DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Biostatistics

STATISTICAL REVIEW AND EVALUATION

BLA

BLA/Supplement Number: 125324/0

Product Name: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM_{197} Protein)

Proposed Indication(s): Active immunization of infants and toddlers for the prevention of invasive disease caused by Streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; and active immunization of infants and toddlers for the prevention of otitis media caused by serotypes included in the vaccine

Applicant: Wyeth Pharmaceuticals, Inc.

Date(s): Received on March 31, 2009

Review Priority: Priority Review

Statistical Branch: FDA/CBER/OBE/DB/VEB

Primary Statistical Reviewer: **Jingyee Kou, Ph.D** _____
Mathematical Statistician Date

Concurring Reviewer (1): **Tammy Massie, Ph.D** _____
Lead, Bacterial & Allergenic Team Date

Concurring Reviewer (2): **A. Dale Horne, Dr.PH** _____
Second concurring reviewer's name Date

Medical Office/Division: FDA/CBER/OVRR/DVRPA

Clinical Reviewer(s):	Tina Khoie, M.D., M.P.H.
Chair:	CAPT Julienne Vaillancourt, R. Ph., M.P.H.
Project Managers:	CDR Colleen Sweeney, M.S.
	LCDR Michael Smith, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The reviewer recommends that OVRR take into consideration the following points in making the decision on licensing this product:

1. Pre-specified non-inferiority criteria were not met for three of the *Streptococcus pneumoniae* serotypes in the US pivotal trial (study 004); however, pre-specified non-inferiority criteria were met for the remaining ten serotypes in this trial.

2. Serotype 6B either did not meet or narrowly met the primary immunogenicity objectives in all 3 trials reviewed in the efficacy section. Since a serologic correlate of protection has not been established, the clinical significance of this result is not clear.

3. In general, the antibody concentrations appear to be lower in the 13vPnC group than in the 7vPnC group for the seven common serotypes. The product and clinical reviewers may wish to comment on the potential for interference as a result of the additional serotypes in the 13vPnC vaccine.

4. For the six new serotypes not included in Prevnar, comparisons of the 13vPnC vaccine were made to the lowest response rate observed among the Prevnar serotypes in Prevnar recipients. Because all serotypes in Prevnar are considered effective in preventing invasive pneumococcal disease, the lowest serotype response was still considered a comparison to an effective serotype. With regard to licensure criteria for future pneumococcal conjugate vaccines, consideration should be given to whether this non-inferiority criterion used in study 004 for the six additional serotypes should be redefined given the low antibody response observed by serotype 3.

5. The WHO's recommendation states that failure of some serotypes to meet the pre-specified acceptance criteria may not necessarily preclude licensure of a product with multiple serotypes.

1.2 Brief Overview of Clinical Studies

Prevnar is a 7-valent pneumococcal vaccine licensed in year 2000 to Wyeth Pharmaceuticals, Inc. The company has since developed a 13-valent vaccine and this submission contains the clinical studies of this vaccine.

There were 13 studies submitted to CBER, 4 of which were conducted in the US. Studies 002 and 003 were phase1/2 studies, mainly to assess the safety and the immunogenicity of the new product.

Study 004 was a phase 3 study to confirm that the immune responses of the 7 serotypes are non-inferior to the corresponding 7 serotypes in Prevnar. For the new 6 serotypes, study 004 was to demonstrate that each serotype is non-inferior to the lowest immune response measured among the 7 Prevnar serotypes.

Study 3005 was a phase 3 lot consistency trial. The goal was to demonstrate that the 2 pilot lots and one manufacturing scale lot are equivalent in terms of immune responses.

Detailed reviews for the two phase 3 studies -- study 004 and study 3005 -- are included in this review.

1.3 Major Statistical Issues and Findings

1. Of the 13 serotypes contained in the test vaccine, 10 serotypes met the primary objectives in pivotal study 004; in this study, 3 serotypes, namely 6B, 9V, and 3, failed to meet the pre-specified primary objectives.

2. The safety evaluation of 13vPnC was based on comparisons with the licensed 7-valent vaccine, Prevnar. Therefore, the safety profile described in the submission and in this review is that of relative safety rather than absolute safety (i.e., vaccine compared to placebo).

3. There were no data on the efficacy for prevention of otitis media for 13vPnC submitted in this application. Therefore, the effectiveness of 13vPnC against otitis media cannot be evaluated statistically at this time.

