.4	11.7	**0.003**
Any Significant Reaction	5.2	2.4	0.373	4.7	0	0.072	5.6	1.3	0.202

Adapted from Table 32, page 67, Volume 27, Part IV of PLA.
Pilot lots were combined for these comparisons.
The number of children with available reaction data may be smaller and vary by reaction.
* P-value based on Fisher's exact test.

Review Comments Regarding Local Reactogenicity of 7VPnC

Local reactions due to 7VPnC appear to be less frequent and severe than those due to DTP-HbOC, but more frequent than local reactions due to DTaP, HbOC and for the investigational vaccine MnCC. Local reactogenicity attributable to 7VPnC did not appear to increase with sequential doses of the primary series.

No data are presented in the PLA addressing local and systemic reactions of 7VPnC when administered with DTaP for all 4 doses.

Systemic Reactions in NCKP Efficacy Trial (118-8)

Assessment of systemic reaction rates and adverse events attributable to 7VPnC in the NCKP efficacy trial is complicated by concurrent recommended immunizations and use of an investigational vaccine (MnCC) in the comparator group.

Systemic Reactions with Concurrent DTP-HbOC

Against a background of concurrently administered DTP-HbOC , fever ?38?C and irritability were reported significantly more frequently in the 7VPnC group than in the MnCC group after each dose of the primary series. Rates of fever ?39?C increased with subsequent doses (1.3%, 3.0%, and 5.3%), and were significantly more frequent after doses 2 and 3 in the 7VPnC group, compared to the MnCC control group. Other systemic reactions, such as prolonged crying, restless sleep, loss of appetite and vomiting were also significantly more common in the 7VPnC group for 1 or more doses of the primary series.

Convulsions within 48 hours of a study vaccine inoculation were reported for 2 children in the 7VPnC (1 each after doses 1 and 2), and 1 child in the MnCC group (after dose 3).

The list of events solicited by telephone interview in the NCKP trial is shown in the following table.

118-8: Reported Systemic Events Within 48 Hours of Injection by Dose Among Infants Receiving Tetramune, OPV, Hepatitis B[1], and 7VPnC or MnCC

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC N[1]=2996 %	MnCC N=2976 %	p-value[2]	7VPnC N=2784 %	MnCC N=2758 %	p-value[2]	7VPnC N=2590 %	MnCC N=2588 %	p-value[2]
Fever ?38?C	33.4	28.7	**0.001**	34.7	27.4	**0.001**	40.6	32.4	**0.001**
Fever ?39?C	1.3	1.3	0.934	3.0	1.6	**0.001**	5.3	3.4	**0.001**
Irritability	71.3	67.9	**0.004**	69.4	63.8	**0.001**	68.9	61.6	**0.001**
Cry 3+ Hours	0.6	0.8	0.510	0.7	0.3	**0.029**	0.5	0.4	0.391
Restless Sleep	18.1	17.9	0.868	27.3	24.3	**0.009**	33.3	30.1	**0.012**
More Sleep	49.2	50.6	0.294	32.5	33.6	0.393	25.9	23.4	**0.040**
Loss of Appetite	24.7	23.6	0.358	22.8	20.3	**0.022**	27.7	25.6	0.083
Vomiting	17.9	14.9	**0.002**	16.2	14.4	0.067	15.5	12.7	**0.005**
Diarrhea	12.0	10.7	0.095	10.9	9.9	0.212	11.5	10.4	0.169
Hives	0.7	0.6	0.651	0.8	0.8	0.974	1.4	1.1	0.379
Wheezing	0.1	0.1	>.999[3]	0.2	0.2	0.987	0.2	0.3	0.779
Blue Skin Tone	0.03	0.1	0.624[3]	0.1	0.0	0.500[3]	0.04	0.04	.999[3]
Gray/Ashen Skin	0.03	0.0	>.999[3]	0.04	0.0	.999[3]	0.0	0.0	?
Weak/letharg/limp	0.1	0.1	0.687[3]	0.1	0.1	0.686[3]	0.0	0.1	0.249[3]
Twitching	0.1	0.1	>.999[3]	0.1	0.1	0.687[3]	0.04	0.1	0.625[3]
Convulsions	0.3	0.0	>.999[3]	0.04	0.0	.999[3]	0.0	0.04	0.500[3]
Loss of Consc.	0.0	0.0	?	0.0	0.0	?	0.0	0.0	?

Adapted from Tables 56, 57, and 58, Volume 13, Part IV of PLA.
Number of subjects reporting may vary with systemic reaction reported.
[1] 91%, 58%, and 52% of infants received hepatitis B vaccine, and 91%, 93%, and 94% received OPV at doses 1, 2, and 3, respectively.
[2] Chi-Square test.
[3] Fisher's Exact test

Systemic Reactions with Concurrent DTaP + HbOC

Systemic reaction rates among the actively monitored subset of infants who received DTaP with the primary series are likely relevant to current practice in the U.S. In the NCKP efficacy trial, rates of febrile reactions were significantly greater in the 7VPnC group than in the MnCC group when administered with DTaP in the primary series (See table below).

Rates of fever ?39?C and irritability were significantly greater in the 7VPnC group after the 2nd dose. Hives were reported more commonly in the 7VPnC group after the first dose; however, no trend was apparent for subsequent doses. Loss of appetite occurred more frequently in the 7VPnC group after each dose; the difference was significant at the 3rd dose.

The list of systemic events solicited through telephone interviews in the NCKP trials are also shown in the following table. No convulsions were reported in either vaccine group. One event, possibly consistent with a hypotonic hyporesponsive episode, was reported in the 7VPnC group after the 2nd dose.

118-8: Reported Systemic Events Within 48 Hours of Injection by Dose Among Infants Receiving DTaP, HbOC, OPV or IPV, Hepatitis B, and 7VPnC or MnCC

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC N=710 %	MnCC N=710 %	p-value[1]	7VPnC N=556 %	MnCC N=507 %	p-value[1]	7VPnC N=460 %	MnCC N=414 %	p-value[1]
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	0.178[2]	**2.5**	**0.8**	**0.029**	1.7	0.7	0.180
Irritability	48.0	48.2	0.936	**58.7**	**45.3**	**0.001**	51.2	44.8	0.059
Cry 3+ Hours	0.1	0.3	?.999[2]	0.4	0.0	0.501[2]	0.2	0.5	0.606[2]
Restless Sleep	15.3	15.1	0.914	20.2	19.3	0.705	25.2	19.0	**0.030**
More Sleep	40.7	42.0	0.637	25.6	22.8	0.296	19.5	21.9	0.380
Loss of Appetite	17.0	13.5	0.064	17.4	13.4	0.073	**20.7**	**13.8**	**0.008**
Vomiting	14.6	14.5	0.974	16.8	14.4	0.278	10.4	11.6	0.568
Diarrhea	**11.9**	**8.4**	**0.029**	10.2	9.3	0.611	8.3	9.4	0.539
Hives	**1.4**	**0.3**	**0.020**	1.3	1.4	0.857	0.4	0.5	?.999[2]
Wheezing	0.4	0.3	0.687[2]	0.0	0.6	0.108[2]	0.0	0.7	0.106[2]
Blue Skin Tone	0.1	0.0	0.500[2]	0.0	0.0	?	0.0	0.2	0.473[2]
Gray/Ashen Skin	0.0	0.0	?	0.0	0.0	?	0.0	0.0	?
Weak/letharg/limp	0.0	0.0	?	0.2	0.0	?.999[2]	0.0	0.0	?
Twitching	0.1	0.0	0.500[2]	0.2	0.2	?.999[2]	0.0	0.0	?
Convulsions	0.0	0.0	?	0.0	0.0	?	0.0	0.0	?
Loss of Consc.	0.0	0.0	?	0.0	0.0	?	0.0	0.0	?

Adapted from Tables 64, 65, and 66 of Clinical Study report, Volume 13, Part IV of PLA.
[1] Chi-Square test (Sponsor's analysis).
[2] Fisher's Exact test (Sponsor's analyss)
Number of subjects reporting may vary with systemic reaction reported.

After a 4th dose of 7VPnC given concurrently with DTaP, rates of fever ?38?C and ?39?C within 48 hours were 21% and 1.3%, respectively (Table not shown). Fever rates in the MnCC group did not differ significantly. The subsets of subjects who received DTaP with study vaccine as a 4th dose may have received mixed regimens of pertussis vaccine for the primary series. Concurrently with the 4th dose, 90% of subjects received HbOC, 88% received MMR, and 49% received VZV.

As allowed by the study protocol, some subjects received a 4th dose of study vaccines without any concurrent immunizations. Fever and common systemic reaction rates for these subjects are shown below. Irritability was reported significantly more often in the 7VPNC group. Fever rates did not differ appreciably between study groups.

118-8: Reported Systemic Events Within 48 Hours of Injection Among Infants Receiving 7VPnC or MnCC Only, Dose 4

	7VPnC N=644		MnCC N=627		p-value[1]
	n	%	n	%	
Fever ?39?C	9	1.4	6	1.0	0.467
Fever ?38?C	88	13.7	76	12.1	0.412
Irritability	294	45.6	221	35.1	**0.001**
Cry 3+ Hours	1	0.2	0	0.0	?.999[2]
Restless Sleep	133	20.7	133	21.3	0.806
More/Sounder Sleep	102	15.9	94	15.0	0.676
Loss of Appetite	125	19.4	115	18.3	0.617
Vomiting	44	6.8	39	6.2	0.653
Diarrhea	79	12.3	71	11.3	0.588

Adapted from Table 72, Clinical Study Report, Volume 13, Part IV of PLA
N may vary with systemic reaction
[1] Chi-square test
[2] Fisher's Exact test.

Systemic Reactions in Supporting Studies 118-12 and 118-16

In studies 118-12 and 118-16, the control groups did not receive MnCC or other investigational vaccines, and all infants received DTaP with the primary series. Safety data from these trials provide the clearest view of systemic reactions attributable to 7VPnC. In both studies active monitoring for fever and systemic events within 72 hours of injections were reported, rather than 48 hours as in the NCKP efficacy study.

Rates of systemic reactions in study 118-12 were similar between the pooled 7VPnC pilot lot groups and controls. Rates of fever ?38?C were numerically greater in the 7VPnC groups after doses 2 and 3, however comparisons to control were not statistically significant. Fever rates may have been spuriously low due to use of antipyretics, which were used significantly more often in the 7VPnC group after dose 2.

118-12: Percent of Infants Reporting Systemic Event Within 72 Hours of Injection

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC N=256 %	Control N=86 %	p-value[3]	7VPnC N=245 %	Control N=82 %	p-value[3]	7VPnC N=239 %	Control N=80 %	p-value[3]
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
Drowsiness	48.6	38.8	0.132	31.5	22.8	0.156	27.4	9.1	**<0.001**
Fussiness	39.9	31.8	0.198	39.1	37.5	0.895	37.6	31.2	0.340
Decreased Appetite	17.8	15.3	0.740	12.7	16.5	0.448	13.2	14.3	0.848
Any Event	68.1	58.5	0.140	61.4	50.0	0.088	56.9	39.5	**0.011**
Use of Antipyretics	27.3	20.0	0.198	39.1	24.1	**0.021**	28.6	26.0	0.770

Adapted from Table 27, page 55, Volume 27, Part IV of PLA
* P-value based on Fisher's exact test (Sponsor's analysis).

In study 118-16, conducted at Kaiser Permanente centers, two manufacturing lots and one pilot lot were compared for safety and immunogenicity. Systemic events for the pooled 7VPnC groups versus control were provided in the clinical summary of the PLA. Fever ?38?C was reported more frequently after each dose; differences relative to control were statistically significant after doses 1 and 2. Fever ?39?C was reported more frequently after the 2nd dose (3.8%). Use of antipyretic agents was not reported in this study.

118-16: Percent of Infants Reporting Systemic Event Within 72 Hours 7VPnC (All Lots) vs Control

Systemic Reaction	Dose 1			Dose 2			Dose 3		
	7VPnC N=498 %	Control N=108 %	p-value[1]	7VPnC N=452 %	Control N=99 %	p-value[1]	7VPnC N=445 %	Control N=89 %	p-value[1]
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
Irritability	59.7	60.2	1.0	65.3	52.5	**0.021**	54.2	50.6	0.56
Drowsiness	50.8	38.9	0.026	30.3	31.3	0.90	21.2	20.2	1.0
Decreased Appetite	19.1	15.7	0.49	20.6	11.1	**0.033**	20.4	9.0	**0.011**

Adapted from Table 30 of Integrated Clinical Summary, Volume 33, Part IV of PLA.
All subjects received DTaP+HbOC at each dose, Hep B at dose 1 and 3, and IPV at dose 1 and 2.
Pilot lot and 2 Manufacturing lots data pooled.
[1] P-value for comparison of pooled data to control (Sponsor's analysis).

