response to pneumococcal antigens. In the presentation of these data, results from all 3 pilot lots were combined, as they had been shown to be similar.

After 2 doses of vaccine, GMCs for vaccine serotypes 6B and 23F had not yet attained a level of 0.5 μg/mL. The GMC for serotype 6B after 2 doses was similar to the pre-dose 1 GMCs. After 3 doses, GMCs for all vaccine serotypes exceeded 1.0 μg/mL.

**Table 49: Lot Consistency Study 118-12 Kinetics of Pneumococcal IgG Response, Pooled 7VPnC Group, GMC (μg/mL) with 95% C.I.**

| | Pooled 7VPnC Group | | |
|---|---|---|---|
| Serotype | 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 7, page 58, Volume 27, Part IV of PLA.

### 12.3 Manufacturing bridging: Study 118-16

Vaccine lots used in the pivotal efficacy study (118-8) were produced in sub-manufacturing (pilot) scale quantities. FDA/CBER considers demonstration of "bridging" pilot to manufacturing scale in terms of safety and immunogenicity as an essential component of the license application. (See attachment B for a description of the trial design used to demonstrate bridging).

Immune responses induced by vaccine from pilot scale lot used in the efficacy study were compared to responses elicited by vaccine from a manufacturing scale lot. Two co-primary immunogenicity endpoints were defined for each of the 7 vaccine serotypes:

1) GMCs
2) % responders above defined threshold antibody concentrations.

**Comment:** The most appropriate antibody level on which to base seroresponsiveness is not readily apparent. The antibody level associated with protection from invasive disease is unknown. Moreover, it is not clear that a single level is appropriate for each of the 7 serotypes.

The chosen threshold values for each serotype were determined by the maximal difference in serum antibody concentrations between immunized and unimmunized children at the 7-month bleed observed in previous studies using lots of vaccine from clinical scale production (i.e., studies 118-12 and 118-8).

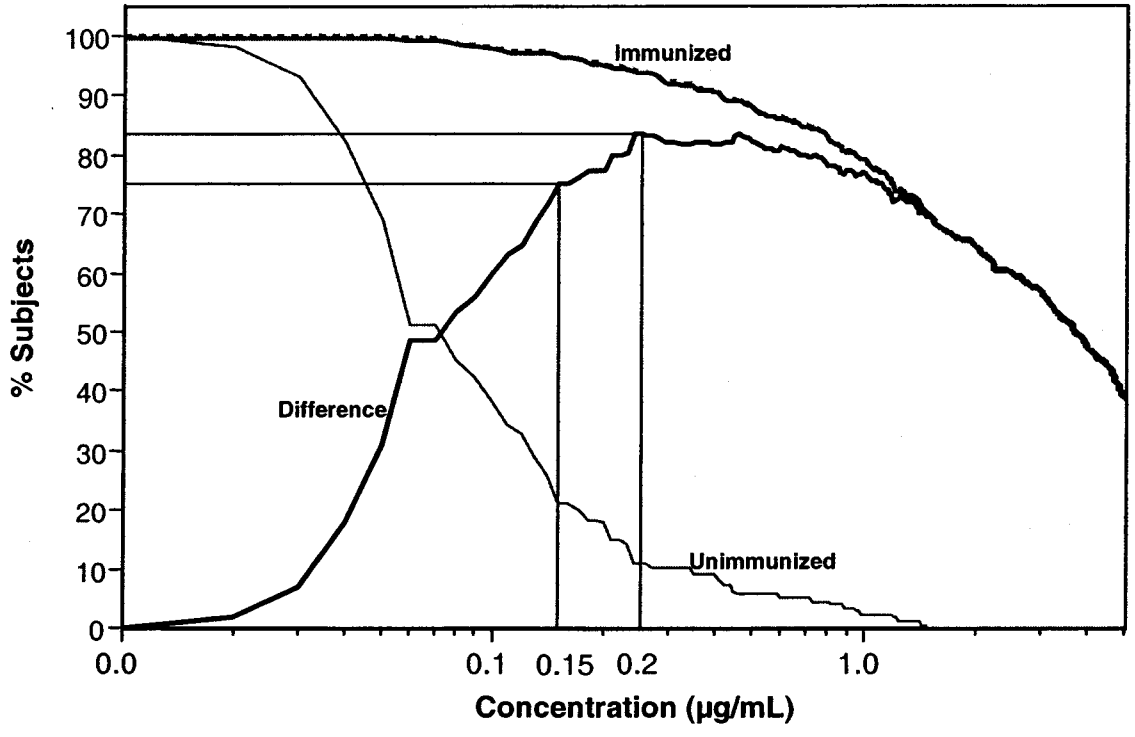
**Table 50: Manufacturing Bridging Study 118-16 Threshold Serum Antibody Concentrations Used to Determine Percent Responders**