2. INTRODUCTION

2.1 Overview

Prevnar® is the first vaccine indicated for the prevention of invasive pneumococcal diseases and was licensed in 2000. The pharmaceutical company, Wyeth, which developed Prevnar, has expanded the coverage from 7 serotypes in Prevnar (7vPnC) to 13 serotypes (13vPnC) in this new vaccine. The original 7 serotypes are: 4, 6B, 9V, 14, 18C, 19F, and 23F. The 6 new serotypes are: 1, 3, 5, 6A, 7F, and 19A.

13vPnC is to be given as a infant series at 2, 4, and 6 months of age, and the toddler dose at age 12-15 months.

2.2 Data Sources

The clinical trials were carried out in many countries including the US. In this BLA submission, the following clinical studies were submitted:

Study number	Study type	Study design	Location
6096A1- 009	Formulation bridging	Phase 3, controlled	Poland
6096A1- 004	Pivotal non-inferiority	Phase 3, controlled	USA
6096A1- 006	Pivotal non-inferiority	Phase 3, controlled	Germany
6096A1- 3000	Manufacturing scale bridging	Phase 3, controlled	Poland
6096A1- 3005	Manufacturing scale bridging	Phase 3, controlled	USA
6096A1- 007	Concomitant immunogenicity	Phase 3, controlled	United Kingdom
6096A1- 008	Concomitant immunogenicity	Phase 3, controlled	France
6096A1- 500	Concomitant immunogenicity	Phase 3, controlled	Italy
6096A1- 501	Concomitant immunogenicity	Phase 3, controlled	Spain
6096A1- 3007	Concomitant immunogenicity	Phase 3, controlled	Spain
6096A1- 011	Concomitant immunogenicity	Phase 3, controlled	India
6096A1- 3008	Concomitant immunogenicity	Phase 3, controlled	Canada
6096A1- 3002	Catch-up	Phase 3, open-label	Poland
6096A1- 002	Phase 1-2 trial	Phase 1, open-label	USA
6096A1- 003	Phase 1-2 trial	Phase 1/2, active-controlled	USA

This review includes the following:

- Amendment 1 (submitted on 10/24/2008)
  - m5.3.5.1 Study Reports of Controlled Clinical Studies: Studies 003, 004, 009
- Amendment 3 (submitted on 3/6/2009)
  - m5.2 Tabular Listing of Clinical Studies
  - m5.3.5.1 Study Reports of Controlled Clinical Studies: Studies 3005
- Amendment 4 (submitted on 3/31/2009)
  - m1.16 Risk Management Plans
  - m2.2 Common Technical Document Introduction
  - m2.5 Clinical Overview
  - m2.7 Clinical Summary
  - m5.3.5.1 Study Reports of Controlled Clinical Studies: Studies 3005
  - m5.3.5.3 Reports of Analysis of Data from More than One Study: Integrated Summary of Safety and Integrated Statistical Analysis Plan
- Amendment 11 (submitted on 5/14/2009)
  - m1.11.3 Efficacy Information Amendment: Response to Agency Request – CBER Clinical Comments
- Amendment 14 (submitted on 6/11/2009)
  - m1.11.3 Efficacy Information Amendment: Response to Agency Request on Post-Marketing Protocols 6096A1-4002 and 6096A1-4010
  - m5.3.5.2 Study 4010, Post-Marketing Study Synopsis: Effectiveness of Prevnar 13 in reducing acute otitis media and nasopharyngeal colonization in young children
- Amendment 58 (submitted on 12/2/2009)
  - m1.11.3 Efficacy Information Amendment: Response to Agency Comments 01-Dec-2009 on Safety Study 6096A1-3005: Toddler and 6-month Follow-up Safety Data 6096A1-4010
  - m5.3.5.1 Analysis Datasets

- Amendment 60 (submitted on 12/9/2009)
  m1.11.3 Efficacy Information Amendment: Response to Agency Request from 25-Nov-2009 with Clinical PMC Information and
  m1.14 Draft Labeling

3. STATISTICAL EVALUATION

Due to the availability of the licensed 7-valent pneumococcal vaccine, Prevnar, it is difficult to conduct a placebo-controlled clinical trial for this new product. Therefore, immunogenicity is used as a surrogate endpoint in evaluating 13vPnC.