Review Comments Regarding Systemic Reactogenicity

In the NCKP efficacy trial, fever and systemic reactogenicity due to 7VPnC were detectable above background rates due to DTP-HbOC and other concurrent vaccines, as determined by comparisons to the MnCC group. Some systemic reactogenicity is likely due to MnCC. Therefore, comparisons to systemic reaction rates for MnCC may mask excess reaction rates attributable to 7VPnC.

In both the NCKP efficacy study, and in the supporting study 118-16, when administered with DTaP and other concurrent vaccines in the primary series, increased rates of fever ?38?C, and fever ?39?C were associated with 7VPnC, compared to control groups. Increased use of antipyretic agents was reported int study 118-12. Irritability, decreased appetite, and drowsiness were also associated with 7VPnC, but without consistent pattern.

Rates of fever increased with sequential doses when 7VPnC was administered with DTP-HbOC. When administered with DTaP and HbOC, rates of fever and systemic reactions did not appear to increase with sequential doses of 7VPnC.

Across studies, when 7VPnC was administered against a background of the most relevant concurrent vaccines (DTaP, HbOC, IPV, Hep B), rates of fever ?38?C, and >39?C, were reported most frequently after dose 2. By dose, rates of fever ?38?C ranged from 5%-22% after dose 1, 19%-34% after dose 2, and 19-28% after dose 3. Fever ?39?C was reported for 0.6%-0.9% after dose 1, 1.8%-3.8% after dose 2, and 0.9%-2.2% after dose 3.

Adverse Events

NCKP Efficacy Study (118-8)

All subjects in the NCKP efficacy trial were followed for 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, and wheezing, shortness of breath and asthma) were also assessed and provided in the PLA.

Events resulting in study termination were also reported. Incidence of SIDS in the study population was to be evaluated and compared to the SIDS rate in the entire NCKP population and to the overall state-wide rate. Diagnoses of neurologic disorders and anaphylactic reactions were to be followed for outcome.

Deaths

Eighteen deaths (8 in 7VPnC recipients and 10 in MnCC recipients) occurred in the NCKP efficacy trial on or prior to April 30, 1998. None of the deaths were considered to be related to study vaccines by the investigators or the sponsor.

Sudden Infant Death Syndrome (SIDS) was listed as the cause of 9 deaths (5 in the MnCC group, and 4 in the 7VPnC group). All of the deaths attributed to SIDS occurred ? 5 days after study inoculations.

Other causes of deaths were accidental (n=2), homicide (n=2), congenital anomalies (n=2), complications of prematurity (n=1), and bacterial leptomeningitis (n=1), Leigh's syndrome (1).

An additional 12 deaths (2 in 7VPnC, 10 in MnCC) were reported in a planned safety update, received September 13, 1999, for the period May 1,1998, through December 31, 1998. Causes of death in the 7VPnC group were diabetic ketoacidosis (1) and traumatic asphyxia (1). Causes of death in the MnCC group were SIDS (3), drowning (2), pneumococcal meningitis (1), SCIDS (1), glioblastoma (1), metachromatic leukodystrophy (1), and pneumonia in a child with Werdnig-Hofffman disease (pneumococcal meningitis and SCIDS case were discussed among case characteristics, above, and in attachment A). None of the deaths were judged related to study vaccines by the investigators.

The rate of SIDS for cases through December 31, 1998, were compared to State of California rates for 1996 and 1997:

118-8: Rate of SIDS in Study Groups Compared with California SIDS Rates

	7VPnC	MnCC	State CA 1996	State CA 1997*
Number of SIDS cases	4	8		
Number vaccinated[1]	18,927	18,941		
Rate per 1000	0.2	0.4	0.6	0.6

Reproduced from October 18, 1999 submission to PLA

* 1997 rate is provisional

[1]Number of subjects receiving at least 1 dose

Hospitalizations

Statistical analysis of comparative rates of hospitalizations for particular diagnoses was possible because of the size of the study. Rates of hospitalizations reported within 3, 14, 30 and 60 days were calculated.

Rates of hospitalizations for febrile seizures within 30 days and 60 days of a study vaccine dose were significantly greater in 7VPnC group than the MnCC group during the primary series and across all doses, when given concurrently with whole cell pertussis vaccine.

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

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

Hospitalizations for epilepsy within 30 days of a vaccine dose were more significantly more frequent in the MnCC group

Emergency Room Visits

Rate of ER visits for croup within 3 days, breath holding and urinary tract infections within 30 days of a vaccine dose were significantly more frequent in the 7VPnC group.

ER visits for gastroesophageal reflux and cellulitis were more common in the MnCC group.

Outpatient Clinic Visits

Outpatient visits for seizures within 30 days of a vaccine dose, and for asthma after the booster dose were more significantly more frequent in the MnCC group.

Serious Adverse Events Considered Related to Study Vaccines

In the NCKP efficacy trial, six serious adverse events were considered by investigators to be possibly, probably or definitely related study vaccines. Four of these events were seizures, and 3 of the 4 seizures occurred in the 7VPnC group.

All seizure events considered serious and possibly related to study vaccines occurred among children receiving concurrent DTP-HbOC.

118-08: Serious Adverse Events Considered Possibly, Probably or Definitely Related to Study Vaccines

Event	Treatment Group	
	7VPnC	MnCC
Seizures	3	1
Allergy/Rash	0	1
Apnea	0	1

Reproduced from Table 75, page 243 of Clinical Study Report for Study 118-P8 in PLA.

Adverse Events Resulting in Termination from the Study

A total of 127 subjects were dropped from the study due to an adverse event, of which 85 experienced some type of seizure activity (most not temporally related to vaccine) and per protocol, were dropped from the study. Other adverse events for which more than one subject was dropped included allergic reaction/rash (n=4), idiopathic thrombocytopenic purpura (n=4), evolving neurological disorder/developmental delay (n=8), trauma/shaken baby (n=6), and apnea/breath holding (n=3).

Ten of these events were considered at least possibly related to immunization with study vaccine by the investigator. These included 5 episodes of seizure (2 in MnCC recipients, 3 in 7VPnC recipients), 3 allergic-type reactions (2 in MnCC recipients, 1 in 7VPnC recipient), and 2 episodes of apnea/breath-holding (2 in MnCC recipients). All of these events were temporally related to immunization in that they occurred either on the day of or one to two days after immunization.

118-8: Number of Adverse Events Resulting in Study Termination by Vaccine Group

Adverse Event	7VPnC	MnCC
Any	53	74
Seizures	40	43
ITP	0	4
Infection/Pneumonia	2	4
Allergic reaction/Rash	1	3
Evolving Neurol. Disorder/Develop Delay	3	5
Stroke	0	2
Apnea/Breath Holding	0	3
Congenital Heart Disease	2	0
Neoplasm/Histiocytosis	2	1
Head Trauma/Shaken baby	2	4

Compiled from Table 14.3.2.3 of Clinical Study Report, Part IV of PLA (Updated October 12, 1999)
List is not comprehensive of all events; some children with more than 1 adverse event.

Seizures Events in NCKP Study (118-8)

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

FDA asked the sponsor to provide an integrated summary of all seizure events in which discrete events would be counted only once, and acute events were distinguished from follow-up visits or an ongoing seizure disorder by means of chart review. The sponsor also reviewed other potential sources of information, including spontaneous reports from clinic study nurses (not in the original PLA). 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.

118-08: Number of Subjects with Acute Seizure Events

Period after Study Vaccine	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 febrile seizures, and 7 had received a whole cell pertussis vaccine concurrently with study vaccines. Two subjects with febrile seizures were also diagnosed with urinary tract infections. The one subject in the 7VPnC group who had a seizure after DTaP was thought to have a viral infection.

Of the 4 subjects in the MnCC group with acute seizure events within 3 days, two had febrile seizures. One subject had a history of cerebral palsy, and another had a history of seizures. One event, an afebrile seizure, could not be clearly distinguished from a breath-holding episode.

118-08: Characteristics of Acute Seizure Events Occurring within 3 Days of Study Vaccine

	7VPnC	MnCC
Acute Seizure Events	8	4
Febrile	7	2
Afebrile	1	2
Concurrent DTP	7	3
Concurrent DTaP	1	1
Post dose 1	1	0
Post dose 2	2	1
Post dose 3	3	3
Post dose 4	2	0

From October 18, 1999 submission to PLA.

In a safety update for the period ending December 31, 1998, one additional seizure episode occurring within 3 days of a study vaccine was reported: A febrile seizure 3 days post 4th dose of 7VPnC.

Seizure Events in Supporting Studies

In study 118-12, two subjects in the 7VPnC group experienced seizures temporally related to vaccine. Both subjects received DTaP concurrently (See attachment A for narratives). No seizures were reported in the control group.

No seizure events related to study vaccines were reported in other supporting studies conducted among infants.

Immune Thrombocytopenic Purpura (ITP)

Four cases of ITP were reported as reasons for study termination in the NCKP trial for the period ending April 30, 1998. All cases were in the MnCC vaccine group. Onset of illness ranged from 46 to 191 days following a dose of study vaccines. One child had varicella in the month preceding onset of ITP.

ITP Case Characteristics

Study Vaccine	Age months	Days Since Vaccine	Vaccine Dose	Concurrent Vaccines
MnCC	3	56	2	DTP-HbOC, OPV
MnCC	6	46	2	DTP-HbOC, OPV, HepB
MnCC	10.5	62	3	DTP-HbOC, OPV, HepB
MnCC	13	191	3	DTP-HbOC, OPV, HepB

Compiled from case narratives and October 18, 1999 submission to PLA

Safety Update

Deaths, and line listings of hospitalizations within 60 days and emergency room visits within 30 days of a vaccine dose were provided for the period June 1 through December 31, 1998, without rate calculations, statistical comparisons, or narratives.

Adverse events in the safety update considered possibly or probably related to study vaccines by study investigators were compiled from the line listings, and are summarized below. The seizure event, which occurred 3 days after a dose of 7VPnC, was noted above.

118-8: Adverse Events Possibly or Probably Related to Vaccine During Safety Follow-up, May 1, 1998 through December 31, 1998

Vaccine Group	Adverse Event	Source of Report	Days Since Vaccine	Vaccine Dose
7VPnC	Febrile Seizure	ER, Hospitalization	8	4
	Febrile Seizure	ER	3	4
MnCC	Fever	ER	1	3
	Fever, Hives	ER	1	2
	Fever, Irritable	ER	2	4
	Local Swelling	ER	3	3
	Fever, Local reaction	ER	0	3

Compiled from line listings provided in July 7, 1999 submission to the PLA.

Question #3: Do the data presented support concurrent use with vaccines according to the recommended schedule of immunizations?

Hemophilus influenza type B

Compatibility of 7VPnC with Hib responses in the primary series was examined in the context of DTP-HbOC in study 118-03, and with DTaP + HbOC in studies 118-12 and 118-16.

In study 118-03, no decreases in Hib responses were observed when 7VPnC was administered concurrently with DTP-HbOC in the primary series.

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118-03: Hib-PRP Responses Post Dose 3
Concurrent Administration of DTP-HbOC and 7VPnC or MnCC

Study Group	N	GMC (?g/mL) (95% CI)	% ? 0.15?g/mL (95% CI)	% ? 1.0 ?g/mL (95%CI)
7VPnC	94	7.29 (5.3, 10.0)	100 (96-100)	89.4 (81-95)
MnCC	86	5.58 (4.1, 7.6)	97.9 (93, 100)	86.5 (78-93)

Adapted from Tables 30a, and 31a, Volume 8, Part IV of PLA

In studies 118-12 and 118-16 Hib-PRP responses were assessed for groups receiving either 7VPnC or control (no vaccine) administered concurrently with DTaP + HbOC. 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 is represented. No evidence of interference of 7VPnC with concurrent HbOC was observed; a slight enhancing effect was apparent.

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

Hib-PRP responses following concurrent and separate administration of 7VPnC and HbOC with the 4th dose were assessed in studies 118-03 and 118-07. In both studies, the primary series of 7VPnC was administered with DTP-HbOC. In study 118-07, DTaP and HbOC were administered concurrently with 7VPnC, or one month after. Differences in GMCs between groups were statistically significant, however in both groups the GMCs were relatively high, and proportions responding at ? 1.0 ?g/mL exceeded 97%.