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

The choice of threshold value for serotype 6B is illustrated by the reverse cumulative distribution curves for serotype 6B from data obtained in earlier studies. The top of the difference curve (in black) defined the threshold level.

**Figure 1: Maximal Difference in GMCs
Immunized and Unimmunized Populations
(Based on Combined Data from Study 118-8 and 118-12)**

**Serotype 6B**




Successful bridging of manufacturing to pilot scale lot was to be claimed both of the following were demonstrated:

1) Rule out 2-fold ratio in GMCs with 90% confidence for all serotypes

2) Rule out ≥ 10% difference in seroresponders with 90% confidence for all serotypes, applying the serotype-specific threshold antibody levels.

Results are shown in the following tables:

**Table 51: Manufacturing Bridging Study 118-16**
**GMCs (µg/mL) of Pneumococcal Antibodies, Post Dose 3**

| GMC (µg/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.

**Table 52: Manufacturing Bridging Study 118-16**
**Proportions of Subjects Achieving Given Antibody Concentrations**

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

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

The lower 90% CI for the ratio of GMCs exceeded 0.5 for all 7 serotypes.

The lower 90% CI for the difference in % seroresponders at the defined threshold levels did not exceed –10% for any serotype.

**Comment:** Based on these immune response data, and taken together with safety data from this study, FDA reviewers accepted that the clinical evidence provided to support bridging of pilot to manufacturing scale is sufficient.

## 13.0 Safety and immunogenicity of Prevnar among older infants and children

### 13.1 Immunogenicity

A schedule of inoculations proposed by the sponsor for inclusion in the vaccine label is reproduced below as it appeared in the original proposed package insert:

In the original PLA submission, and at the time of the advisory committee meeting on November 5, 1999, safety and immunogenicity data available to support this schedule were quite limited, as shown below:

**Table 53: Safety and Immunogenicity Data to Support Vaccine Schedules in Older Infants and Children, (Data in Original PLA Submission)**

| Study | To Support | Safety | Immunogenicity |
|---|---|---|---|
| 118-12 | 3 Doses, 7-11 mo | N= 24 | N= 22 |
| 118-15 | 2 Doses, 12-17 mo | None | N= 100 |
| 118-15 | 2 Doses, 18-24 mo | None | N= 54 |
| 124-501 (9-valent) | 1 Dose, 24+ mo | N= 85 | N= 85 |

Additional data (not shown) were provided for other schedules studied that were not chosen as most appropriate for older infants and children. In all cases where two schedules for the same age group were studied, the sponsor chose the schedule providing more doses of Prevnar, based on superior antibody responses.

The advisory committee was not asked to specifically comment on the data or proposed schedules for older children because of the limited data available, and because additional data would be forthcoming (see below).

**Comments:** FDA/CBER did not view the data from study 124-501, which studied immunogenicity using Wyeth-Lederle's 9-valent formulation, to be sufficiently representative of 7VPnC to support catch-up in the absence of a study directly bridging safety and immunogenicity to 7VPnC. Data bridging 7VPnC and 9VPnC were collected in study 124-2, in which immunogenicity of both formulations were directly compared after the primary series; these data were not available for FDA review.

Responding to FDA concerns about the amount of safety and immunogenicity data likely to be available in the PLA to support schedules for vaccination of older children, the sponsor initiated an additional study, 118-18, intended to provide additional safety and immunogenicity data for older infants and children. These

additional safety and immunogenicity data were submitted late in the review cycle (December 17, 1999), after the advisory committee meeting.