3.1 Evaluation of Immunogenicity

3.1.1 Study 6096A1-009 (Study 009)

Polysorbate 80 (P80) is nonionic surfactant used to ----(b)(4)--- proteins; it was not in the originally licensed vaccine, Prevnar. The applicant believes that addition of P80 will result in a more robust manufacturing process for 13vPnC. Study 009 was to evaluate the safety, tolerability, and immunogenicity of 13vPnC formulated with P80 (13vPnC+P80) and without P80 (13vPnC-P80) when given concomitantly with routine pediatric vaccines.

3.1.1.1 Objectives for Immunogenicity

Primary Objective

The primary objective of study 009 was to demonstrate that the immune responses to the 13 common pneumococcal conjugates (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) induced by 13vPnC+P80 are non-inferior to the immune responses induced by 13vPnC-P80 when measured 1 month after the infant series.

Secondary Objective

The secondary objective of this study was to assess the pneumococcal immune response induced by 13vPnC+P80 relative to the immune response induced by 13vPnC-P80 when measured 1 month after the toddler dose.

3.1.1.2 Study Design

Study 009 was a parallel-group, randomized, double-blind, multicenter trial.

Approximately 500 subjects (250 subjects per group) were to be enrolled in this study to achieve 222 evaluable subjects per group at 12 to 15 sites in Poland. Subjects were randomly assigned (in a 1:1 ratio prospectively) to receive either 13vPnC+P80 or 13vPnC-P80. In addition, all subjects were to receive Pentaxim at the 2-, 3-, and 4-month visits; Engerix-B at the 2-month visit; and Priorix at the 12-month visit.

Blood samples were to be obtained 1 month after the third dose (visit 4, at approximately 5 months of age), just before the toddler dose (visit 5, at approximately 12 months of age), and at 1 month after the toddler dose (visit 6, at approximately 13 months of age). These samples were to be tested for immunoglobulin G (IgG) antibodies against the 13 pneumococcal serotypes present in 13vPnC.

Statistical analyses were based on the statistical plans outlined in the statistical analysis plan (SAP) for this study, version 1 dated 4 Apr 2007 and version 2 dated 16 Nov 2007.

Because this study was conducted in Poland with an infant schedule of 2-, 3-, and 4-months instead of the US schedule 2-, 4-, and 6-months, the sponsor did not submit the protocol and the SAPs for FDA/CBER review or comment.

3.1.1.3 Interim Analyses

Two (2) interim analyses were planned. The initial interim analysis (formulation decision analysis) was conducted when immunogenicity data, measured 1 month after the infant series, were available from approximately 150 evaluable subjects per group (formulation decision population). In this initial interim analysis, the 2-sided type I error was 0.002 and the non-inferiority criterion was -0.10. Type I error rates were chosen in part based on the O'Brien-Fleming error spending function and overall type I error was permitted to exceed 0.05 (using 0.002 and 0.05 resulted in an overall alpha of 0.051). The second interim analysis (infant series analysis) was planned after the immunogenicity data associated with the blood sample obtained 1 month after the infant series were available from all subjects. However, the conduct of this second interim analysis was dependent on the outcome from the first interim analysis.

If non-inferiority was declared based on the formulation decision analysis, then no additional subjects were to have immunologic assays performed on the blood sample collected 1 month after the infant series, and no second interim analysis was to be conducted. If non-inferiority was not declared, then the second interim analysis (the primary analysis) was to be performed using assay results from all subjects. For this analysis, the 2-sided type I error was 0.05, and the same non-inferiority criterion was used.

The study statistician performed the initial interim analysis because it was also the primary analysis if non-inferiority could be shown. The database remained blinded until all data were collected, but the statistician performing the analysis was provided with randomized treatment information, as well as actual treatment packaging assignment

information. The study was unblinded to the sponsor following the infant series for regulatory submission. Results of the unblinded assay data were not available to Wyeth personnel involved with the study, except as necessary to perform any interim or primary analyses. For the final analysis of the 6-month follow-up data, the database was unblinded.

3.1.1.4 Statistical Methodologies

Endpoints and Statistical Criteria

(a) Proportions of Subjects Achieving Prospectively Defined Antibody Concentration Levels

Within each vaccine group and for each serotype separately, the proportion of subjects achieving an antibody concentration ≥ 0.35 μg/mL was computed for each blood sample.