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

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

Adapted from Table 26, page 72, Volume 11, part IV of PLA
[1] Fishers exact (Sponsor's analysis)

In study 118-03, 7VPnC or MnCC were administered concurrently with DTaP + HbOC at the 4th dose, after use of DTP-HbOC for the primary series. Direct statistical comparisons between 7VPnC and MnCC groups were not made in the PLA. The proportion of subjects with anti Hib-PRP antibody ? 1.0 ?g/mL appears to differ substantially between groups, and the lower 95% CI of the response rate extends to 70%.

118-03: Hib-PRP Responses Post Dose 4
Concurrent Administration of DTaP + HbOC and 7VPnC or MnCC

Study Group	N	GMC (?g/mL) (95% CI)	% ? 0.15?g/mL (95%CI)	% ? 1.0 ?g/mL (95%CI)
7VPnC	26	19.7 (10.3, 37.6)	100 (86.8, 100)	88.5 **(69.9,** 97.6)
MnCC	33	21.6 (13.44, 34.73)	100 (89.4, 100)	100 (89.4, 97.6)

Adapted from Tables 30a and 31a, Statistical Report, Volume 8, Part IV of PLA

Hib-PRP response rates at the 4th dose following priming with DTP-HbOC, presented above, may not be most relevant to current practice, as DTaP is used predominantly with all doses of the primary series. Data for concurrent immunizations using DTaP for all doses of the primary series and for the 4th dose are not included in the PLA.

Inactivated Poliovirus Vaccine

Responses to IPV (IPOL?) following concurrent immunization with 7VPnC and IPV in the primary series was evaluated in a single study, 118-16. IPV was administered at 2 and 4 months of age. Serum neutralizing antibody titers were determined at 7 months. Data for the preferred manufacturing lot only is shown below for simplicity of presentation.

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 between 7VPnC and polio type II and III was observed.

The clinical significance of this apparent interference of 7VPnC with IPV I responses is not clear. The sponsor points out that responses 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 I exceed response rates for polio type III in both groups, which met the difference criteria. No other studies in the PLA address concurrent immunization of 7VPnC and IPV.

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 I	? 1:10	88.96 (82.9, 93.5)	93.59 (85.6, 97.9)	-4.63	-13.29
Polio II	? 1:10	94.16 (89.1, 97.3)	93.59 (85.6, 97.9)	0.57	-6.31
Polio III	? 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).

Studies of the compatibility of 7VPnC with OPV are not presented here for lack of relevance to current practice.

Hepatitis B

Responses to Hepatitis B following concurrent immunization with 7VPnC and Hepatitis B vaccines in the primary series were evaluated in two studies: 118-7 (Recombivax HB), and 118-16 (Engerix-B).

In study 118-16, Hepatitis B vaccine was administered at 0-2 weeks, 2 months, and 6 months of age. Concurrent immunizations included DTaP/HbOC, IPV, and either 7VPnC or no vaccine control. In the table below, only results for the preferred manufacturing lot are presented; results for the pilot lot were similar. Non interference of 7VPnC and Hepatitis B vaccine was demonstrated in this study.

Study 118-16: Percent of Subjects Achieving ? 10 mIU/mL Hepatitis B Antibody Level, Post Dose 3

Concurrent Study Vaccine	N	Percent Achieving ? 10 mIU/mL	95% CI[1]
7VPnC	146	99.35%	96.4%, 100%
Control: No 7VPnC	80	96.15%	89.1%, 99.2%

Adapted from Table 10, page 56, Volume 29, Part IV of PLA
* Exact 95% confidence intervals calculated using StatXact (sponsor's analysis).

In study 118-07, Hepatitis B vaccine was administered at 2, 4, and 6 months of age. Concurrent immunizations included DTP-HbOC, OPV, and either 7VPnC or MnCC.

Study 118-07: Percent of Subjects Achieving ? 10 mIU/mL Hepatitis B Antibody Level

Concurrent Study Vaccine	N	Percent Achieving ? 10 mIU/mL	95% CI
7VPnC	81	92.6%	84.6%, 97.2%
MnCC	41	100%	93%, --

Adapted from Table 34 page 59 and Table 53 page 71, Volume 12, Part IV of PLA

These data suggest that 7VPnC may interfere with Hepatitis B vaccine responses when administered on the 2, 4, and 6 months schedule. The lower bound of the 95% confidence interval for the proportion of subjects attaining the clinically relevant antibody titer of 10 mIU/mL was less than 85%. GMCs for Hep B responses were not provided. No statistical comparison of the difference between responses to Hep B vaccine by concurrent 7VPnC or MnCC vaccines were provided in the study report.

DTaP

Compatibility of 7VPnC with DTaP responses in the primary series was examined in study 118-12. The control group received concurrent vaccines only. In the tables below, data from the 3 pilot lots of 7VPnC were combined for comparisons to control.

GMCs for tetanus toxoid were significantly higher in the control group, which did not receive 7VPnC, but the proportion of subjects exceeding relevant antibody levels were similar in the two groups.

Forty-five percent (45%) of the children who received concurrent 7VPnC achieved a 4-fold rise in fimbriae, as compared to 62.5% of the children in the control group. The significance level of the difference was 0.015, and the 90% lower confidence limit of the difference was -30.8%.

Study 118-12: Comparisons of GMCs of Antibody to Antigens in DTaP Between 7VPnC Recipients and Control, Post Dose 3

Antigen	GMC (95% Confidence Interval) of Post Dose 3 Antibody			Ratio of GMC of Concurrent 7VPnC to Control (with 90% CI)
	with Concurrent 7VPnC N[1]= 214	without Concurrent 7VPnC N[1] = 67	P-value[2]	
Diphtheria	0.88 (0.79, 0.97)	0.80 (0.63, 1.01)	0.741	1.04 (0.87, 1.23)
Tetanus	3.45 (3.11, 3.83)	4.14 (3.39, 5.07)	0.037	0.80 (0.67, 0.95)
Pertussis Toxin	19.05 (17.15, 21.15)	17.83 (14.93, 1.28)	0.404	1.09 (0.92, 1.29)
Fimbriae	3.29 (2.79, 3.86)	4.17 (3.24, 5.37)	0.316	0.81 (0.58, 1.14)
69K	40.11 (35.52, 45.29)	50.93 (41.65, 2.27)	0.067	0.80 (0.65, 0.98)
FHA	43.77 (39.50, 48.49)	46.70 (39.85, 4.74)	0.595	0.95 (0.81, 1.12)

Adapted from Table 21, page 49 of Statistical Report, Volume 27, Part IV of PLA

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

[2] P-values based on an ANCOVA model (Sponsor's analysis)

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)**
69K				
? 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 and exact confidence intervals computed using StatXact.

Responses to DTaP administered with 7VPnC at the 4th dose were also examined in study 118-7. However, these data may not be most relevant to current practice, as all subjects had been primed with DTP-HbOC. No data were presented in the PLA addressing responses to 4 doses of DTaP administered concurrently with 7VPnC.

MMR

Responses to measles, mumps and rubella following concurrent administration with 7VPnC were examined in studies 118-3 and 124-2.

In study 118-3, 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 are presented in the PLA.

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 no significant differences are apparent between the study arms, response rates to mumps and rubella are low by historical standards.

Draft Question #4: Please comment on the "Catch-Up" schedule proposed for the package insert.

Catch-up Schedules

The catch-up schedule proposed for inclusion in the vaccine label is reproduced below:

> **For Previously Unvaccinated Older Children**
> Previously unvaccinated infants should be vaccinated according to the following schedule:

Age at first dose	Total number of 0.5 mL doses
7-11 months of age	3*
12-23 months of age	2**
24+ months of age	1

* 2 doses at least 4 weeks apart; third dose after the one-year birthday, separated from second dose by at least 2 months.
** 2 doses at least 2 months apart.

The efficacy trial provided evidence of protection after 3 doses of 7VPnC until the 4th dose was administered, and subsequently after the 4th dose. To make inferences about long-term protection from available immunogenicity data based on data from the efficacy trial, it may also be relevant to make comparisons to post dose 4 antibody levels.

Of the 188 subjects in the NCKP efficacy study who received 3 doses 7VPnC concurrently with DTP-HbOC in the primary series, and had at least one serum sample drawn, 88 met the eligibility criteria for the primary series immunogenicity analysis, and 68 met criteria for 4th dose immunogenicity analyses. GMCs for pneumococcal serotypes pre and post doses 3 and 4 are shown below.

118-8: Geometric Mean Concentration of Pneumococcal Antibodies Prior to and Following the Primary Series and 4th Dose

Serotype	Pre dose 3 N=86[1]	Post dose 3 N=88[1]	Pre dose 4 N=68	Post dose 4 N=68
4	0.078	1.458	**0.314**	2.384
6B	0.327	4.696	1.714	14.446
9V	0.180	1.994	0.572	3.510
14	0.198	4.601	1.451	6.521
18C	0.146	2.160	**0.496**	3.431
19F	0.374	1.394	0.550	**2.067**
23F	0.174	1.848	**0.435**	3.820

Adapted from Tables 39 and 42, Volume 13 Part IV of PLA.
[1] N=87 for pre GMC and N=87 for post GMC, but N=86 in this table because one subject had pre but no post concentration and another subject had post but no pre concentration.

Pre dose 4, GMCs had declined to less than 0.50 ?g/mL for 3 of the pneumococcal serotypes (4, 18C, and 23F). Post dose 4, GMCs exceeded 2 ?g/mL for all serotypes. Response to the 4th dose was least robust for serotype 19F.

(Pre and post dose 4 pneumococcal serological data when 7VPnC was given with concurrent DTaP were available for only 9 subjects).

Available immunogenicity data from various vaccine schedules obtained in various trials are summarized in the table on the following page, with comparisons to antibody levels observed in the efficacy trial after the primary series, but not after the 4th dose.

It should be noted that in the age group > 24 months, all catch-up data in the PLA derives from study of a 9-valent formulation. Data from small studies (N<30) of an investigational 9-valent formulation intended to support catch-up schedules indicate that GMCs for the 9-valent formulation were numerically greater than GMCs for the 7-valent formulation for some serotypes following similar dosing schedules in different studies. In study 124-2, immunogenicity of 7VPnC and 9-valent PnC were directly compared during the primary series; these data bridging 9VPnC to 7VPnC were not included in the application. Responses observed with the 9-valent formulation in this age group may not be representative of responses due to Prevenar.

Two 23-valent pneumococcal polysaccharide (23VPS) vaccines are licensed and available in the U.S. The 23VPS vaccines are recommended for selected immunocompetent individuals over the age of 2 years, including Alaskan and certain American Indian populations. No data comparing responses to 7VPnC and 23VPS vaccine in children over the age of 2 years were provided in the PLA. Comparative responses to 7VPnC and 23VPS in adults following a single dose are available from study 118-02 (see attachment B). These data demonstrated superior responses to 7VPnC only for serotype 19F.

Safety and immunogenicity data for responses to 23VPS following a primary series of 7VPnC during infancy were not provided in the PLA. In study 92-05 (attachment B), children 15-18 months received 23VPS after a primary series of a 5-valent conjugate formulation. While a “booster” response to 23VPS among children primed with 5-vaent conjugate vaccine was apparent, the study design did not provide for comparisons of responses to 23VPS and 5-valent conjugate vaccine at the 4th dose. Thus, based on data submitted to the PLA, it remains to be demonstrated whether children over the age of 2 years respond better to 7VPnC than to a licensed 23-valent pneumococcal polysaccharide vaccine, whether primed with 7VPnC in infancy or not.

Catch-Up Studies: Geometric Mean Concentrationsfor all Serotypes and 'Age, Dose' Regimens

Age group (months) # doses	Study**	Sample size	4	6B	9V	14	18C	19F	23F	*Number of serotypes exceeding 118-8
7-11, 2 doses	118-12	37 – 38	2.785	1.159	1.330	4.895	1.983	1.807	1.729	4
7-11, 3 doses*	118-12	22	2.336	3.663	2.113	9.329	2.312	1.600	2.504	7*
12-17, 1 dose	118-09	25	0.746	0.232	0.535	0.373	0.628	0.666	0.443	0
	118-15	98 –103	2.985	0.547	1.015	0.856	1.390	1.097	0.797	1
12-17, 2 doses*	118-15	82 – 84	3.908	4.670	1.935	6.919	2.252	3.780	3.287	7*
	124-501 (9-valent)	18	10.32	31.55	7.083	22.12	9.866	7.237	8.348	7*
18-23, 1 dose	118-09	33	1.617	0.442	2.125	0.450	1.653	1.312	0.690	2
	118-15	45 – 48	2.906	0.804	0.890	0.719	1.487	0.963	1.497	2
	124-501 (9-valent)	25	16.16	1.905	2.299	0.822	2.618	1.823	0.711	4
18-23, 2 doses*	118-15	52 – 54	3.36	4.918	1.805	6.689	2.651	3.174	2.710	7*
24+ 1 dose	124-501 (9-valent)	85	6.205	3.272	3.491	2.054	3.975	1.866	1.628	6
118-8†, DTP/HbOC	118-08	87 – 88	1.458	4.696	1.994	4.606	2.160	1.394	1.848	
118-8†, DTaP	118-08	31 – 32	1.474	2.181	1.519	5.052	2.235	1.540	1.478	

Adapted from Table 45, page 110, Volume 33, Part IV of PLA
* All seven serotypes exceeded post dose 3 GMCs in study 118-8; historical comparisons using similar assays.
** Study vaccine is Prevenar, unless otherwise indicated
Geometric means exceeding 118-8 geometric mean are bolded
† GMCs following 3 doses

Draft Questions to the Committee

#1: Do the data presented provide sufficient evidence of efficacy for Prevenar at 2, 4, 6, and 12-15 months of age?