Among the oldest age group studied, 5-9 years of age, the distribution of subjects by age across this relatively wide range was well balanced by year (data not shown). Immune responses among the older children after a single vaccine dose were quite robust compared responses in the younger children.

**Table 54: Summary Geometric Mean Concentrations (μg/mL) to Vaccine Serotypes Following Immunization of Children Ages 7 Months Through 9 Years of Age**

| Age group (months) # doses | Study | Sample size† | 4 | 6B | 9V | 14 | 18C | 19F | 23F |
|---|---|---|---|---|---|---|---|---|---|
| 7-11, 3 doses | 118-12 | 22 | 2.34 | 3.66 | 2.11 | 9.33 | 2.31 | 1.60 | 2.50 |
| | 118-16 | 39 | 3.60 | 4.63 | 2.04 | 5.48 | 1.98 | 2.15 | 1.93 |
| 12-17, 2 doses | 118-15* | 82 – 84 | 3.91 | 4.67 | 1.94 | 6.92 | 2.25 | 3.78 | 3.29 |
| | 118-18 | 33 | 7.02 | 4.25 | 3.26 | 6.31 | 3.60 | 3.29 | 2.92 |
| 18-23, 2 doses | 118-15* | 52 – 54 | 3.36 | 4.92 | 1.80 | 6.69 | 2.65 | 3.17 | 2.71 |
| | 118-18 | 45 | 6.85 | 3.71 | 3.86 | 6.48 | 3.42 | 3.86 | 2.75 |
| 24-35 1 dose | 118-18 | 53 | 5.34 | 2.90 | 3.43 | 1.88 | 3.03 | 4.07 | 1.56 |
| 36-59 1 dose | 118-18 | 52 | 6.27 | 6.40 | 4.62 | 5.95 | 4.08 | 6.37 | 2.95 |
| 5-9 years 1 dose | 118-18 | 101 | 6.92 | 20.84 | 7.49 | 19.32 | 6.72 | 12.51 | 11.57 |
| 118-8, DTaP Post dose 3 | 118-08 | 31 – 32 | 1.47 | 2.18 | 1.52 | 5.05 | 2.24 | 1.54 | 1.48 |

Adapted from Table 45, page 110, Volume 33, Part IV of PLA, and package insert.
*Study in Navajo and Apache populations.
† Numbers vary with serotype

To provide a measure by which responses in the older infants and children could be judged similar to responses of children in the efficacy study, FDA requested that comparisons of GMC's from proposed schedules for older children be made to GMCs observed among children in the efficacy trial. Data collected post dose 3 with concurrent DTaP were chosen for comparisons. A test criteria was set that the one-sided lower limit of the 95% CI of GMC ratio be > 0.50.

The GMCs obtained for the older children with the chosen schedules met the specified non-inferiority criteria for all schedules and serotypes except for serotype 14 among the 24-35 month age group, which received 1 dose. However, for this serotype, a relatively high GMC was attained after 3 doses in the efficacy trial.

### 13.2 Safety data to support vaccination schedules for older children

Rates of local and systemic reactogenicity data following administration of Prevnar to older infants and children are summarized in the following tables.

These data were provided as supplemental to the original PLA with the December 17, 1999 submission.

Local reactions were generally more frequent and severe with older age at vaccination. Among children over 3 years of age, erythema, induration and pain were reported by more than 20% of subjects. More severe pain and induration were also more commonly reported by the older children; over 9% of 5-9 year old children reported induration > 2.4 cm, and nearly 40% reported pain interfering with limb movement.

