Urinary tract infections: ER visits for urinary tract infections within 30 days of a vaccine dose were significantly more frequent in the 7VPnC group, but only after the 4th dose.

Poisoning/Ingestions: ER visits for poisoning/ingestions were increased in the 7VPnC group, for the 3 (5 cases in 7VPnC group vs. 0 in MnCC group) and 14 day (7 cases in 7VPnC group vs. 1 in MnCC group) intervals, when all doses were combined.

> **Note:** FDA/CBER sought clarification of the type of ingestions to rule out possible overdoses of antipyretics taken in response to a vaccine reaction. This was addressed in a submission dated 12/22/99. Only one ER visit for ingestion due to antipyretic use occurred in the 7VPnC group during these intervals; the visit was for parental concern about the dose taken, rather than a true overdose.

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

10.5.1.4 Outpatient Clinic Visits

Outpatient visits for selected adverse events (allergic reactions, hives, asthma, wheezing, and seizure events) were analyzed over intervals of 3, 14 and 30 days after vaccine doses. Comparisons between treatment grops of office visit rates were made by diagnosis across dose series and by concomitant pertussis containing vaccine, in a manner similar to that used to compare hospitalization and ER rates.

Increased rates of clinic visit for seizures within 30 days of a vaccine dose for all doses combined, and for asthma within 3 days after the 4th dose only, differed significantly, but were more frequent in the MnCC group.

10.5.1.5 Serious Adverse Events Considered by Investigators to be 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; 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 concomitant DTP-HbOC.

Table 29: Efficacy Study 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.

10.5.1.6 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.

Table 30: Efficacy Study 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.

Comment: Examination of the adverse events that resulted in withdrawal of subjects from study participation does not reveal any particular diagnosis that raises safety concerns regarding the 7VPnC vaccine.

10.5.1.7 Selected chronic and immune mediated diseases in NCKP efficacy study (118-8)

Serious adverse events resulting in hospitalizations and occurring more than 60 days after vaccinations were not systematically reported in the efficacy trial. FDA requested that certain medical conditions that might plausibly be related to an immune-mediated pathologic process, be tabulated and reported, regardless of temporal relationship to vaccine administration. These data were submitted as supplemental to the PLA on October 19, 1999, and were presented by Dr. Black of NCKP at the VRBPAC.

Table 30: Efficacy Study 118-8
Hospitalizations[a] for Selected Discharge Diagnoses among Children with No Hospitalizations for these Diagnoses Prior to Enrollment

Diagnosis	MnCC Group Children with Diagnosis[b]	7VPnC Group Children with Diagnosis[b]
Aplastic anemia	4	6
Autoimmune hemolytic anemia	0	1
Diabetes mellitus	5	1
Neutropenia	4	5
Autoimmune disease NOS	17	11
Thrombocytopenia	8	10
Any of the above[c]	35	25

Reproduced from Table 1 of October 18, 1999 supplemental submission to PLA
[a] Includes patients hospitalized within NCKP hospitals and outside NCKP hospitals
[b] May include more than one hospitalization for these diagnoses
[c] This row is less than sum of the rows above because several hospitalizations had multiple diagnoses in more than one row

The diagnoses presented occurred in a range of 4 to 911 days post study vaccine dose. The identification of the selected conditions involved screening the database for related ICD9 hospital diagnostic codes. Included in the autoimmune category were 23 cases of Kawasaki's disease (13 in MnCC group vs. 10 in 7VPnC group).

Some conditions in these clinical categories did not result in hospitalizations, but were ascertained by other monitoring modalities (deaths, dropped due to adverse event, nurse report). Among the additional reports was a death due to diabetic ketoacidosis in the 7VPnC group, 1 case of neutropenia in the 7VPnC group, and 3 cases of thrombocytopenia, all in the MnCC group.

Comment: None of the selected conditions appears to be over represented in the 7VPnC group. Additional comparisons of the rates of these selected conditions to historical rates within the NCKP health care system were reported by Dr. Black at the VRBPAC; none of the selected conditions were observed in excess of anticipated background rates in the 7VPnC group. Additional assurance that vaccination with Prevnar does not result in any of these immune mediated pathologic conditions could be obtained through longer follow-up of subjects. This may be possible in post-marketing studies.