If not, what additional information should be requested?

#2: Do the data presented provide adequate evidence of safety for Prenevar?

If not, what additional information should be requested?

#3: Do the data presented support concurrent use with vaccines according to the recommended schedule of immunizations?

#4: Please comment on the proposed "catch-up" schedule?

Attachment A: Narratives of Selected Cases and Events

Study 118-8: Cases of Invasive Disease Among 7VPnC Recipients

Per Protocol

A 24-month old Causcasian male, who received 4 doses of 7VPnC, presented in the ER with temperature 99.6 ?F, cough and URI of 3 days duration. Ceftriaxone was given and the child was seen in clinic next day when the blood culture was obtained. Chest X-ray showed a right lower lobe pneumonia. He was treated outpatient with ceftriaxone and oral antibiotics and recovered fully. The isolate was serotype 19F, penicillin sensitive. There was no evidence the child was immunocompromised.

ITT

A 12.5 month old African-american female who received 1 dose of 7VPnC became ill with fever (104.8°F), nasal discharge, and injection of throat and ears 317 days after the 1st dose. She was treated with trimethoprim/sulfa p.o., ceftriaxone, and then amoxicillin. She recovered fully. The isolate was serotype 6B, penicillin sensitive. There was no evidence the child was immunocompromised.

A 2.5 year old Caucasian male, who received 4 doses 7VPnC per schedule, was diagnosed with acute megaloblasitc leukemia, and received one round of chemotherapy prior to onset of pneumococcal bacteremia, 570 days after 4th dose. The isolate was serotype 19F and penicillin resistant. He was treated with vancomycin, but died 2 months later. This case was classified as intent-to-treat, despite being fully vaccinated, due to his immunocompromised condition.

Study 118-8: Deaths Among Subjects with Invasive Disease

MnCC Group

An 8-month old Caucasian female was diagnosed with pneumococcal pneumonia and meningitis. The child developed cerebral edema and cerebral infarcts. Pneumococcal serotype 14, relatively resistant to PCN grew from blood and CSF. Causes of death were listed as cardiopulmonary failure due to metabolic derangement (not specified), failure to thrive, and bilateral cerebral infarcts. There was no evidence the child was immunocompromised (results of immune function tests not provided).

A 28-month old male with a history of asthma, was diagnosed with RML, RLL, and LLL pneumonia, and respiratory distress. Pneumococcal serotype 19F, PCN sensitive, grew from a blood culture. The child was not receiving corticosteroids prior to hospitalization. There was no evidence the child was immunocompromised (results of immune function tests not provided).

A 4-month old Hispanic male with severe combined immunodeficiency disease (SCIDS) developed pneumonia with RLL consolidation. Blood culture grew a non- vaccine serotype 18B, sensitive to PCN. He recovered, but died over a year later after unsuccessful bone marrow transplant.

7VPnC Group

A 2.5-year old Caucasian male in the 7VPnC group with acute megaloblastic leukemia, recovered from pneumococcal bacteremia due to a PCN resistant pneumococcal serotype 19F, but died at home 6 weeks later (described above).

Study 118-8: Acute Seizures within 3 Days of Study Inoculation as Serious Adverse Events Considered by Investigator to Be Possibly, Probably, or Definitely Related to Study Vaccines

7VPnC Subjects

07-1132: A 5-month-old male infant who was immunized with 7VPnC on 1/22/97 and 4/23/97. He also received DTP-HbOC, OPV, and Hep B vaccines concurrently. Twelve hours following the second dose, the subject experienced a seizure lasting approximately 3 minutes. Following the seizure, the subject's temperature was 100?F. He was brought to the ER for observation and discharged with a diagnosis of febrile seizure. This event is considered possibly related to immunization by both the investigator and the medical monitor for the sponsor because of the close temporal association of the event with the immunization.

10-0662: A 7.5-month-old female received three doses of 7VPnC on 10/21/96, 1/23/97, and 3/21/97. She was also immunized with Tetramune, OPV, and hepatitis B at the same visits. Three hours following the third dose, she developed a fever of 100.8?F and experienced a tonic seizure lasting approximately 2 minutes. Following an examination in the ER, the subject was discharged. Later that evening, she experienced another seizure, was seen in the ER where her urine was positive for *E. coli*. She was started on trimethoprim/sulfamethoxazole and on 3/22/97 was afebrile. She experienced another febrile seizure on 3/27/97 and was started on phenobarbital. The febrile seizures were thought most likely due to the UTI, but a possible causal relationship with investigational vaccine could not be ruled out by both the investigator and the medical monitor for the sponsor because of the temporal association.

12-0397: A 10-month-old male received three doses of 7VPnC on 7/8/96, 9/10/96, and 11/7/96. He also received Tetramune and OPV concurrently with all doses and hepatitis B vaccine with doses 1 and 2. On 11/8/96, the mother reported that the child had a rectal temperature of "109.48?F," and that the infant's body was jerking and that his eyes rolled back into his head. The episode lasted from 30 to 45 minutes. When his temperature was rechecked 2 hours later, it was 99.8?F. Based on the medical history provided, it is likely that the subject experienced a febrile seizure possibly related to immunization as assessed by both the investigator and the medical monitor. Although it is considered a serious event associated with a high fever, a temperature of109.48?F is most likely an inaccurate report. This subject was discontinued from the study at the request of the parents.

MnCC Subjects

04-0343: A 7-month-old Caucasian female with no significant past medical history prior to this episode, was immunized with MnCC on 3/23/96 and 5/17/96. She also received Tetramune and OPV concurrently. On 5/17/96, later in the afternoon, she experienced an episode of emesis and appeared pale with dusky lips. Her temperature was 101?F. She had a second episode of emesis followed by shaking of her head and left arm. This was associated with continuing fever. She was brought to the ER and a presumptive diagnosis of febrile seizure secondary to immunization was made. She was subsequently dropped from the study. Based on the history, this event is suggestive of a febrile seizure. The study vaccine was administered concurrently with Tetramune and OPV. Since the exact cause of the fever and resulting seizure cannot be determined, a possible relationship to study vaccine cannot be ruled out as assessed by the investigator and the medical monitor for the sponsor.

118-8: Acute Seizure Events Within 3 Days of Study Vaccine Resulting in Termination from the Study

7VPnC

15-0159: This 4 month old received 7VPnC, Tetramune and OPV on 1/16/96 and 3/11/96, and Hep B vaccine on 1/16/96. Approximately 45 minutes after receiving his second dose of vaccine, he experienced an episode of focal seizures, characterized by a blank stare, left eyelid twitching, and eye deviation. This was followed by bilateral clonic seizures lasting 3 minutes. He experienced another seizure 3 days later lasting 3 minutes. Head CT and EEG were unremarkable. He was dropped from the study, and the investigator considered these events to be possibly related to immunization.

MnCC

14-1265: This subject received a 3 doses of MnCC, with DTaP, and HbOC on 4/28/98. Two days after the 3rd dose, while afebrile and nursing, the infant stiffened and arms shook. The event last 1 minute followed by sleep. The event was diagnosed as probable seizure versus possible GE reflux or breath holding episode. The investigator coded the event as not being related to study vaccine, however the subject was dropped from further doses per study protocol.

13-0217: This subject was an 8-month old female who received 3 doses of MnCC, Tetramune, OPV and Hepatitis B. On the day of immunization, she developed a fever of 104.5?F, and experienced a grand mal seizure. The subject had a history of seizures and was diagnosed with epilepsy and discontinued from further study participation. The investigator considered this event not related to study vaccine, but possibly related to DTP vaccine.

118-8: Acute Seizure Events Within 3 Days of Study Vaccine Considered Possibly Vaccine Related By The Medical Monitor For The Sponsor

7VPnC

07-0843: This subject was a 6-month-old female who received three doses of 7VPnC on 9/30/96, 12/02/96, and 2/3/97, respectively. She also received Tetramune and OPV concurrently with each study vaccine, and received hepatitis B vaccine concurrently with the 1st and 3rd vaccinations. The subject was reported as having a tactile fever and irritability for 3 days following the third dose. On 2/6/97, 3 days after dose 3, she experienced 20 episodes of eye fluttering, and on 2/8/97 she experienced 10 such episodes. She was admitted to the hospital on 2/8/97. During the 2-day hospitalization, she experienced 4-5 more episodes. Physical and neurological evaluations were normal, and the EEG and CSF were unremarkable. The infant was discharged on 2/10/97 with the diagnoses of possible new onset seizures and meningitis ruled out. A possible causal relationship to study vaccine cannot be ruled out for these possible seizures because of the temporal association to the third dose of study vaccine.

08-0876: This subject was a 17-month-old male who was immunized with his 4th dose of 7VPnC on 10/7/97. He also received MMR and DTaP at the same visit. During the night of 10/9/97, more than 48 hours following immunization, the child developed a fever of 104.0?F and experienced a seizure lasting approximately 2 minutes. He was seen on 10/10/97 in the clinic where he presented with a temperature of 102.0?F. Physical exam was otherwise normal, CBC revealed a WBC of 2.9, and blood culture was negative. Diagnosis was viral syndrome. The investigator considered this event unrelated to immunization. Because of the temporal association, a possible relationship to study vaccine cannot be ruled out even though other routine pediatric vaccines were administered simultaneously.

118-8: Acute Seizure Events Within 3 Days of Study Vaccine Regardless of Investigator's Assessment of Relatedness to Study Vaccine

7VPnC

03-0588: This subject was vaccinated with the 4th dose of 7VPnC and DTP on June 27, 1997. The next day the subject became febrile to 105.3 (not specified how temperature was taken), and had 2 seizures. The subject was taken to urgent care at the local hospital where acetamenophen was given. Subject also had tenderness in left leg that interfered with movement until July 1, 1997. The investigator coded this event as being possibly related to study vaccination.

20-2576: This subject was a 2 month old male who was immunized with 7VPnC, Tetramune, and IPV on 3/10/98. Approximately 11 hours later the infant woke up from a nap and was noted to have his eyes deviated upwards. He had a weak cry and his body stiffened. At the ER his rectal temperature was 102.2?F. Four hours later the child had a 10 minute episode of leg and arm stiffness with eyes rolled back. Urine revealed pyuria and > 100,000 E. coli. Because of the underlying urinary tract infection, the event was considered unrelated to immunization.

Seizure Events in Supporting Studies

Study 118-12

7VPnC

Subject 4-25 was immunized with 7VPnC on 10/18/96. Four days after vaccination (10/22/96) the infant had seizure activity lasting about 3 minutes. The subject was seen in the ER and hospitalized for observation. EEG, CT Scan, and MRI were normal. The patient was discharged on 10/25/96 with a diagnosis of questionable new onset seizure disorder. There was no family history of seizure and no medications were given. The investigator judged a possible temporal relationship between vaccination and this event. Subject was taken off the study.

Subject (1-76) experienced seizures 1 day after a 3rd dose of vaccine that lasted 5-10 minutes and resulted in a 3 day hospitalization. The investigator judged the event only remotely related to vaccine.

Attachment B

A brief description of the supporting studies submitted to the PLA with summary findings of regulatory significance follows:

118-P16: Bridging Study Comparing the Safety and Immunogenicity of a Full-Scale Manufacturing Lot of Heptavalent Pneumococcal Conjugate Vaccine to a Pilot Plant 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 previous pilot scale lots, in terms of safety and immunogenicity. Such "bridging" of pilot to manufacturing scale is intended to evaluate whether the vaccine used in the efficacy trial is clinically equivalent to the vaccine intended for marketing. Compatibility of 7VPnC with simultaneously administered 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 "catch-up" immunizations of subjects randomized to the control group; inoculations were to occur at 7 and 9 months of age. Immunogenicity data from the "catch-up" portion of the study were not submitted with the application. At the time of the study report, it was described as ongoing.