For each of the 13 serotypes, exact, unconditional, 2-sided 95% confidence intervals (CIs) on the single proportions were calculated using the F distribution. The 95% CIs for the difference in proportions ([13vPnC+P80] – [13vPnC-P80]) were computed using the non-inferiority procedure of Chan and Zhang, using the standardized test statistic and γ=0.000001. Non-inferiority is declared if the lower CI for the difference is >-0.10. Similar procedures were used for the evaluation of antibody concentrations after the toddler dose. Since the type one error was set at 0.002 for the formulation decision analyses, 99.8% CIs on proportions were calculated.

(b) Geometric Means

For the secondary endpoints, the pneumococcal IgG serotype antibody concentrations were logarithmically transformed for analysis. Within each treatment group and for each antibody concentration separately, geometric means of the antibody concentrations were calculated for each vaccine group. Two (2)-sided 95% CIs were constructed by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student *t* distribution. To assess differences between the 2 vaccine groups, the 95% CIs for geometric mean ratio were computed using the Student *t* distribution for the mean difference of the measures on the log scale (13vPnC+P80 relative to 13vPnC-P80). Non-inferiority was declared if the lower limit of the CI for the ratio was greater than 0.5 (2-fold criterion). In addition, the geometric mean fold rises from before the toddler dose to after the toddler dose, and corresponding 2-sided 95% CIs, were calculated for each of the serotype-specific pneumococcal IgG responses. For formulation decision analyses, 99.8% CIs were calculated.

Determination of Sample Size

Sample size estimation was based on the proportion of responders in each vaccine group. Data from Wyeth study 6096A1-003 were used for pneumococcal serotypes.

The sample sizes needed to declare non-inferiority with respect to the proportion of subjects achieving an antibody concentration ≥0.35 µg/mL are displayed in the following Table 3-1 (Table 6-2 in the submission). Sample size calculations assumed (a) power of at least 90%; (b) non-inferiority criterion of -0.10; (c) difference in true proportion between the groups ([13vPnC+P80] – [13vPnC-P80]) is -0.01; (d) a 2-sided, type I error of 0.05; and, (e) a drop out rate of at most 10%.

Table 3-1. Sample size needed to declare non-inferiority with respect to the proportion of subjects achieving an antibody concentration ≥ 0.35 µg/mL with a type 1 error = 0.05, non-inferiority criterion of -0.10 and specified power

Serotype	Proportion in 13vPnC + P80	Proportion[a] in 13vPnC – P80	Power	Sample size Per group
1	97	97	99	107
3	98	98	99	73
4	96	96	99	142
5	99	99	99	37
6A	96	96	99	142
6B	88	88	99	222
7F	98	98	99	73
9V	96	96	99	142
14	97	97	99	107
18C	96	96	99	142
19A	99	99	99	37
19F	97	97	99	107
23F	94	94	99	208
Overall			90%	

a. Proportion of subjects achieving an antibody concentration ≥ 0.35 µg/mL to the specified serotype from infant series of study 6096A1-003.

Sample sizes of 222 evaluable subjects per group would provide at least 90% overall power to declare non-inferiority for all 13 pneumococcal antigens using a 2-sided, type I error of 0.05 and a non-inferiority criterion of -0.10 for the proportion of subjects achieving a pre-specified antibody level. Because non-inferiority for the study was demonstrated only if the lower bounds for all 13 comparisons were greater than -10%, type 1 error adjustment for multiplicity was not performed. Assuming a drop out rate of at most 10%, 500 subjects overall were to be enrolled to ensure that 444 subjects were evaluable.

Analysis populations

For the immunogenicity analyses, 5 analysis populations were defined: formulation, evaluable infant immunogenicity, all-available infant immunogenicity, evaluable toddler immunogenicity, and all-available toddler immunogenicity. The formulation decision population is a subset of subjects in the evaluable infant series population with available assay data at the time of the first interim analysis.

If there were no important differences between the evaluable toddler and all-available toddler immunogenicity populations, a single all-available toddler immunogenicity analysis was to be performed.

3.1.1.5 Results and Conclusions

Results of the Formulation Decision Analysis (first interim analysis)

The following table, Table 3-2 (Table 9-1 in the submission), provides the number of subjects in the all-available formulation decision population which is a subset of the infant series population. There were 192 randomized into the 13vPnC+P80 group and 194 into the 13vPnC-P80 group. There were 174 evaluable subjects in the 13vPnC+P80 group and 176 in the 13vPnC-P80 group.