10.5.1.8 Seizures events in NCKP Study (118-8) and supporting studies

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.

A seizure event could be recorded for a subject seen in the ER, and then recorded again if the child is admitted to the hospital as a hospitalization diagnosis. Additionally, seizures could be recorded as a reason for an office visit for a child seen in follow-up for seizure events already recorded in the ER and/or hospital.

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.

Table 31: Efficacy Study 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.

Acute seizure events occurring within 3 days of a vaccine dose were more common in the 7VPnC group, however the difference was not statistically significant. For intervals of 14 and 30 days, no excess in acute seizure events was observed in the 7VPnC treated group.

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.

Table 32: Efficacy Study 118-08
Characteristics of Acute Seizure Events
Occurring Within 3 Days of Receipt 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.

In the lot consistency 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.

10.5.2 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.

Table 33: Efficacy Study 118-8
Adverse Events Possibly or Probably Related to Vaccine,
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.

10.6 Review Comments Regarding Adverse Events and the Safety of Prevnar

Active monitoring of a subset of the NCKP population studied in the efficacy trial clearly demonstrated that administration of Prevnar resulted in an incremental increase in the percent of subjects reporting fever, regardless of the concomitant vaccines administered. Supporting studies largely confirmed this finding, although receipt of antipyretic agents may have obscured the full effect. Nevertheless, the observed rates of all reported fevers, and of high-grade fevers, associated with use of Prevnar fall within post vaccination fever rates that have been acceptable historically in the U.S.

Of greater concern regarding the safety profile of Prevnar, is the potential for complications of febrile reactions, such as febrile seizures. The NCKP efficacy study enrolled a sufficient number of subjects to detect relatively uncommon adverse events associated with Prevnar, such as febrile seizures, and to provide an estimate of the risk of febrile seizure following vaccination.

The 8 reports of febrile seizures within 3 days of a dose of Prevnar likely represent a fairly complete assessment of febrile seizure episodes in the study, as multiple ascertainment modalities were used. Based on approximately 55,000 doses administered in the efficacy trial, the febrile seizure rate was approximately 1 per 7000 doses. This rate is substantially less than the historical rate of 1 per 1750 reported for whole cell pertussis vaccines (AAP Redbook 2000). It is also reassuring that of these 8 acute seizure events, only 1 occurred after concurrent use of DTaP, while the other 7 were associated with concurrent use of whole cell pertussis containing vaccines, which are no longer recommended in the U.S. for use in infants and toddlers. On the other hand, available safety data for Prevnar when administered with DTaP vaccine are not as extensive as when used with DTP. While it is reasonable to expect a safety profile for Prevnar that is even more favorable when administered with DTaP, this remains to be demonstrated with wider use.

The possible impact of antipyretic use on febrile seizure rates in the NCKP efficacy trial was also considered. (Information about antipyretic use in the actively monitored subset was submitted upon FDA request as supplemental to the PLA after the VRBPAC meeting in a submission of 12/22/99). The efficacy study protocol did not prohibit or provide instructions regarding use of antipyretics during the trial, however, the use of antipyretics was recorded and assessed. Overall use of antipyretics within 48 hours of vaccinations exceeded 90% for concurrent DTP-HbOC, and 75% for concurrent DTaP. Antipyretic use data were also tabulated by prophylactic or therapeutic use, however, this distinction was not well defined, and appeared to be of limited use. The common use of antipyretics in the efficacy trial may help explain why the observed rate of febrile seizures was lower than might be expected based on historical rates for DTP vaccines, even though Prevnar was also administered with whole cell pertussis vaccines for the greater part of the study.

The increase in hospitalizations for asthma in the group administered Prevnar (11 cases vs. 3 cases) with DTaP in the primary series also deserves comment. A possible association between asthma and vaccinations appears to be biologically plausible, and so is not easily dismissed. However, it seems likely that the observed association is spurious, because the finding is not confirmed by examination of the ER data base, by comparisons between groups receiving concomitant DTP containing vaccines, by comparisons after the 4th dose, or for all doses combined. Nevertheless, the available database using Prevnar with concomitant DTaP is not extensive. Close monitoring for increased rates of asthma through post marketing studies and through the VAERS database appears warranted.