Study Design and Conduct

Two manufacturing lots were compared to the pilot lot for immunogenicity. A "no vaccine control was included for safety comparisons. The manufacturing lots differed in type of aluminum phosphate used and type of vial.

D118-P16: Study design and subject allocation

Vaccine group	Vaccine lot (lower left thigh @ 2, 4, 6 months)	N planned (evaluable)	Concurrent vaccines & schedule (all groups)
1	Pilot scale lot (Adjuphos adjuvant; blow-molded vials) Lot# 7-5018-013A	175 (150)	DTaP (right thigh) @ 2, 4, 6 mos) HbOC (upper left thigh) @ 2, 4, 6 mos) IPV (left upper deltoid) @ 2, 4 mos) Hepatitis B (upper right thigh) @2, 6 mos)
2	Full-scale manufacturing lot "P" (Adjuphos adjuvant; Blow-molded vials) Lot# 7-5018-016A	175 (150)	
3	Full-scale manufacturing lot "N" (w/Lederle AlPO4 adjuvant; single dose tubing vials) Lot# 7-5029-002A	175 (150)	
4	Control group (no control vaccine or placebo)	125 (100)	

Infants randomized to the 7VPnC 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).

Monitored Parameters and Endpoints

Signs and symptoms of local and systemic reactions were recorded by caretakers for 3 days following each dose. Prompted local reactions included erythema, induration, and tenderness. The worse local reaction on each leg will be recorded. Prompted systemic reactions included irritability, change in sleep patterns, vomiting, diarrhea, hives, wheezing, change in skin tone, lethargic/limp, loss of consciousness and fever. Parents were also queried about whether fever medication was given.

IgG antibody concentration (GMC) to 7VPnC vaccine serotypes was measured before the first dose and one month after the third dose. Responses to polio and hepatitis B were assessed at 7 months of age.

The study had 2 co-primary immunogenicity endpoints for all 7 vaccine serotypes: 1) GMCs, and 2) response rates above defined threshold antibody concentrations. 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 D118-P12 and D118-P8).

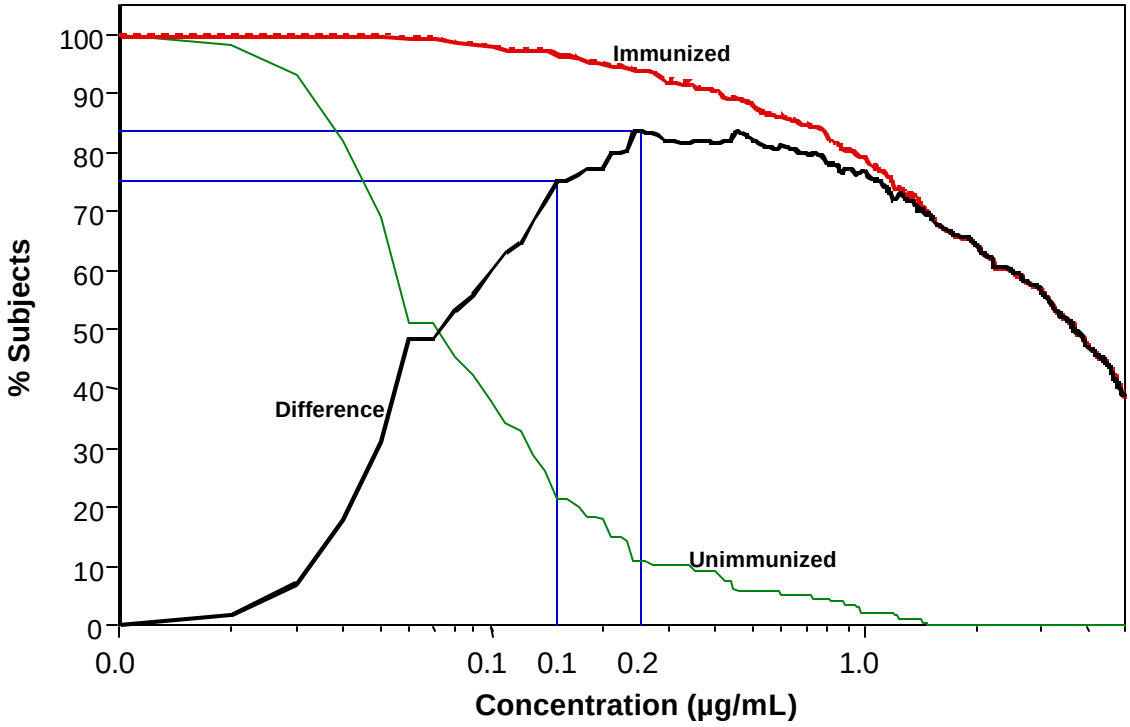
118-16: Threshold Serum Antibody Concentrations Used to Determine Percent Responders

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

The following figure illustrates the choice of threshold value for serotype 6B.

Maximal Difference in GMC:
Immunized and Unimmunized Populations
(Based on Combined Data from Study 118-8 and 118-12)

Serotype 6B



Pre-defined criteria demonstrating acceptable bridging were: 1) ? 2-fold difference in GMTs between pilot and manufacturing lot ; 2) ? 10% difference in response rate between pilot and manufacturing lot at the defined threshold values for each serotype. Thus, successful demonstration of bridging in this study required multiple comparisons (14), due to the multivalent nature of the vaccine. The sponsor identified the preferred manufacturing lot for initial comparisons as lot N.

Results: Bridging

Successful bridging of lot N to the pilot lot was demonstrated for all 7 serotypes, as shown in the following tables:

118-16: Comparisons of Post-dose 3 GMCs of Pneumococcal Antibodies

GMC (?g/mL)			Manuf. N Lot (Lederle Alum) versus Pilot Lot	
	Pilot Lot	Manuf. N Lot (Lederle Alum)	Ratio	90% Lower Limit*
Serotype	N=152	N=159		
4	1.53	2.03	1.33	1.11
6B	3.62	2.97	0.82	0.65
9V	1.45	1.18	0.82	0.69
14	5.83	4.64	0.80	0.64
18C	2.09	1.96	0.93	0.78
19F	1.91	1.91	1.00	0.84
23F	2.21	1.71	0.78	0.63

* The lower limit of the 90% confidence interval. The 90% confidence interval was derived based on t-distribution of the difference between the two lot groups in the mean of log concentrations.
Adapted from Table 6, page 46, Volume 29, Part IV of PLA.

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 (?g/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

Safety

Local and systemic reaction rates among infants receiving vaccine from the pilot lot, or the preferred manufacturing lot, were similar for each dose. The sponsor pooled reactogenicity data from all 3 lots for presentation in the clinical summary. The pooled reactogenicity data from this study provided an important source of safety data in the context of co-administration of DTaP, IPV, and Hep B vaccines (selected tables shown with discussion of safety, above).

One death occurred during the study, 47 days after the first dose of 7VPnC; reported cause of death was Sudden Infant Death Syndrome (SIDS).

No seizures or other significant or unusual adverse reactions were reported for any vaccine group.

Study Conclusions

Bridging of manufacturing scale to pilot scale based on pre-defined immunogenicity criteria was successfully demonstrated.

D118-P12: 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. Demonstration of consistency of production is required for vaccine licensure. Assessment of compatibility of 7VPnC with HbOC and DTaP when co-administered 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 the 7-valent conjugate pneumococcal vaccine 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.

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 mos) HibTITER (upper left thigh) @ 2, 4, 6 mos) OPV @ 2, 4, and 6 mos, or IPV right thigh or upper extremity @ 2 and 4 mos
2	Lot B 7-5018-010A	75	
3	Lot C 7-5018-008A	75	
4	Control group (no control vaccine or placebo administered)	75	

Subjects in the control group were re-enrolled and administered two doses of the 7VPnC vaccine at 7 and 9 months of age, with a boost at 15 - 18 months of age. Serological data from these subjects contribute to the data to support regimens for "catch-up" immunizations.

Parents were asked to monitor their children for local reactions (induration, erythema, and tenderness), systemic events (fussiness, drowsiness, decreased appetite, and temperature), and use of antipyretics on the day of each immunization and for three days following each immunization, and to record such information on a symptom report form.

Blood was collected from each subject prior to the first immunization (at 2 months of age), prior to the third immunization (at 6 months of age), and one month after the third dose (at 7 months of age). Serum samples were analyzed for IgG antibodies to all seven pneumococcal vaccine serotypes by standard ELISA methods. Sera were also analyzed for antibody responses to the components of DTaP and Hib-PRP.

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

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

The 2-fold, 90% CI criterion for GMCs was breeched 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). However, the magnitude of the differences in GMCs was not large, and no pattern suggestive of a failed lot of vaccine was evident. Moreover, with 21different comparisons in this analysis, the opportunities to exceed set are increased due to chance alone. Thus, the immunogenicity data provide evidence of lot-consistency.

118-12: Comparisons of GMCs of three 7VPnC 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

Sufficient blood samples were available after 2 and after 3 doses of vaccine to examine the time course of the antibody response to pneumococcal antigens. Responses to at least 2 vaccine serotypes (6B and 23F) following 2 doses of vaccine were not robust. The GMC for serotype 6B after 2 doses was similar to the pre-dose 1 GMCs for both the pooled 7VPnC groups.

118-12: Kinetics of Pneumococcal IgG Response GMC (? g/mL) and 95% CI

Serotype	Pooled 7VPnC Lots		
	Pre Dose 1 N = 211	Post Dose 2 N = 218	Post Dose 3 N = 211
4	0.10 (0.08, 0.12)	1.25 (1.10, 1.43)	1.59 (1.41, 1.79)
6B	**0.44** **(0.37, 0.53)**	**0.45** **(0.38, 0.54)**	2.63 (2.14, 3.24)
9V	0.22 (0.19, 0.26)	0.94 (0.82, 1.07)	1.56 (1.38, 1.77)
14	0.28 (0.22, 0.36)	2.36 (1.96, 2.84)	4.56 (3.88, 5.37)
18C	0.24 (0.20, 0.28)	0.99 (0.87, 1.12)	2.30 (2.03, 2.61)
19F	0.51 (0.42, 0.62)	0.93 (0.81, 1.07)	1.60 (1.40, 1.83)
23F	0.22 (0.18, 0.26)	0.38 (0.33, 0.45)	1.38 (1.16, 1.64)

Adapted from Table 13, page 41, Volume 27 of PLA.

Safety

The power of the present study to identify safety concerns and to describe the reactogenicity profile of 7VPnC was increased by pooling subjects who received one of the three 7VPnC lots for making comparisons to the control group. This approach is justified based on the similar immunogenicity and safety profiles of the three vaccine lots.

Vaccine reactogenicity data from this trial were discussed above.

Serious adverse events were reported for 18 (7%) of 256 subjects in the pooled 7VPnC groups and 4 (4.7%) of 84 subjects in the control group. The most common serious adverse event was bronchiolitis or RSV bronchiolitis, accounting for 9 of the 22 serious adverse events. No statistical analysis of serious significant events was provided or performed by the sponsor, due to the small number of events in each treatment group.

No deaths occurred during the study period.

Two seizures were recorded during the study period, both in subjects who received 7VPnC (discussed above, and see attachment A).

Another subject who received 7VPnC was terminated from the study for inconsolable crying on the day of receiving dose 2, considered by the investigator as moderate in severity, and possibly related to immunization.

118-12: Healthy Infants Previously Enrolled as Control Group were Immunized with Heptavalent Pneumococcal Conjugate Vaccine Administered at 7, 9, and 15-18 Months of Age

Amendments 2 and 4 to 118-12 provided for immunization of control subjects at 7 and 9 months of age, with a 4th dose to be administered at 15-18 months of age. This part of the trial, completed in December 1998, was intended to provide safety and immunogenicity data to support catch-up immunization schedules.

The trial was conducted open-label. Of the 54 control subjects enrolled, 38 were analyzed for immunogenicity after 2 doses, and 22 after a 3rd dose at 15-18 months.

Results of immunogenicity assessments are included in the summary table for Catch-up Immunizations.

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

This study of pentavalent pneumococcal conjugates was initiated in May, 1993 and completed in January, 1996. The purpose of the study was to determine the optimal formulation (oligosaccharide vs polysaccharide) and saccharide dose level (5, 2, or 0.5 ?g) of a vaccine for use in infants. The 5 vaccine serotypes studied were among those chosen for inclusion in Prevenar.

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 completed the primary series.
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.

Local and systemic symptoms during the first 3 days post-inoculation were recorded by the parent/guardian on symptom report forms that were returned to the investigator. Subjects were monitored for adverse events for the entire study duration (7 months).