**Table 55: Summary Safety Data for Older Infants and Children, Percentage of Subjects Reporting Local Reactions within 3 Days of Immunization among Infants and Children, Ages 7 Months to 9 Years**

| Age at 1st Dose | 7 – 11 Mos. | | | | | | 12 – 23 Mos. | | | 24-35 Mos. | 36-59 Mos. | 5-9 Yrs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study No. | 118-12 | | | 118-16 | | | 118-9* | 118-18 | | 118-18 | 118-18 | 118-18 |
| Dose No. | 1 | 2 | 3† | 1 | 2 | 3† | 1 | 1 | 2 | 1 | 1 | 1 |
| No. Subj. | 54 | 51 | 24 | 81 | 76 | 50 | 60 | 114 | 117 | 46 | 48 | 49 |
| Reaction | | | | | | | | | | | | |
| Erythema | | | | | | | | | | | | |
| Any | 16.7 | 11.8 | 20.8 | 7.4 | 7.9 | 14.0 | 48.3 | 10.5 | 9.4 | 6.5 | 29.2 | 24.2 |
| >2.4 cm‡ | 1.9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 6.7 | 1.8 | 1.7 | 0.0 | 8.3 | 7.1 |
| Induration | | | | | | | | | | | | |
| Any | 16.7 | 11.8 | 8.3 | 7.4 | 3.9 | 10.0 | 48.3 | 8.8 | 6.0 | 10.9 | 22.9 | 25.5 |
| >2.4 cm‡ | 3.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 3.3 | 0.9 | 0.9 | 2.2 | 6.3 | 9.3 |
| Tenderness | | | | | | | | | | | | |
| Any | 13.0 | 11.8 | 12.5 | 8.6 | 10.5 | 12.0 | 46.7 | 25.7 | 26.5 | 41.3 | 58.3 | 82.8 |
| Interfered with limb movemnt§ | 1.9 | 2.0 | 4.2 | 1.2 | 1.3 | 0.0 | 3.3 | 6.2 | 8.5 | 13.0 | 20.8 | 39.4 |

* For 118-9, 2 of 60 subjects were ≥ 24 months of age.
† For 118-12, dose 3 was administered at 15 - 18 mos. of age. For 118-16, dose 3 was administered at 12 -15 mos. of age.
‡ For 118-16 and 118-18, ≥ 2 cm.
§ Tenderness interfering with limb movement.

Fever and systemic reactions among the older children did not show the same pattern of increasing frequency and severity with age as observed with local reactions.

**Table 56: Summary Safety Data for Older Infants and Children, Percentage of Subjects Reporting Systemic Reactions Within 3 Days of Immunization among Infants and Children Ages 7 Months to 9 Years**

| Age at 1st Vaccination | 7 – 11 Mos. | | | | | | 12 – 23 Mos. | | | 24 – 35 Mos. | 36 – 59 Mos. | 5 – 9 Yrs. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study No. | 118-12 | | | 118-16 | | | 118-9* | 118-18 | | 118-18 | 118-18 | 118-18 |
| Dose No. | 1 | 2 | 3† | 1 | 2 | 3† | 1 | 1 | 2 | 1 | 1 | 1 |
| No. Subjects | 54 | 51 | 24 | 85 | 80 | 50 | 60 | 120 | 117 | 47 | 52 | 100 |
| Reaction | | | | | | | | | | | | |
| Fever | | | | | | | | | | | | |
| ≥ 38.0°C | 20.8 | 21.6 | 25.0 | 17.6 | 18.8 | 22.0 | 36.7 | 11.7 | 6.8 | 14.9 | 11.5 | 7.0 |
| > 39.0°C | 4.4 | 1.9 | 5.9 | 0.0 | 1.6 | 3.9 | 2.6 | 0.0 | 0.0 | 4.2 | 2.3 | 1.2 |
| Fussiness | 29.6 | 39.2 | 16.7 | 54.1 | 41.3 | 38.0 | 40.0 | 37.5 | 36.8 | 46.8 | 34.6 | 29.3 |
| Drowsiness | 11.1 | 17.6 | 16.7 | 24.7 | 16.3 | 14.0 | 13.3 | 18.3 | 11.1 | 12.8 | 17.3 | 11.0 |
| Decreased Appetite | 9.3 | 15.7 | 0.0 | 15.3 | 15.0 | 30.0 | 25.0 | 20.8 | 16.2 | 23.4 | 11.5 | 9.0 |

*For 118-9, 2 of 60 subjects were ≥ 24 months of age.
†For 118-12, dose 3 was administered at 15 - 18 mos. of age. For 118-16, dose 3 was administered at 12 -15 mos. of age

## 13.3 Review comments regarding safety and immunogenicity data intended to support schedules for use of Prevnar among older children

### 13.3.1 Immunogenicity

The efficacy trial provided evidence of protection from invasive disease after 3 doses of 7VPnC, until the 4th dose was administered, and subsequently after the 4th dose. To make inferences about long-term protection, it may be most relevant to compare to GMCs obtained after all doses are administered in the proposed schedules for older children to GMCs elicited after the 4th dose of 7VPnC in the efficacy trial.