The observed association between increased hospitalizations for gastroenteritis within 14 days of a dose of Prevnar is likely a spurious finding inherent in multiple comparisons. Some increased reporting of gastrointestinal complaints among the actively monitored subset was noted (diarrhea post dose 1 with DTaP, vomiting post doses 1 and 3 with DTP-HbOC). However, hospitalizations for gastroenteritis within 3 days, 30 days, and 60 days were not significantly elevated for any comparison, regardless of concomitant pertussis vaccine type or dose series. Likewise, examination of the ER visit database failed to confirm the association. No plausible underlying mechanism is to explain the possible association is readily apparent.

Observed associations between Prevnar and ER visits for croup (within 3 days of primary series dose), and ER visits for urinary tract infections (within 30 days of 4th dose) are also likely to be spurious findings, some of which are to be expected when making multiple comparisons. No plausible underlying mechanism is readily apparent to explain how these adverse events might be related to use of Prevnar. The findings were not confirmed among the comparisons made in the hospitalization database.

Increased ER visits for breath holding in the Prevnar group is also likely to be as spurious finding as it was observed within the 30 day interval, but not within 3 day or 14 days of vaccine dose. If breath holding episodes were related to vaccination with Prevnar, one would expect most of the events to occur more proximal to the time of vaccination.

The comparative SIDS data are reassuring with respect to the safety of Prevnar, as rates of SIDS observed among Prevnar recipients in the efficacy trial were less than the rate observed in the MnCC group, and less than comparative data for the state of California over a two-year period. The California SIDS data appears to be an appropriate comparator, as the participants in the NCKP efficacy trial largely reflect the racial and ethnic distribution of California.

The safety evaluation of Prevnar was complicated by the use of an investigational vaccine in the control arm, and by the background of concurrent immunizations. Serious adverse events resulting in hospitalizations and occurring more than 60 days after vaccinations were not systematically reported in the efficacy trial. Increased rates of less common adverse reactions may not have been detected if the events occur with similar frequency in each vaccine group.

FDA reviewers sought to assure that the safety of Prevnar was further evaluated by comparing rates of selected uncommon adverse event rates to historical rates. Of particular concern in the safety review were those events that could be immune mediated. Vaccine safety advocates have proposed that these types of immune-mediated conditions may be linked to vaccinations. The observed data were reassuring in that rates of the specified adverse events among Prevnar recipients did not exceed historical rates within the NCKP health care system.

The observed increased rates for those adverse events in the 7VPnC group which were reached a 5% significance level, whether spurious or not, provide some guidance for directed follow-up in post-marketing studies.

11.0 Compatibility of Prevnar with Routine Concurrent Immunizations

Immune responses to routine childhood immunizations administered concomitantly with Prevnar were examined in various studies to assess for possible interference. During the course of clinical development, the recommended immunization schedules changed, such that some of the data collected was no longer the most relevant to current practice.

11.1 Hemophilus influenza type B

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

In study 118-03, antibody responses to Hib-PRP after the 3rd dose were slightly higher in the group that received 7VPnC concurrently with DTP-HbOC compared to the MnCC control group, as determined by GMCs and % responders at 0.15 and 1.0 μg/mL.

Table 34: Supporting Study 118-03
Hib-PRP Antibody Responses Post Dose 3,
Concurrent Administration of DTP-HbOC and 7VPnC or MnCC

Study Group	N	GMC (μg/mL) (95% CI)	% ≥ 0.15μg/mL (95% CI)	% ≥ 1.0 μg/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 additional vaccine) administered concurrently with DTaP + HbOC. In the lot consistency study 118-12, data for the 3 pilot 7VPnC lot groups were pooled. In the manufacturing bridging study 118-16, data from the preferred manufacturing lot data is represented.

No evidence of interference with HbOC responses was observed after dose 3. A significant enhancing effect of 7VPnC on Hib GMCs was evident in study 118-16.