Serum antibody concentration to each of the 5 serotypes contained in the vaccine were determined by ELISA, at 2, 4, 6, and 15 months of age, and one month after inoculations following the 6 and 15 month inoculations, and at 24 months of age. Antibody to Hib PRP was assessed for all groups. Antibodies to diphtheria, tetanus,

pertussis antigens (PT, pertactin, FHA, and Fim 2) were assessed only for the 2 ?g polysaccharide model, as this was the model chosen for subsequent development.

In the primary series, local reactions did not differ substantially among the 5-valent conjugates, and local reactions were no more common at the sites of 5-valent PnC than at the HbOC injection sites. Rates of systemic reactions among groups receiving the different 5-valent PnC conjugates were similar. However, when compared to the control group, fever ?38?C, and fever >39 ?C occurred with greater frequency among the 5-valent PnC treated groups with each dose of the primary series. The highest fever rates were reported for the 5?g PS conjugate: 39% with ?38?C; 9% with >39 ?C after the 3rd dose, compared to 19% and 0% for the control group. These data suggest that febrile reactions may be related to polysaccharide antigen content of the vaccine formulation.

No deaths were reported during the study period. No convulsions were reported within 3 days following any dose. One hypotonic-hyporesponsive episode was recorded after the 1st dose in a recipient of 2 ?g OS; this episode was considered probably related to study vaccine. Four episodes of high-pitched crying and six episodes of persistent crying were reported in the study vaccine groups; all were considered definitely or probably study vaccine related. No such episodes occurred in the control group. All occurred after the first dose, and none received subsequent study vaccines. No clear dose effect was apparent, although 2 infants with high-pitched cries received 5?g PS.

Results of the immunogenicity assessments supported the manufacturer's choice of the polysaccharide model and the 2 ?g polysaccharide dose. GMC's to Hib PRP post dose 3 were significantly enhanced by co-administration of all 5VPnC formulations, and particularly so for the chosen 2 ?g dose group. No interference with responses to diphtheria, tetanus, pertussis antigens were observed after the 3rd dose.

Pre and post dose sera for the 23V-polysaccharide booster were available for 16 to 20 subjects per group. Pre dose antibody concentrations were significantly lower for the control group, which did not receive 5VPnC with the primary series. Following boost, the 5VPnC treated groups achieved a substantial increase in GMCs to all serotypes. Little appreciable response to polysaccharide vaccine was observed among the "unprimed" control group, as might be expected among children under 2 years of age.

Study 92-05: Antibody Responses to Vaccine Serotypes following Administration of 23-Valent Polysaccharide Vaccine (PNU-IMUNE®23) as 4th Dose at 15-18 months of Age, GMCs (? g/mL) and 95% CI

Vaccine Serotype		P5VPnC (PS)			Control
		5 ?g N=18	2 ?g N=17	0.5 ?g N=20	N=16
6B	Pre	0.9 (0.5, 1.7)	1.4 (0.7, 3.2)	0.4 (0.2, 0.8)	0.1 (0.1, 0.3)
	Post	18.0 (9.1, 35.6)	16.6 (7.4, 37.4)	18.9 (9.5, 37.4)	0.2 (0.1, 0.6)
14	Pre	0.7 (0.5, 1.2)	0.6 (0.3, 1.5)	0.6 (03, 0.9)	0.0 (0.0, 0.0)
	Post	10.4 (5.5, 19.6)	11.4 (5.5, 23.5)	21.0 (11.3, 39.0)	0.0 (0.0, 0.1)
18C	Pre	0.3 (0.2, 0.5)	0.3 (0.2, 0.5)	0.2 (0.1, 0.2)	0.0 (0.0, 0.1)
	Post	4.5 (3.0, 6.9)	6.3 (3.6, 10.9)	10.3 (7.4, 14.4)	1.2 (0.6, 2.3)
19F	Pre	0.7 (0.5, 1.1)	1.1 (0.4, 2.7)	0.9 (0.3, 2.5)	0.1 (0.0, 0.2)
	Post	18.7 (9.6, 36.3)	29.6 (15.0, 58.3)	13.7 (9.2, 20.5)	0.2 (0.1, 0.4)
23F	Pre	0.5 (0.2, 1.0)	0.5 (0.2, 1.3)	0.4 (0.1, 0.9)	0.0 (0.0, 0.1)
	Post	7.0 (3.7, 13.2)	8.1 (3.5, 18.7)	4.2 (1.7, 10.4)	0.2 (0.1, 0.7)

Adapted from Table 6, page 51, Volume 1 of Clinical Section of PLA.
Conjugate oligosaccharide formulations data not shown for simplicity of presentation.

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 study was intended to demonstrate safety of 7VPnC in adults before initiation of studies in children and infants. Initiated in December 1994 and completed February 1995, this was the first clinical study conducted under U.S. IND using the 7-valent pneumococcal conjugate vaccine (7VPnC).

Thirty adult subjects, 18 to 60 years of age, were enrolled at a single center, and randomized to receive a single dose of either 7VPnC or 23-valent pneumococcal polysaccharide vaccine (PNU-IMUNE®23). Local and systemic reactions were assessed over the first 72 hours post inoculation through use of diary cards; data entry was solicited for specific local and systemic reactions. Blood samples were obtained before, and one month after inoculations, for assessment and comparison of antibody responses to polysaccharide antigens common to 7VPnC and the licensed pneumococcal polysaccharide vaccine.

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. No adverse events were reported during the 1-month post-immunization observation period.

Antibody responses to the 7 pneumococcal serotypes included in 7VPnC did not differ significantly in this small study. An exception was the response to serotype 23F, which was significantly greater in the conjugate vaccine group.

Study 118-02: Geometric Mean Concentrations (95% CI) Pre- and Post-Inoculation of 7VPnC and PNU-IMUNE23 in Adults

		7VPnC N=14		PNU-IMUNE23 N=15		p-value[1]
Serotype	Visit	GMC (?g/mL)	95% CI	GMC (?g/mL)	95% CI	
4	Pre	1.1	0.4, 3.3	0.6	0.3, 1.4	0.37
	Post	5.6	3.1, 10.3	2.9	1.2, 6.7	0.32
6B	Pre	3.7	1.8, 7.8	2.2	1.0, 4.5	0.26
	Post	22.7	12.1, 42.4	11.9	5.6, 25.1	0.37
9V	Pre	1.5	0.7, 3.3	1.5	0.8, 2.8	0.97
	Post	7.6	3.2, 18.1	8.5	4.4, 16.3	0.79
14	Pre	1.9	0.5, 7.0	1.1	0.3, 4.5	0.53
	Post	38.1	12.1, 119.6	14.1	3.4, 58.4	0.35
18C	Pre	1.9	1.0, 3.8	1.1	0.5, 2.7	0.33
	Post	20.3	8.7, 47.2	7.7	3.3, 18.0	0.18
19F	Pre	6.7	4.0, 11.3	4.8	2.2, 10.4	0.46
	Post	28.4	16.3, 49.4	16.0	9.2, 27.8	0.19
23F	Pre	1.1	0.5, 3.1	1.0	0.3, 2.9	0.82
	Post	34.1	14.1, 82.4	5.1	1.9, 13.2	**<0.01**

Reproduced from Table 3 of IND 5832, amendment 160, clinical study report

[1] GMTs compared suing analysis of covariance model; group comparisons adjusted for pre-immunization log-titers (Sponsor's analysis)

Study 118-03: A Randomized Double-Blind, Trial of the Safety and Immunogenicity of Heptavalent (4, 6B, 9V, 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 polysaccharide C vaccine (MnCC) as a control for 7VPnC. Safety data from the MnCC served to support continued use of MnCC as a control in subsequent phase II and III studies. The 4-study conducted from February 1995 through June 1997, at 4 study sites. The original protocol was amended to allow for open-label study of the "booster 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.

Subjects were actively monitored for local and systemic reactions and antipyretic use for 3 days after each dose. Adverse events included clinic visits within 7 days of a dose, hospitalizations during the 24-month study period, or any event resulting in study termination.

Blood samples were obtained for IgG antibody concentration (ELISA) assessments pre dose 1, pre and post doses 3 and 4, and at 24 months of age. Opsonophagocytic antibody for the 7 pneumococcal serotypes was also assessed.

Immunogenicity

After the primary series, GMCs ranged from 0.98 ?g/mL for serotype 9V, to 3.48 ?g/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 ?g/mL) and 18C (0.22 ?g/mL). After the 4th dose, GMCs for each serotype exceeded 2.0 ?g/mL. Duration of antibody levels assessed at 24 months of age were not included in the PLA.

118-03: GMC (?g/mL) of Pneumococcal Antibodies Prior to and Following the Primary Series and 4th Dose

Serotype	4	6B	9V	14	18C	19F	23F
Pre dose 1 (N=90)	0.05	0.31	0.12	0.18	0.09	0.28	0.11
Post dose 3 (N=90)	1.36	1.37	0.98	3.48	1.24	3.45	1.80
Pre dose 4 (N=55)	**0.20**	0.68	0.37	1.77	**0.22**	0.76	0.35
Post dose 4 (N=55)	2.32	8.13	3.75	9.33	3.01	4.50	5.11

Adapted from Tables, 6, 7, and 9, pages 50, 51, 57 Volume 7, Part IV of PLA

Safety

No deaths occurred during the study period. Five 7VPnC recipients were hospitalized, none for events within 1 week of vaccinations or for events considered related to vaccine by investigators. One subject in the 7VPnC group had onset of a seizure disorder 8 months after the 4th dose.

Seven subjects were withdrawn from the study due significant adverse events: 4 7VPnC recipients and 3 MnCC recipients. In the 7VPnC group, 3 infants were discontinued for persistent or unusual cry, and one for an apparent hypotonic-hyporesponsive episode accompanied by urticaria.

The sponsor concluded that there were no trends in adverse events that were clinically significant for either study vaccine.

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 was a phase II study 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.

The main 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; 2) compatibility of 7VPnC with concurrent immunizations.

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.

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, which was injected into the left thigh muscle. All subjects received DTaP and HbOC vaccines at 2, 4 and 6 months of age into the anterior thigh muscle of the right leg, and a dose of OPV at 2, 4 and 6 months of age. 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.

Local and systemic reactions during the first 48 hours post dose were assessed by parents or caretakers and recorded on diary cards. Systemic events and body temperature were recorded daily on days 0, 1, and 2 post-immunization, and at any time within 14 days post-immunization. Data was collected by telephone interviews at 48-72 hours and again at 10-14 days.

Adverse events included hospitalizations within 60 days and emergency room visit within 30 days of vaccination, and any event resulting in study termination.

Blood samples were obtained immediately prior to the first dose of vaccine and the 4th dose, and one month following the 3rd (7 months) and 4th (13 months) doses. IgG antibody concentration (GMC) and response rates at 0.15 and 0.5 ?g/mL serum levels to 7VPnC vaccine serotypes were assessed.

A substantial decline in % of subjects achieving 0.50 ?g/mL was observed between dose 3 and dose 4 for some serotypes; only 15% of subjects were able to maintain 0.50 ?g/mL of serum antibody for serotype 4 until the 4th dose. Although the serum antibody concentration associated with protection from disease is unknown, these data indicate that protection against disease afforded by 3 doses of 7VPnC may vary

considerably with serotype. It is noteworthy that no cases of invasive disease due to serotype 4 were observed in the efficacy trial in either vaccine group; the ability of 7VPnC to protect against invasive disease due to serotype 4 may not have been effectively tested.

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. Two additional events, both in the 7VPnC group, resulted in study termination: inconsolable crying 1 day after 1st dose, and fever, fussiness, vomiting 2 days after dose 2. This latter event resulted in hospitalization, but investigators did not consider the event related to vaccine.

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.

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.

Immunogenicity results were categorized by age at enrollment: 12-17 months and 18-23 months. Immunogenicity results for the two lots were similar, so they were combined for inclusion in the tables for “Catch-Up Immunizations”.

Safety and immunogenicity data were presented by age at vaccinations: 12-17 months and 18-23 months. Local reactions occurred with similar frequency in the two age groups. More severe, clinically significant, local reactions were uncommon.

Systemic reactions occurred more commonly in the younger age group. Fever ?38.0?C was reported by 52% (13 of 25) subjects in the 12-17 month age group, vs. 24% (8 of 33) in the 18-23 age group. No subject in either group reported fever ?39?. Fussiness, drowsiness, decreased appetite and antipyretic use were all reported more frequently in the younger age group.

No serious or unusual adverse events were reported.