While such comparisons of GMCs to post-dose 4 GMCs might be highly relevant, available data for the concurrent DTaP cohort are quite limited (N=9). Comparisons to GMCs obtained following a four dose series with DTP-HbOC in the efficacy study were possible (see Table 46). Statistical comparisons to rule out non-inferiority to post dose 4 GMCs based on a GMC ratio > 0.5 were not made. However, simple comparisons of GMCs reveal that some schedules did not achieve comparable GMCs for some serotypes (notably, 6B in 24-35 mo, 9V in 7-11, 12-17, and 24-35 mo, 18C in 7-11 and 18-23 mo, 19F in 7-11 mo, and 23F in 7-11, 12-17, 24-35, and 36-59 mo age groups). Interpretation of these data in the absence of knowledge about the antibody level that correlates with long-term protection cannot be made with any confidence. Information from ongoing studies that examine antibody duration will be of interest. Long-term follow-up of vaccinated cohorts for incidence of invasive disease could provide useful information about the adequacy of the vaccine schedules for older children.

Two 23-valent pneumococcal polysaccharide (23VPS) vaccines are licensed and available in the U.S. The 23VPS vaccines are recommended for adults and individuals over the age of 2 years in some high-risk groups, 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.

Comparative safety and immunogenicity data for responses to 23VPS and 7VPnC among older children were not provided in the PLA. In study a study of a 5-valent conjugate, study 92-05 (attachment B), children 15-18 months received 23VPS after a primary series of a 5-valent conjugate formulation. While a "booster" type of response to 23VPS among children primed with 5-valent conjugate vaccine was apparent, the study design did not provide for comparisons of responses to 23VPS and 5-valent conjugate vaccine at the 4$^{th}$ 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 for serotypes included in 7VPnC, whether "primed" with 7VPnC in infancy or not.

The 23VPS vaccines were not recommended for universal immunization of children above the age of 2 years, however not for lack of an immune response to the vaccine, as more limited recommendations for children in this age range were made. Considerations for not stating a universal recommendation for older children included the diminishing risk of serious disease among the older children. In this regard, an indication for Prevnar to be used routinely for older children may have less merit than for the 23-valent vaccines, because of the fewer serotypes represented in Prevnar, and a broadening of the distribution of serotypes with increasing age.

### 13.3.2 Safety

The number of older children followed for vaccine reactions and other safety outcomes was quite limited. The duration of follow-up time for safety outcomes among older children in Study 118-18 was 7 days for vaccine reactions reported on diary cards or which resulted in physician visits or prescription medications. Follow-up for adverse events resulting in hospitalizations or ER visits continued for the duration of the study, which was until sera were collected 1 month after the last vaccine dose. Clearly, the safety data for older children receiving the proposed vaccine schedules do not provide the same measure of assurance that the large safety database from the efficacy trial provided.

The available safety data do appear to show that systemic reactions, and febrile reactions in particular, did not occur with greater frequency among the

older children, and in fact, appear to be less frequent. The frequency and severity of local reactions do appear to be more common in the older age groups.

Local reactions following the 23-valent pneumococcal polysaccharide vaccine are also relatively common. In part due to local reactogenicity, revaccination with polysaccharide vaccine is not routinely recommended. Some evidence indicates that the severity of local reactions is related to anti-pneumococcal antibody levels at the time of vaccination. The observed increased rates of local reactions among the older children following Prevnar™ may be due to existing immunity among some children as a result of previous exposure to pneumococcal serotypes that are represented in the vaccine.