Table 35: Supporting Studies 118-12 and 118-16
Anti Hib-PRP GMCs (μg/mL) Post Dose 3,
With or Without Concurrent Administration of 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)

No significant differences between 7VPnC and control recipients in the proportions of subjects who attained 0.15 μg/mL and 1.0 μg/mL serum antibody concentration to Hib were observed after the 3rd dose.

Table 36: Supporting Studies 118-12 and 118-16
Hib-PRP Seroconversion Rates, Post Dose 3
With or Without Concurrent Administration of 7VPnC

		% Children Achieving Antibody Level (95% CI)			Concurrent – Control Lower 90% confidence limit
Study	Serum Ab Conc.	Concurrent 7VPnC	No Concurrent 7VPnC	p-value	
118-12		N = 214	N = 67		
	≥ 0.15µg/mL	99.5 (97.4, 100.0)	97.0 (89.6, 99.7)	0.142	-1.8
	≥ 1.0 µg/mL	88.3 (83.2, 92.3)	88.1 (77.8, 94.8)	1.000	-8.0
118-16		N=159	N=83		
	≥ 0.15µg/mL	100 (97.7,100)	98.8 (93.4, 100)	-	-2.51
	≥ 1.0 µg/mL	96.9 (92.8, 99.0)	92.77 (84.9, 97.4)	-	-2.35

Adapted and compiled from Table 9b of 118-16 clinical study report, and Table 22 statistical report for study 118-12.
Exact 90% confidence intervals calculated using StatXact.

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 first 3 doses of 7VPnC were administered with DTP-HbOC. In study 118-07, DTaP and HbOC were administered concurrently with 7VPnC, or one month after. Differences in GMCs between groups were statistically significant, however in both groups the GMCs were relatively high, and proportions of subjects responding at ≥ 1.0 µg/mL exceeded 97%.

Table 37: Pilot efficacy study 118-07
Hib-PRP Responses Post Dose 4,
Concurrent Administration of DTP, HbOC and 7VPnC

Study Group	N	GMC (µg/mL)		% ≥ 0.15µg/mL	% ≥ 1.0 µg/mL
7VPnC + DTaP + HbOC	47	22.73		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 receipt of DTP-HbOC with the infant 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 µg/mL appears to differ substantially between groups (lower 95% confidence limit extends to 70%). However, the sample sizes were small in this study.

Table 38: Supporting study 118-03
Hib-PRP Antibody Responses Post Dose 4,
Concurrent HbOC and 7VPnC or MnCC

Study Group	N	GMC (µg/mL) (95% CI)	% ≥ 0.15µg/mL (95%CI)	% ≥ 1.0 µg/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

Comments:

1) The finding of no interference, but rather slight enhancement of HIB responses when administered concurrently with Prevnar in the infant series is reassuring, as decreased Hib responses have been observed with some other vaccine combinations.

2) No data were included in the PLA for responses to Hib-PRP among subjects who received DTaP + HbOC concurrently with study vaccine for all 4 doses. Hib-PRP response rates after 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 and 4th dose.

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

11.2 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.

For poliovirus type 1, the lower 90% confidence limit for the difference between groups in percent responders at an antibody titer 1:10 was -13.3%. This exceeds the typical 10% difference criteria for equivalence. Results of the comparison between pilot lot and control were similar.

No interference in responses to polio type II and III was observed.

Table 39: Manufacturing Bridging Study 118-16
Percent of Subjects Achieving Defined Antibody Levels to IPV, With or Without Concurrent Administration of 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).

Comment: The clinical significance of this apparent interference of 7VPnC with IPV type 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, yet Polio type 3 responses met the difference criteria. No other studies in the PLA address concurrent immunization of 7VPnC and IPV.

The sponsor studied compatibility of 7VPnC with OPV, however these data are not presented here due to lack of relevance to current practice.

11.3 Hepatitis B

Responses to Hepatitis B vaccine following concurrent immunization with 7VPnC and Hepatitis B vaccines in the primary series were evaluated in two studies using Hepatitis B vaccine from different manufacturers.

In study 118-16, Hepatitis B vaccine (Engerix-B, Smith-Kline-Beecham) 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, however results for the pilot lot, and other manufacturing scale lot were similar.