Study 118-15: A Double-Blinded, Controlled Study of the Efficacy, Immunogenicity, Safety and Tolerability, and Effectiveness of a Pneumococcal Conjugate Vaccine Containing Seven Serotypes (6B, 14, 19F, 23F, 18C, 4 and 9V) Compared to a Control Meningococcal C Vaccine in Navajo and Apache Indian Infants

The primary objective of the study is to demonstrate effectiveness of 7VPnC in preventing invasive pneumococcal disease occurring in infants and toddlers. Subjects received either 7VPnC or meningococcal C conjugate (MnCC). Randomization was 1:1 for 40 allocation units based on geographical criteria. All subjects in a unit receive the same vaccine. Infants 6 weeks to < 7 months of age receive 3 doses at least 1 month apart and a 4th dose at 12-15 months. Infants 7 to 12 months of age receive 2 doses at least 1 month apart and a 3rd dose at 12-15 months. Infants 12 to 24 months of age receive 2 doses, approximately 2 months apart. Total planned enrollment is 18,000 children. The study is ongoing.

Only subjects who received the first vaccination after 12 months of age and who consented to participate in a serology subset were included in the data submitted to the PLA to support catch-up schedules. There were 204 subjects available at the time of the analysis. Results are shown in the summary table for catch-up immunizations.

No safety data were provided.

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 9VPnC vaccines. 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.

Antibody responses to measles, mumps and rubella were determined by ELISA methods. Seroconversion was defined as a change from seronegative to seropositive or a 4-fold rise in antibody titer.

No comparative immunogenicity data (7VPnC vs. 9VPnC) were provided in the PLA. Only data intended to support concurrent immunization of 7VPNC with MMR were provided. Because the MMR concurrent immunization data was obtained using 9VPnC at the 4th dose, these data may not be adequate to support concurrent immunization of MMR with Prevenar.

Study 124-501: A Randomized, Blinded, Controlled Trial Evaluating the Effect of Immunization with 9-valent Pneumococcal Conjugate Vaccine on Nasopharyngeal Carriage of S. pneumoniae in Israeli Toddlers Enrolled in Day Care Centers

Immunogenicity data from this study were intended to support catch-up vaccination schedules. Subjects age 12-17 months were randomized 1:1 to receive two injections 2-3 months apart of either 9VPnC or MnCC. Subjects age 18-35 months were randomized 1:1 to receive a single injection of 9VPnC or MnCC.

The 9-valent formulation used in this study contains pneumococcal conjugates for all serotypes represented in the 7-valent formulation, plus serotypes 1 and 5. The 9-valent vaccine is reconstituted from a lyophylized preparation, while Prevenar is a liquid formulation. Safety and immunogenicity data for the 9-valent formulation may not be directly applicable to Prevenar.

Attachment C

Preliminary Review Comments Regarding Otitis Media Analysis

FDA's review of the otitis media analysis from the NCKP study has not been completed, and VRBPAC members will not be asked to comment on these data at the meeting. Furthermore, data from the Finnish otitis media efficacy trial was only recently announced and have not yet been submitted to the license application. Unlike the NCKP trial, the Finnish otitis media trial design utilized tympanocentesis, allowing a pneumococcal serotype specific diagnosis. The sponsor projects that the QCed Finnish trial data will be submitted to a license application in early 2000.

Some preliminary review comments based on the sponsor's analysis of the NCKP trial follow.

Otitis media analysis overview

The effect of immunization on the occurrence of acute otitis media was examined as a secondary endpoint in the NCKP efficacy study. Cases of otitis media were identified through the computerized databases of Kaiser Permanente. Identification of an "episode" of acute otitis media (AOM) was made when a Kaiser clinician checked off a box on a patient encounter form, provided no other visits for otitis media had occurred in the preceding 21 days. This latter provision was intended to identify discrete episodes of otitis media, by reducing the number of clinic visits that were more likely to be follow-up visits. A separate check-off box was provided for otitis media with effusion; visits checked as otitis media with effusion did not contribute to the AOM analysis. Uniform diagnostic criteria of acute otitis media were not specified; diagnoses were based on normal clinical practice.

The follow-up period for all cases in the otitis media analysis ended on April 30, 1998. For the per-protocol analysis, follow-up began 14 days after the 3rd dose. In the intent-to-treat analysis, follow-up began after each randomized subject received the first dose of vaccine and continued until April 30, 1998.

The final analysis plan differed from the analysis described in the original protocol. One primary endpoint and 6 secondary otitis media endpoints were specified in a revised analysis plan, as agreed upon by representatives of NCKP, Wyeth-Lederle, and FDA/CBER, in November 1998, prior to unblinding of the otitis media data set.

A total of 52,789 AOM episodes had been identified at the time the otitis media database was locked on April 30, 1998. The sponsor's analyses are summarized below:

Summary of Vaccine Effect on Acute Otitis Media

Acute Otitis Media Outcome	Per protocol Analysis		Intent-to-Treat Analysis	
	Est. Risk Reduction	(95% Conf. Interval)	Est. Risk Reduction	(95% Conf. Interval)
All AOM Episodes - Primary Outcome	7.0%	(4.1%, 9.7%)	6.4%	(3.9%, 8.7%)
First AOM Episode	5.4%	(2.3%, 8.4%)	4.9%	(2.3%, 7.5%)
Frequent AOM	9.5%	(3.2%, 15.3%)	9.2%	(4.3%, 13.9%)
Tympanostomy Tube Placement	20.3%	(1.8%, 35.4%)	20.6%	(4.0%, 34.3%)
All AOM Visits	8.9%	(5.8%, 11.8%)	7.8%	(5.2%, 10.5%)
Ruptured Ear Drum with Vaccine Serotype Isolates	55.6%	(-59.3%, 90.0%)	57.1%	(-18.7%, 86.5%)

Adapted from Table 10 of the Integrated Clinical Summary, Volume 33, Part IV of PLA.

Primary acute otitis media endpoint: Overall incidence of acute otitis media episodes

Overall incidence of acute otitis media episodes (new visits) during per protocol follow-up was chosen as the primary otitis media endpoint. Results of secondary analyses were to be considered exploratory if efficacy for the primary endpoint was not demonstrated. Choice of overall incidence of AOM episodes as the primary endpoint was based on its inclusiveness of all discrete episodes of AOM, whether recurrent or first episode. Overall incidence of AOM in the 7VPnC group was reduced by 7% (95% CI 4.1%, 9.7%); results of the intent-to-treat analysis were similar.

Secondary otitis media endpoints

Six secondary acute otitis media endpoints were specified on a per protocol basis. In addition, all otitis media endpoints were analyzed using the principle of intent-to-treat.

Risk of at least one episode

Risk of first episode of acute otitis media, or the proportion of children with any AOM episode, was the primary otitis media endpoint in the original protocol. Risk of first episode remained among the secondary endpoints in the revised analysis plan. Reduction in the risk of first episode was 5.4% (95% CI: 2.3% to 8.4%). Results of the intent-to-treat analysis were consistent with the per protocol analysis.

Frequent otitis media

Frequent otitis media was defined as 3 episodes (new visits) within 6 months, or 4 episodes within a 1-year period of follow-up. A total of 1,647 (13.9%) children in

the 7VPnC group met the definition of frequent acute otitis media, compared to 1,809 (15.2%) children in the MnCC group. The risk reduction for frequent otitis media was 9.5% (95% CI: 3.2% ,15.3%). Results of the intent-to-treat analysis were consistent with the per protocol analysis.

Two alternative definitions of frequent acute otitis media were used in exploratory analyses:

- 4 episodes (new visits) within 6 months, or 5 episodes within 12 months of follow-up.
- 5 episodes within 6 months, or 6 episodes within 12 months of follow-up.

In the per protocol analysis, risk reduction for 4 episodes in 6 months, or 5 episodes in 12 months was 11.9% (95% CI: 1.6%, 21.1%).

For 5 episodes/6 months or 6 episodes/12 months, risk reduction was 22.8% (95% CI: 6.7%, 36.2%)

The apparent trend toward increased effectiveness with more frequent episodes was less clear for the intent-to-treat analysis.

Tympanostomy tube placement

A total of 157 (1.3%) children in the 7VPnC group had tympanostomy tubes placed during the per-protocol follow-up, compared to 198 (1.7%) children in the MnCC group. The reduction in tube placement was 20.3% (95% CI: 1.8% to 35.4%). Results of the intent-to-treat analysis were consistent with the per protocol analysis.

Overall incidence of otitis media visits ("All Visits")

A total of 22,478 clinic visits for acute otitis media were recorded in the 7VPnC group during the per-protocol follow-up period, compared to 24,914 visits in the MnCC group. For this endpoint, a subject may be counted multiple times for the same otitis media episode, as all follow-up visits for AOM would also be included in the analysis.

Ruptured eardrums due to pneumococcal infection

Although the otitis media database was "locked" April 30, 1998, cases of ruptured tympanic membranes were analyzed by the sponsor for data accumulated through 2 later time points. Results at the time of the planned analysis were not presented in the PLA. Data for ruptured membranes presented in the table above, apply to cases accrued through November 6, 1998. Although not prospectively defined, this analysis took place prior to unblinding of the otitis media dataset. Of 13 cases of ruptured eardrums due to vaccine serotypes recorded during the per-protocol follow-up period, 4 were in the 7VPnC group and

9 in the MnCC group. The estimate of risk reduction was 55.6% (95% CI: –59.3% to 90%).

An additional analysis was conducted of cases accrued through March 24, 1999; 16 cases of ruptured eardrums of vaccine serotype accrued in the per protocol analysis; 4 were in the 7VPnC group. For the per-protocol population, risk of tympanic membrane rupture was reduced by 66.7% (95% CI –10%, 92.2%).

Analyses of cases of ruptured eardrums accrued after April 30, 1998, were not prospectively defined. Therefore, these analyses should be considered exploratory.

For data collected through March 24, 1999, vaccine serotypes accounted for 79.3% (23/29) of all isolates from ruptured eardrums. The most common isolate was serotype 19F, which accounted for 65.2% (15/23) of all vaccine serotype isolates from ruptured eardrums, and all 6 isolates due to vaccine serotype in the 7VPnC group.

Sponsor's commentary of effect of 7VPnC on acute otitis media

The sponsor acknowledges that the "check off" system for recording episodes of acute otitis media on the patient encounter form likely results in diagnoses which are not highly specific. The estimate of vaccine efficacy would be expected to be lower than an estimate based on a more specific diagnosis. Culture data obtained from tympanocentesis in a Finnish otitis media trial (not submitted with the PLA) were used to estimate the proportion of acute otitis media due to pneumococcus in the NCKP trial. Making some assumptions, the sponsor proposed that a reasonable estimate of vaccine efficacy against acute otitis media caused by vaccine serotypes could be 80%.

Among the assumptions are:

1) 50% of episodes reported as acute otitis media in the NCKP trial would meet a clinical case definition in the Finnish trial.
2) 59% of clinical otitis media is caused by bacteria (data from the Finnish trial)
3) 41% of bacterial otitis media is caused by pneumococcus (data from Finnish trial)
4) 66% of pneumococcal otitis media is due to vaccine serotypes

It then follows that:
100% (reported AOM) * 0.5 (clinical AOM) * 0.59 (bacterial AOM) * 0.41 (pneumococcal AOM) * 0.66 (vaccine serotypes) * **0.8** (presumed vaccine efficacy) = 6% (approximate demonstrated efficacy in Kaiser trial).

FDA Review Comments Regarding Sponsor's Otitis Media Analysis

The assumptions made in the sponsor's commentary appear to be reasonable, and lead one to conclude that true vaccine efficacy for AOM due to vaccine serotype is likely much greater than was demonstrated in the NCKP trial for AOM due to all causes. However, other reasonable assumptions would lead to different estimates.

Criteria used to diagnose acute otitis media in the Finnish trial are similar to diagnostic criteria used in the U.S., i.e., abnormal tympanic membrane (in regard to color, position, mobility), with signs or symptoms of acute infection, such as fever, ear ache, irritability. Therefore, the initial assumption that only 50% of AOM reported by Kaiser clinicians would qualify as clinical episodes of AOM in Finland, may be spuriously low. For the alternative estimate below, an assumption of 80% diagnostic concordance was used.

In the sponsor's commentary, the proportion of clinical otitis media due to bacterial causes (59%), and proportion of bacterial AOM due to pneumococcus (41%) are based on data from the Finnish trial, in which tympanocentesis was performed for all children diagnosed with clinical AOM. These data have not yet been submitted to the license application. However, these estimates appear reasonable, and may well be applicable to children in northern California.

The assumption that 66% of pneumococcal AOM is due to vaccine serotypes is also taken from the Finnish data. However, data are available from the NCKP trial showing that 85% of all invasive isolates were of vaccine serotype. Of isolates from ruptured tympanic membranes in the NCKP study, 79% were of vaccine serotype. Based on these data, one might choose 80% to estimate the proportion due to vaccine serotype.