While available safety data among older children are not extensive, they do not show a pattern that would be prohibitive to use of the vaccine in these age groups using the proposed schedules. Nevertheless, collection of additional safety data among the older age groups post-marketing is desirable.

## 14.0 Clinical Summary

### 14.1 Efficacy

Prevnar was highly efficacious in preventing invasive disease due to pneumococcal serotypes represented in the vaccine in an infant population. Prevnar was also efficacious in reducing invasive disease due to all pneumococcal serotypes, as replacement of vaccine serotypes by non-vaccine serotypes was not observed during the efficacy trial. The efficacy data clearly support licensure of Prevnar for the age groups in which efficacy was studied.

Among the cases of invasive disease in the extended follow-up dataset were 2 deaths and 6 cases of meningitis attributable to pneumococcal disease, all of which occurred in the in control group. While the study was not powered to examine death or meningitis as efficacy outcomes, it is likely that by preventing invasive disease, the vaccine will be effective in preventing these serious outcomes in the general population.

Efficacy of Prevnar in preventing acute otitis media and pneumonia among infants and small children has not been completely evaluated by FDA. No specific indication for prevention of these diagnoses was under consideration with this priority review.

### 14.2 Safety

The reactogenicity profile of Prevnar in infants and small children was characterized by fever, irritability and local reactions of pain and induration. Fever ($\geq$ 38 °C) was reported at rates above background rates of concurrent

immunizations in the large safety and efficacy (NCKP) study, and generally across studies. When administered with concurrent DTaP in clinical studies, Prevnar was associated with fever rates that ranged from 5% to 34% during the primary series across studies. Thus, fever associated with Prevnar appears to be less frequent than fever reported for whole cell pertussis vaccines, and within a range that would likely be generally acceptable.

Of potential concern was a finding of an greater number of seizures events temporally associated (within 3 days) with a dose of Prevnar when compared to the control group; the difference was not statistically significant. Most of the seizures were reported as febrile seizures, and most occurred with concurrent whole cell pertussis vaccine (DTP-HbOC). Close attention to post-vaccination seizure rates in post-marketing studies and in general use through monitoring of VAERS reports is indicated.

Automated databases in the NCKP study were exploited to search for adverse events among the study population. These searches, accompanied by directed chart reviews, and statistical analyses provided reassuring safety data with respect to serious adverse events including death, SIDS, blood disorders, autoimmune diseases, diabetes mellitus, and an extensive list hospital and ER diagnoses which were analyzed for potential associations.

Among the multiple analyses, a few adverse events were found to be associated with administration of Prevnar, based on p-values uncorrected for multiple comparisons. Among the associated adverse events were hospitalizations for asthma (within 60 days of a vaccine dose, concurrent DTaP only) and gastroenteritis (within 14 days of vaccine dose), and ER visits for croup, breath holding, and urinary tract infections. While these adverse events most likely represent spurious findings resulting from the large number of comparisons, the sponsor has agreed to further examine the possible associations in post marketing safety studies.

### 14.3 Compatibility with routine childhood immunizations

Adequate studies have been conducted to rule out clinically significant interference with responses to tetanus, diphtheria, HIB-PRP, Hepatitis B, and IPV type 2 and 3 antigens, when these vaccines were administered concurrently with Prevnar in the primary series. Interference of Prevnar with responses to IPV type 1, pertussis toxoid, pertactin, fimbrae, and MMR could not be ruled out.

### 14.4 Immunization of older infants and children

Safety and immunogenicity data have been provided for children through age 9, thus enabling a rational choice of vaccine schedule for older infants and children. Older children responded well to a single dose of Prevnar based on GMCs. Older children were also more prone to develop more severe local reactions.

## 15.0 Post Marketing Evaluation of Prevnar

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

Wyeth-Lederle chose to conduct these studies at NCKP. Extended safety and efficacy follow-up of subjects enrolled in the efficacy trial will continue. Additional studies are comprised of 5 components:

### 15.1 Phase 4 safety study

This study, to be conducted at Kaiser Permanente over a 2.5 year period, will enroll 60,000 infants who will be followed for safety outcomes.