Non interference of 7VPnC and Hepatitis B vaccine was demonstrated in this study, as responses to Hepatitis B in the 7VPnC group exceeded slightly responses in the control group.

Table 40: Manufacturing Bridging Study 118-16
Percent of Subjects Achieving ≥ 10 mIU/mL Hepatitis B Antibody Level, Post Dose 3, With or Without Concurrent Administration with 7VPnC

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 (Recombivax, Merck) was administered at 2, 4, and 6 months of age. Concurrent immunizations included DTP-HbOC, OPV, and either 7VPnC or MnCC.

Table 41: Pilot Efficacy Study 118-07
Percent of Subjects Achieving ≥ 10 mIU/mL Hepatitis B Antibody Level, Post Dose 3, Concurrent Administration with 7VPnC or MnCC

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

Data from study 118-07 suggest that 7VPnC might interfere with Hepatitis B vaccine responses when administered on the 2, 4, and 6 months schedule. The lower 95% confidence limit 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.

Comment: Studies 118-16 and 118-07 appear to show conflicting results with regard to potential interference of Prevnar with Hepatitis B responses when the vaccines are administered concurrently. No interference was observed for each of 3 lots in the larger, Manufacturing Bridging study, which also is most relevant to current practice in that DTaP was the concurrent pertussis vaccine, while DTP-HbOC was used with the infant series in study 118-07. Thus, based on the larger and more clinically relevant data set, it appears unlikely that interference with responses to Hepatitis B responses by Prevnar occurs. However, vaccine interaction due to a schedule effect or an effect of the specific Heb B vaccine products cannot entirely be ruled out based on the available data.

11.4 DTaP

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

11.4.1 DTaP Geometric Mean Concentrations

After 3 doses, GMCs for diphtheria toxoid and all pertussis antigens were similar (ANCOVA) irrespective of concurrent 7VPnC administration. Pertactin GMCs were lower with concurrent 7VPnC, though not significantly so.

GMCs for tetanus toxoid were significantly greater in the control group, which did not receive 7VPnC.

Two-fold differences in GMC ratios between vaccine groups could be ruled out with 90% confidence for all antigens in DTaP.

Table 42: Lot Consistency Study 118-12
GMCs (µg/mL) for Antigens in DTaP, Post Dose 3,
With or Without Concurrent Administration with 7VPnC

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)
Pertactin	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)

11.4.2 DTaP Seroconversion rates

After the 3rd dose, the proportions of subjects exceeding clinically relevant antibody levels for both diphtheria and tetanus toxoids were similar in the two groups. Percent responders were also consistent with what would be expected historically.

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

However, a 10% difference in seroresponders could not be ruled out with 90% confidence for any of the pertussis antigens. For seroresponders defined by a 4-fold rise, the lower 90% confidence limit of the difference for fimbrae was -31%, for pertactin, -24%, for FHA, -16%. Inferior response rates for pertussis toxin based on a 4-fold rise, could be ruled out, but based on a 2-fold rise, pertussis toxin responses might be lower by -12%.

Table 43: Lot Consistency Study 118-12
Seroconversion Rates to Antigens in DTaP Post Dose 3,
With or Without Concurrent Administration of 7VPnC

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

Reproduced from Table 22, page 50, Volume 27, Part IV of PLA
[1] Maximum number of samples available; actual varies slightly with antigen.
[2] Exact P-values determined using Pearson's Chi-square; Exact confidence intervals computed using StatXact.

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

Significantly inferior GMCs for diphtheria, pertussis toxoid, and FHA were observed when 7VPnC was administered concurrently with DTaP at the 4th dose. The sponsor also examined the data using ANCOVA using pre-dose 4 GMCs as a covariate; similar differences were observed. Ratios of GMCs with confidence intervals were not provided.

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

Table 44: Pilot Efficacy Study 118-7
Antibody Responses to Antigens in DTaP, Post Dose 4
With or Without Concurrent Administration of 7VPnC

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

Adapted from Tables 25 and 26, Volume 11 of PLA.
[1] p-value assesses differences between treatment groups using the t-test
[2] p-value assesses differences between treatment groups using Fisher's exact (PT, pertactin) or Kruskal-Wallis (FHA, Fim 2).