Table 3-2. Formulation Decision Analysis - All-available and evaluable immunogenicity population

Vaccine group (as randomize)	13vPnC+P80		13vPnC-P80		Total	
	n	%	n	%	n	%
Randomized	192	100.0	194	100.0	386	100.0
All-available infant immunogenicity population	175	91.1	178	91.8	353	91.5
Subjects excluded form the all-available infant immunogenicity population	17	8.9	16	8.2	33	8.5
No post-infant series assay result for any pneumococcal serotype	17	8.9	16	8.2	33	8.5
Evaluable infant immunogenicity population	174	90.6	176	90.7	350	90.7
Subjects excluded from the evaluable infant immunogenicity population[a]	18	9.4	18	9.3	36	9.3
Not in all-available infant immunogenicity population	17	8.9	16	8.2	33	8.5
Blood draw > 42 days after the infant series	1	0.5	3	1.5	4	1.0
Vaccine received at dose 1 other than randomized	1	0.5	0	0.0	1	0.3
Vaccine received at dose 2 other than randomized	0	0.0	1	0.5	1	0.3

a. Subjects may have been excluded for more than one reason.

The following table, Table 3-3 (Table 9-4 in the submission), provides the numbers and proportions of subjects achieving a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL and the difference in proportions with 99.8% confidence interval (CI) for each serotype for the formulation decision population. The results showed that only one serotype, 18C, met the non-inferiority criteria. The remaining serotypes from the original Prevnar vaccine failed the pre-specified non-inferiority criteria and two of the new serotypes, 5 and 6A, have also failed the criteria. Out of all the lower bounds of the 99.8% CIs, serotype 6B has the lowest value, -22.8%.

Table 3-3. Comparison of subjects achieving a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL after dose 3 of the infant series – evaluable infant immunogenicity population (formulation decision analysis)

Vaccine Group (randomized)	13vPnC+P80 (N[a] = 174)			13vPnC-P80 (N[a] = 176)				
Serotype	**n[b]**	**%**	**(99.8% CI[c])**	**n[b]**	**%**	**(99.8% CI[c])**	**Diff[d]**	**(99.8% CI[e])**
7vPnC								
4	161	92.5	(84.4, 97.3)	164	93.2	(85.3, 97.7)	-0.7	(-10.2, 8.7)
6B	99	56.9	(44.9, 68.3)	112	63.6	(51.8, 74.4)	-6.7	(-22.8, 9.5)
9V	167	96.0	(89.1, 99.1)	174	98.9	(93.8, 100.0)	-2.9	(-10.4, 3.3)
14	162	93.1	(85.1, 97.6)	171	97.2	(91.0, 99.6)	-4.1	(-12.9, 3.6)
18c	169	97.1	(90.8, 99.6)	173	98.3	(92.8, 99.9)	-1.2	(-8.3, 5.2)
19F	165	94.8	(87.5, 98.6)	172	97.7	(91.8, 99.8)	-2.9	(-11.0, 4.2)
23F	148	85.1	(75.1, 92.2)	162	92.0	(83.8, 97.0)	-7.0	(-18.3, 3.7)
Additional								
1	166	95.4	(88.3, 98.8)	164	93.2	(85.3, 97.7)	2.2	(-6.3, 11.2)
3	170	97.7	(91.8, 99.8)	175	99.4	(94.9, 100.0)	-1.7	(-8.4, 3.8)
5	162	93.1	(85.1, 97.6)	165	93.8	(86.1, 98.0)	-0.6	(-10.0, 8.4)
6A	147	84.5	(74.4, 91.8)	151	85.8	(76.1, 92.7)	-1.3	(-13.6, 10.8)
7F	171	98.3	(92.7, 99.9)	175	99.4	(94.9, 100.0)	-1.2	(-7.5, 4.3)
19A	171	98.3	(92.7, 99.9)	176	100.0	(96.2, 100.0)	-1.7	(-7.9, 3.2)

a. N = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥ 0.35 µg/Ml for the given serotype.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
d. Difference in proportions, 13vPnC+P80 – 13vPnC-P80, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC+P80 – 13vPnC-P80, expressed as a percentage.