The objective of this component of the post-marketing studies is to expand the safety database to capture more serious and rare adverse events among children who receive Prevnar at 2, 4, 6, and 12-15 months of age. Surveillance will continue until approximately 60,000 children have been evaluated 120 days after receiving at least 3 doses. It is anticipated that the study will extend over a 2.5-year period.

Because Prevnar was proposed for universal immunization, these additional safety data were viewed as essential to better identify and describe uncommon or rare adverse events, that could not be detected or well described in the pre-licensure trials.

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

Adverse events to be ascertained for specified observation periods include:

- For 14 days post-vaccination, febrile illness resulting in medical utilization, seizures, allergic reactions, and asthma.

- For 30 days post-vaccination, specific adverse events observed more frequently in the efficacy study (i.e., gastroenteritis, febrile seizure, asthma, croup, breath holding).

- For the length of the study, selected diagnoses/outcomes, some possibly related to dysfunctional immune responses, including aplastic anemia, asthma, autoimmune hemolytic anemia, diabetes mellitus, neutropenia, autoimmune disease not otherwise specified, thrombocytopenia, and death (including SIDS).

**Note:** These selected diagnoses were examined in the large efficacy study, and no "signal" indicating possible increased rates was identified. However, concern has been expressed by some vaccine safety advocates regarding the potential relationships of vaccines in general with autoimmune diseases. At the November 1999 VRBPAC meeting to discuss licensure of Prevnar, a presentation was made by Dr. Claussen suggesting a relationship between bacterial polysaccharide conjugate vaccines and diabetes mellitus. This aspect of the post-marketing safety study is intended to help address these concerns.

- Extended follow-up of original efficacy study cohort for diabetes mellitus [redacted]

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

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

### 15.2 Local and systemic reactogenicity of Prevnar when administered to previously unimmunized older children (i.e., 7-11 months of age, 12 months-2 years, 2-5 years, 5-9 years)

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

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

### 15.3 Non-inferiority study of immunogenicity of MMR administered concurrently with Prevnar, compared to MMR alone

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

Six hundred subjects, three hundred per group, who have received 3 doses of Prevnar, will be randomized at 12-15 months of age to receive either MMR with Prevnar, or MMR (Prevnar administered 6 weeks later) in addition to DTaP, Hib, IPV and varicella vaccine. Blood will be obtained for measles, mumps, and rubella serology prior to vaccination and 6 weeks post immunizations. If sufficient blood is available, antibody titers/levels for varicella, poliovirus 1, 2, and 3, pertussis antigens, and Hib will also be assessed. The study is powered to determine whether concurrent administration of Prevnar and MMR results in % responders $\leq$ 90%, with 95% confidence.

Information regarding compatibility of Prevnar with Hib conjugate vaccine(s) not based on $CRM_{197}$ may be available from this study.

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

Objectives for this study are to assess local and systemic reactogenicity of a 4th dose of Prevnar administered concurrently with DTaP for all 4 doses. Little information was available at the time of licensure addressing safety of Prevnar when administered with DTaP with each dose in a 4-dose DTaP series. Because DTaP has been recommended for a 4-dose series, these additional safety data were viewed as necessary to accurately describe the safety profile of Prevnar with current use.

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

### 15.5 Ongoing surveillance of invasive pneumococcal disease in NCKP population

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

The study will provide information about duration of protection and replacement of vaccine serotypes. Surveillance of invasive disease cases among the vaccine cohort will be continue for 5 years post-licensure, at which time some participants may be 10 years old. Cases of invasive disease will be identified through using the NCKP Regional Microbiology Laboratory Database. Reports will be prepared annually.

## 15.6 Compatibility with recommended childhood vaccines

The PLA review identified some vaccine combinations for which available data did not provide convincing evidence for lack of immune interference between Prevnar and recommended vaccines.