Comments:

1. After the 4th dose, no significant differences in % responders were observed relative to control; however, the differences appear substantial for FHA and pertactin. Given the small sample size it is unlikely that a 10% difference could be ruled out with > 90% confidence.

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

3. The clinical importance of the observed decreased pertussis responses with concurrent 7VPnC after dose 3 and dose 4 are unclear. Responses to PT, pertactin and FHA have been most closely associated with protective efficacy and are of greatest concern.

4. It may be difficult to conduct a controlled trial in a post-marketing setting in the U.S. to resolve whether Prevnar interferes with responses to DTaP when the vaccines are administered concurrently, because Prevnar could be universally recommended post-licensure. However, it may be possible to focus on post-dose 4 data, as the vaccines could be separated by a month or more given the flexibility in the 4th dose schedules.

11.5 MMR

Responses to measles, mumps and rubella following concurrent administration with 7VPnC were examined in studies 118-3 and 124-2. In both studies responses were compared using ELISA assays rather than the traditional neutralization tests.

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.

Table 45: Supporting Study 118-3 Seroconversion Rates for MMR, Concurrent Administration of 7VPnC or MnCC

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

Reproduced from Table 30b, Statistical Report, Volume 8, Part IV of PLA.
[1] Antibodies measured by ELISA using Biowhittaker assay kits and reported in Predicted Index Value (PIV). Results with PIV ≥ 1 are considered seropositive.

Although comparative responses between study arms appear similar, response rates to mumps and rubella are low by historical standards, and sample sizes are small. Lower bounds of the 95% CI for the seroconverters were as low as 62% for mumps.

In study 124-2, responses to MMR antigens were determined after MMR was administered concurrently with Wyeth-Lederle's investigational 9-valent pneumococcal conjugate vaccine, which is a lyophylized preparation. These data are not presented or otherwise discussed here as FDA/CBER does not view these data to be sufficiently relevant to Prevnar.

Comment: Insufficient data are presented to determine whether or not Prevnar is likely to interfere with responses to MMR. Responses to mumps in particular are low by historical standards. Sample sizes are small and confidence intervals are wide. An additional study should be conducted to better describe the compatibility of the 4th dose of Prevnar with MMR.

12.0 Immunogenicity, lot consistency, and bridging to manufacturing scale

Antibody responses to the 7 pneumococcal capsular polysaccharides were evaluated in several clinical studies to address various objectives. Immunogenicity results from essential clinical studies are presented in this section. For descriptions of the trial designs for the lot consistency study (118-12) and the manufacturing bridging study (118-16), please see attachment B. Results of immunogenicity evaluations in the tables below refer to serum IgG levels as determined by ELISA.

12.1 Immunogenicity in the efficacy trial

12.1.1 Concurrent DTP

Only subjects who received three doses of DTP-HbOC concurrently with study vaccine and who had blood draws within defined windows were included in the immunogenicity analyses. Subjects receiving DTaP and HbOC concurrently with DTaP were provided with the PLA but as a supplement to the study report.

Of the 366 subjects (188 7VPnC and 178 MnCC) who received DTP-HbOC concurrently with study vaccines for the first three doses, and had at least one serum sample drawn, 180 met the eligibility criteria for the post dose 3 immunogenicity analysis. Subjects were excluded for: 1) pre sera but no post sera (48 7VPnC and 40 MnCC), 2) post sera but no pre sera (6 7VPnC and 7 MnCC), and 3) the time interval from dose 3 to post dose 3 bleed was <21 or >63 days (11 7VPnC and 13 MnCC)

After the 3rd dose of the primary series, GMCs in the 7VPnC treatment group ranged from 1.4 μg/mL for serotype 19F (lower bound 95% CI, 1.16 μg/mL), to 4.7 μg/mL for serotype 6B.

For the 4th dose analysis, 68 subjects in the 7VPnC group met eligibility criteria and provided pre- and post- sera. Pre-dose 4 GMCs had declined to less than 0.50 μg/mL for 3 of the pneumococcal serotypes (4, 18C, and 23F).