Using these alternative assumptions, which appear equally reasonable:

100% * **0.8** (clinical AOM) * 0.59 (bacterial causes) * 0.41 (pneumococcal serotype) * **0.8** (vaccine serotype) * vaccine efficacy = 6%

Under these assumptions: Vaccine Efficacy = 39%.

Labeling issues

The Indications and Usage section of the proposed label includes the following language:

Prevenar is indicated for active immunization of infants and children beginning as early as 6 weeks of age for:

· Reduction in the incidence of ear tube placement associated with frequent otitis media

The proposed indication does not reflect the primary otitis media endpoint, overall incidence of acute otitis media. Nevertheless, ear tube placement is an outcome that has appeal for being clearly defined and easily understood. Ear tube placement was also the endpoint which showed the greatest point estimate of efficacy in the per protocol analysis, 20.3%. However, the 95% confidence intervals for this outcome were wide, with a lower bound of only 1.8% in the per protocol analysis.

Should Prevenar be licensed based on available data from the NCKP study, the following points weigh against including the proposed otitis media **indication** in the vaccine label:

1) Otitis media was not the primary outcome of the efficacy trial.
2) The trial was not specifically designed to identify cases of acute otitis media using prospectively defined diagnostic criteria.
3) Ear tube placement was one of a number of otitis media endpoints, and was not prospectively designated as one of the two most important secondary endpoints for otitis media.
4) Criteria for inserting ear tubes were not prospectively defined.
5) Despite demonstration of statistical significance, there is much uncertainty around the estimate of risk reduction for ear tube placement.
6) Results of a clinical trial (Finnish) specifically designed to evaluate efficacy of 7VPnC to protect against otitis media due to vaccine serotype will be available in the near future.
7) The estimate of efficacy for the primary otitis media endpoint, while statistically significant, was low (7%) for a preventive vaccine indication. A vaccine indication based on the demonstrated level of efficacy may be misleading to the public.

In favor of including a description of otitis media results in the clinical pharmacology section of the vaccine label are the following points:

1) This is the first vaccine for which a preventive effect against acute otitis media cases appears to have been demonstrated.
2) A balanced presentation of the AOM results would provide clinicians and the public a basis for realistic expectations of the effects of Prevenar on rates of AOM.

3) The preventive effects of Prevenar on AOM may enter into the risk/benefit assessment when considering use of the vaccine.

The Clinical Pharmacology section of the proposed label includes a tabular summary of efficacy of the 7VPnC to protect against otitis media, which is reproduced below:

Reduction in Otitis Media After Immunization with Prevenar Against Otitis Media

	Per Protocol N=23,746		ITT N=34,146	
	% Reduction	95 % CI	% Reduction	95 % CI
All episodes OM	7.0	4.1, 9.7	6.4	3.9, 8.7
All OM visits	8.9	5.8, 11.8	7.8	5.2, 10.5
Frequent OM				
3 episodes/6mo; 4/yr	9.5	3.2, 15.3	9.2	4.3, 13.9
4 epidoses/6mo; 5/yr	11.9	1.6, 21.1	10.0	2.4, 17.0
5 episodes/6mo; 6/yr	22.8	6.7, 36.2	12.3	0.0, 23.2
Ear Tube placement	20.3	1.8, 35.4	20.6	4.0, 34.3

Risk of first episode of acute otitis media was identified as the primary otitis media endpoint in the original protocol, and remained among the secondary endpoints. For this endpoint, children could be counted only once as having otitis media. "First episode" may more accurately reflect vaccine benefit for the typical child, as it is not driven by the subset of children who were diagnosed multiple times as having AOM. This endpoint is informative and would provide balance to the vaccine label.

The alternative definitions of frequent AOM were not prospectively defined, and are likely to be highly correlated with the prospectively defined endpoint of frequent AOM. Typically, such exploratory analyses are not described in product labels. Moreover, ITT results are not consistent with per protocol results for the case definition of 5 episodes/6mos, 6/yr.

Prevention of visits for otitis media is listed 2nd in the summary table of the proposed label. While this endpoint may have medico-economic implications, it is not descriptive of clinical outcomes. Prevention of health care visits has not been the basis of previous vaccine licensures. The description of this endpoint may not be appropriate for a vaccine label.

FDA clinical and statistical review of the otitis media data is ongoing.

Attachment D

Preliminary Review Comments Regarding Pneumonia Analysis

FDA's review of the pneumonia analysis has not been completed, and VRBPAC members will not be asked to comment on these data at the meeting. However, some preliminary review comments based on the sponsor's analysis are presented.

The effectiveness of 7VPnC in preventing the occurrence of pneumonia was examined as a tertiary endpoint in the NCKP efficacy trial. Cases of pneumonia were identified retrospectively through the computerized databases of Kaiser Permanente. Identification of an episode of clinical pneumonia was made when a Kaiser clinician checked off a box on an ER or outpatient clinic encounter form, and when the episode was more than 30 days from any prior pneumonia diagnosis. X-rays obtained within –1 to +5 days of the clinical diagnosis were used to identify cases for the primary and secondary analyses.

Follow-up for cases in the pneumonia analysis ended on April 30, 1998. In the per-protocol analysis, follow-up began 14 days after the 3rd dose was administered. In the intent-to-treat analysis, follow-up began after each randomized subject received the first dose and continued until April 30, 1998.

Primary pneumonia endpoint: Clear consolidation

The primary pneumonia endpoint was clear consolidation, based on the readings of two study radiologists. Clear consolidation was defined as an area of opacity 2.5 cm or greater at longest diameter with well defined edges. Investigators' selection of clear consolidation as the primary pneumonia endpoint was based on the following rationale provided in a January 19, 1999 submission to FDA/CBER:

1) Consolidation is "...reasonably reproducibly detected among observers (kappas of 0.57 and 0.79, references provided)."
2) Consolidation is more frequently associated with bacterial pneumonia than other causes of pneumonia. "Classic" (single lobe with well-defined alveolar consolidation) radiologic findings remain less likely to have viral or atypical pneumonia.
3) Utility of clear consolidation endpoint was previously demonstrated for a Hib-conjugate vaccine in a Gambian study.

Results of the primary pneumonia endpoint analysis, as agreed upon between FDA and the sponsor, were not provided in the PLA. In an addendum to the clinical summary, the following explanation was provided explaining why the prospectively-defined primary pneumonia analysis was abandoned: "As the readings progressed, it became apparent that this definition was not specific enough to allow good agreement between the radiologists. Furthermore, an additional set of 53 films with abnormal radiology department reports, but read as normal by the

pediatric investigators, was inadvertently not provided to the study radiologists for reading with the original set, introducing a procedural irregularity."

A preliminary analysis of the "pneumonia with clear consolidation" endpoint was presented during a pre-PLA submission meeting between representatives of FDA and Wyeth-Lederle (May 6, 1999). These analyses indicated that vaccination with 7VPnC provided no statistically significant preventive effect on pneumonia with clear consolidation. That analysis was not included in the PLA.

Secondary pneumonia endpoint: Clinical pneumonia with abnormal chest X-ray

Clinical pneumonia with chest X-ray read as abnormal by the on-site clinical radiologist was prospectively defined as the sole secondary pneumonia endpoint. A chest X-ray could be read as abnormal on the basis of an effusion, an infiltrate, or consolidation. Although clearly identified in the pneumonia analysis plan as the sole secondary pneumonia endpoint, clinical pneumonia with abnormal chest X-ray was described in the clinical study report and in the integrated summary of the PLA as the primary pneumonia endpoint.

A total of 45 cases were identified among 11,849 children in the 7VPnC group and 70 cases among 11,897 children in the MnCC group in the per-protocol population through April 30, 1998. Vaccine effectiveness was 35% (95% CI 4.2, 56.4) in the sponsor's analysis.

In the intent-to-treat analysis, 61 cases were recorded in the 7VPnC group and 91 cases in the MnCC group. Vaccine effectiveness was 33% (95% CI 6.2, 52.3) in the sponsor's analysis.

Ancillary endpoints

FDA/CBER had requested that all episodes of clinical pneumonia, and all episodes of clinical pneumonia with chest X-ray taken (irrespective of X-ray reading), be analyzed to examine consistency of the results. It was not FDA/CBER's intention or understanding that these outcomes be considered endpoints for the purpose of efficacy claims. In the final analysis plan submitted to FDA on March 3, 1999, prior to unblinding, these analyses were not among the prospectively defined study endpoints.

In the clinical study report, episodes of clinical pneumonia and all episodes of clinical pneumonia with chest X-ray taken were identified as secondary endpoints. The proposed label submitted with the PLA includes a table, shown below, in which results of the analyses of clinical pneumonia and clinical pneumonia with chest X-ray are shown.

Table 4

Reduction in Pneumonia After Immunization With Prevenar

Clinical Pneumonia	Per Protocol N=23,746		Intent-to-Treat N=34,146	
	% Reduction	95% CI	% Reduction	95% CI
Any	11	-1, 21	10	0.1, 20
With Any Chest X-Ray	12	-2, 25	13	0.2, 24
With Abnormal Chest X-Ray	35	4, 56	32	5, 52

Clinical pneumonia with chest X-ray taken

In the per-protocol analysis of clinical pneumonia with chest X-ray taken, 323 cases were recorded for the 7VPnC group and 372 cases were recorded for the MnCC group. The estimate of vaccine effectiveness was 12% (95% CI –2.2, 24.7).

In the intent-to-treat analysis of clinical pneumonia with chest X-ray taken, 393 cases were recorded for the 7VPnC group and 456 cases for the MnCC group. The estimate of vaccine effectiveness was 13% (95% CI 0.2, 24.1) in the sponsor's analysis.

All clinical pneumonia

During the per protocol follow-up, 500 episodes of clinical pneumonia were identified in the 7VPnC group, and 566 in the MnCC group. The estimate of vaccine effectiveness in preventing clinical pneumonia was 11 % (95% CI –0.8, 21.1).

In the intent-to-treat analysis, 615 episodes of clinical pneumonia were reported for the 7VPnC group, and 694 in the MnCC group. The estimate of vaccine effectiveness was 10% (95% CI 0.10, 19.8) in the sponsor's analysis.

Review comments regarding the pneumonia analysis

Information about pneumonia was collected in the Kaiser patient database as part of routine data collection. Clinicians were not provided a common set of diagnostic criteria on which to base a diagnosis of clinical pneumonia. No clinical guidelines were utilized to distinguish cases of probable bacterial from probable viral pneumonia. Upper respiratory secretions were not uniformly collected for cultures or rapid diagnostic tests to rule out other pathogens, nor were results of such tests considered in the diagnostic algorithm. Likewise, results of blood cultures were not considered in the diagnosis of pneumonia.

As the investigators pointed out in their rationale for choosing the primary pneumonia endpoint, consolidation on chest X-ray had been shown to be associated with bacterial causes more frequently than with viral causes. Pneumonia with

consolidation was therefore thought to be an endpoint with high specificity for pneumococcus, and represented the most likely scenario for demonstrating vaccine efficacy for pneumonia in the infant and toddler age groups. **However, this endpoint was abandoned, ostensibly due to procedural problems.** Preliminary results had shown no statistically significant treatment effect. Results of a well-conducted analysis of this data set could add importantly to the knowledge base about infant pneumonia and may be useful in designing future trials.

Labeling issues

The Indications and Usage section of the proposed label includes the following language:

The vaccine is indicated for active immunization of infants and children beginning as early as 6 weeks of age for:

· Reduction in the incidence of clinical pneumonia with abnormal chest x-ray

Should Prevenar be licensed, the following points weigh against allowing the proposed **indication** for prevention of clinical pneumonia with abnormal chest X-ray:

1) Pneumonia endpoints were tertiary outcomes in the efficacy trial.
2) The efficacy trial was not designed to identify cases of clinical pneumonia using prospectively defined diagnostic criteria.
3) Investigators failed to demonstrate efficacy for the primary pneumonia endpoint.
4) The estimate of efficacy for the secondary pneumonia endpoint (35%), while statistically significant, was relatively low for a preventive vaccine; the lower bound of the 95% confidence interval was only 4% in the per protocol analysis.

In favor of including a description of the pneumonia results in the vaccine label are the following points:

1) Prevention of pneumonia due to pneumococcus may be greater than was demonstrated for the secondary endpoint, which encompasses pneumonia due to all etiologies.
2) The secondary endpoint reflects normal clinical practice. As such, this endpoint provides a crude, but "real world" estimate of vaccine efficacy against pneumonia.
3) The preventive effects of Prevenar on pneumonia endpoints may enter into the risk/benefit assessment when considering use of the vaccine.

FDA clinical and statistical review of the pneumonia efficacy data is ongoing.