### 15.6.1 Hib conjugate vaccines not based on $CRM_{197}$

Some vaccine advisory committee members remarked that it would be desirable to demonstrate compatibility with Hib conjugate vaccines using different carrier proteins. Wyeth-Lederle indicated that some data will be available from a [redacted] Also, the MMR non-inferiority study, described above, may provide some data utilizing [redacted]

### 15.6.2 Polio virus type 1

As noted in Section 11.2, above, administration of Prevnar with IPV appear to interfere with antibody responses to Polio virus type I. Wyeth-Lederle indicated that immunogenicity data will be available from a randomized, controlled study conducted in [redacted] It is also possible that additional data may be available from the planned Phase 4 MMR non-inferiority study, described above.

### 15.6.3 Pertussis

As noted in Section 11.4, administration of Prevnar with DTaP appears to result in interference with antibody responses some of the pertussis vaccine components. To further address this finding, some data may be available from a [redacted] Data may be available from the planned Phase 4 MMR non-inferiority study, described above.

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

## 15.7 Other ongoing or planned studies relevant to Prevnar

**ACTG 292: A double-blind placebo-controlled trial of the safety and immunogenicity of a 7-valent pneumococcal vaccine in presumed HIV-infected infants**

A total of 48 HIV-infected children were enrolled. Children 2-6 months of age were randomized to receive 7VPnC or placebo for a 4-dose series, to be followed

by 23-valent pneumococcal polysaccharide vaccine at 2 years of age. A study report is to be submitted when available.

**118-4: Open study to evaluate the safety and immunogenicity of a septavalent pneumococcal CRM conjugate vaccine in sickle cell disease children under the age of 12 months**

A total of 35 subjects with sickle cell disease received 3 doses on a 2, 4, and 6-month schedule; 11 additional subjects with sickle cell disease received a single dose of 7VPnC at 12 months of age. Most subjects received 23-valent pneumococcal polysaccharide vaccine at 2 years of age. A study report is to be submitted to FDA when available.

Another randomized study conducted among 23 older children and young adults with sickle cell disease evaluated immune responses following a 2- dose series of 7VPnC compared to 23-valent polysaccharide vaccine alone. Data are to be provided when available.

### 15.8 Premature infants

FDA suggested that a safety and immunogenicity study be conducted among infants born prematurely. Premature infants were not excluded from the efficacy study, if otherwise healthy. However, no specific analysis of safety or immunogenicity outcomes for premature infants was provided. Wyeth-Lederle indicated that discussions were underway to conduct such a study.

### 15.9 Other high risk groups

[redacted]

## 16.0 Labeling

The final version of the package insert varies considerably from the package insert originally proposed. The label was revised subsequent to multiple communications with the sponsor representatives.

The indication section of the vaccine label is clearly limited to prevention of invasive disease among children immunized at 2, 4, 6, and 12-15 months of age, thus reflecting how the bulk of the safety, immunogenicity and efficacy data were obtained.

The label provides an informative description of the pivotal large safety and efficacy study conducted at NCKP. Sufficient information is provided in the label regarding vaccine reactogenicity such that clinicians will be able to appreciate the risks of fever and other systemic and local reactions.

FDA reviewers recognized that Prevnar could be useful in some older children with risk factors for invasive pneumococcal disease. Wyeth-Lederle submitted safety and immunogenicity data to support use of Prevnar among older, previously unimmunized children late in the review cycle. These data were reviewed expeditiously to allow for their inclusion in the vaccine label to provide appropriate guidance for clinicians in the immediate post-licensure period, when the information would be most relevant. Additionally, dosage and administration guidelines for children through age 9 years were accepted for inclusion in the label.

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

For additional information about labeling, please refer to the package insert.

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## 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).

## 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 pilot scale lots used in the efficacy study, in terms of safety and immunogenicity. The "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. The bridging study was the last component of the complete application to be completed prior to submission of the PLA. Immunogenicity data from the "catch-up" portion of the study were not submitted with the application, but were provided as an amendment to the PLA on December 17, 1999.

### Study Design and Conduct

Two manufacturing lots were compared to the pilot lot for immunogenicity The manufacturing lots differed in [redacted]

**Manufacturing Bridging Study 118-P16: Design and subject allocation**

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

A "no additional vaccine" control was included for safety comparisons; all children received recommended immunizations concurrently. Infants randomized to the 7VPnC vaccine groups were followed until blood was drawn 1 month after the 3rd