After dose 4, GMCs exceeded 2 μg/mL for all serotypes. Response to the 4th dose was least robust for serotype 19F for which the GMC was 2.07 μg/mL (lower bound 95% CI, 1.66 μg/mL).

[redacted]

Table 46: Efficacy Study 118-8
GMCs (µg/mL) for Pneumococcal Antibodies
Prior to, and Following 3rd and 4th Doses, Concurrent DTP-HbOC

Serotype	Pre dose 3 GMC (µg/mL) N=86[1]	Post dose 3 GMC (µg/mL) N=88[1]	95% CI	Pre dose 4 GMC (µg/mL) N=68	Post dose 4 GMC (µg/mL) N=68	95% CI
4	0.078	1.46	1.19, 1.78	0.31	2.38	1.88, 3.02
6B	0.327	4.70	3.59, 6.14	1.71	14.45	11.17, 18.69
9V	0.180	1.99	1.64, 2.42	0.57	3.51	2.75, 4.48
14	0.198	4.60	3.70, 5.74	1.45	6.52	5.18, 8.21
18C	0.146	2.16	1.73, 2.69	0.50	3.43	2.70, 4.37
19F	0.374	1.39	1.16, 1.68	0.55	2.07	1.66, 2.57
23F	0.174	1.85	1.46, 2.34	0.44	3.82	2.85, 5.11

Adapted from Tables 39 and 42, Volume 13 , and Table 1, page 90, Volume 17, 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.

12.1.2 Concurrent DTaP

Data were also collected to assess responses to pneumococcal polysaccharide antigens when 7VPnC was administered concurrently with DTaP.

Pneumococcal GMCs among subjects who received 7VPnC with either concurrent DTP-HbOC or DTaP + HbOC, were similar for all serotypes, with the possible exception of type 6B, for which responses were lower when 7VPnC was administered with DTaP. However, 6B GMCs post dose 3 exceeded 2.0 µg/mL in both groups.

Table 47: Efficacy Study 118-8
Pneumococcal GMCs (µg/mL), Concurrent DTP or DTaP, Post Dose 3

Pneumococcal Serotype	DTP- HbOC N=88	DTaP + HbOC N=31
4	1.46	1.47
6B	4.70	2.18
9V	1.99	1.52
14	4.60	5.05
18C	2.16	2.24
19F	1.39	1.54
23F	1.85	1.48

Adapted from Tables 39 and 42, Volume 13 , and Table 1, page 90, Volume 17, Part IV of PLA, and from Table 16 of Statistical report for study 118-8 of subjects receiving DTaP in primary series, electronic file.

Comment: Insufficient data were available post-dose 4 addressing with concurrent administration of DTaP and 7VPnC (N=9) to make meaningful comparisons.

12.2 Lot consistency

Immunogenicity data were obtained for approximately 300 infants vaccinated at 2, 4, and 6 months of age in order to evaluate 3 independently produced pilot scale lots of 7VPnC for consistency of manufacture. 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 control group received only HbOC, DTaP and IPV/OPV.

Post dose 3 GMCs 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. Otherwise stated, lot consistency would fail if the lower bound of the 90% CI for any 2-way comparison of the ratio were < 0.5, or the upper bound of any ratio were 90% CI was > 2.0. A 90% CI was deemed acceptable because of the multiple comparisons required.

Table 48: Study 118-12
Comparisons of GMCs (µg/mL) for Three 7VPnC Pilot Lots, Ratio of GMC between Lots (with 90% Confidence Interval)

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

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

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

Comment: While the test criteria were not met for 3 of 21 comparisons, the margins of error were small, and no clear pattern suggestive of a failed lot of vaccine was evident. Serotype 6B from lot A accounted for 2 of the 3 missed criteria, but appears to have been more immunogenic than serotype 6B from lots B and C, which were similar to one another. Thus, the immunogenicity data provide evidence of lot-consistency. Taken together with safety data from this trial, FDA/CBER accepts that the clinical data provided to demonstrate lot consistency are sufficient.

12.3 Kinetics of the immune response

In the lot consistency study (118-12), sufficient blood samples were available after 2 and after 3 doses of vaccine to examine the time course of the antibody