The following table, Table 3-4 (Table 9-5 and Table 9-6 in the submission), provides the geometric mean concentration (GMC) for each serotype, each group as well as the ratio of the GMCs and its 99.8% CI between the two groups for each serotype. The lower bound of the 99.8% CI for all serotypes are greater than 0.5, the lowest value is 0.56 for serotype 6B.

Table 3-4. Formulation Decision Analysis – Pneumococcal IgG GMCs (µg/mL) and comparisons after dose 3 of the infant series in the evaluable formulation decision population.

Vaccine Group (randomized)	**13vPnC+P80 (N[a] = 174)**		**13vPnC-P80 (N[a] = 176)**			
Serotype	**GMC[b]**	**(99.8% CI[c])**	**GMC[b]**	**(99.8% CI[c])**	**Ratio[d]**	**(99.8% CI[e])**
7vPnC						
4	1.49	(1.18, 1.87)	1.55	(1.24, 1.95)	0.96	(0.69, 1.32)
6B	0.47	(0.34, 0.63)	0.53	(0.38, 0.74)	0.88	(0.56, 1.37)
9V	1.53	(1.28, 1.82)	1.63	(0.39, 1.92)	0.93	(0.73, 1.19)
14	2.00	(1.54, 2.59)	2.33	(1.87, 2.90)	0.86	(0.61, 1.20)
18c	1.96	(1.61, 2.37)	1.99	(1.69, 2.35)	0.98	(0.76, 1.26)
19F	1.43	(1.13, 1.82)	1.76	(1.48, 2.10)	0.81	(0.61, 1.09)
23F	0.95	(0.76, 1.20)	1.16	(0.94, 1.43)	0.82	(0.60, 1.12)
Additional						
1	1.44	(1.18, 1.76)	1.59	(1.29, 1.97)	0.91	(0.68, 1.21)
3	1.60	(1.36, 1.88)	1.74	(1.51, 2.01)	0.92	(0.74, 1.14)
5	1.28	(1.04, 1.57)	1.31	(1.08, 1.60)	0.98	(0.74, 1.30)
6A	0.94	(0.74, 1.18)	1.05	(0.84, 1.32)	0.89	(0.65, 1.23)
7F	1.93	(1.63, 2.29)	1.88	(1.60, 2.21)	1.03	(0.81, 1.29)
19A	2.78	(2.32, 3.34)	3.09	(2.61, 3.66)	0.90	(0.70, 1.15)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotypes.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CI) are back transforms of confidence levels based on the Student *t* distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs; 13vPnC+P80 to 13vPnC-P80.
e. Confidence intervals (CIs) for the ratio are back transforms of confidence levels based on the Student t distribution for the mean difference of the logarithms of the concentrations (13vPnC+P80 – 13vPnC-P80).

Conclusion of the Formulation Decision Analysis

The immunogenicity results of the formulation decision analysis failed to meet the non-inferiority criteria. Hence, the second interim analysis (infant series analysis) was performed.

Results of the Infant Series Analysis (second interim analysis)

The following table, Table 3-5 (Table 9-2 in the submission), provides the number of subjects in the all-available infant series population. There were 250 randomized into the 13vPnC+P80 group and 250 into the 13vPnC-P80 group. There were 238 evaluable subjects in the 13vPnC+P80 group and 238 in the 13vPnC-P80 group. The sponsor noted that subjects who may have been excluded from the evaluable infant population for the formulation decision analysis because of no post-infant series assay results may have been included in the evaluable infant population for the infant series analyses.

Table 3-5. Infant Series Analysis - All-available and evaluable immunogenicity population

Vaccine group (randomize)	**13vPnC+P80**		**13vPnC-P80**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**
Randomized	250	100.0	250	100.0	500	100.0
All-available infant immunogenicity population	245	98.0	245	98.0	490	98.0
Subjects excluded form the all-available infant immunogenicity population	5	2.0	5	2.0	10	2.0
No post-infant series assay result for any pneumococcal serotype	5	2.0	5	2.0	10	2.0
Evaluable infant immunogenicity population	238	95.2	238	95.2	476	95.2
Subjects excluded from the evaluable infant immunogenicity population[a]	12	4.8	12	4.8	24	4.8
Not eligible for the study	1	0.4	1	0.4	2	0.4
Not in all-available infant immunogenicity population	5	2.0	5	2.0	10	2.0
Received vaccine other than randomized	1	0.4	1	0.4	2	0.4
Did not receive all pneumococcal study vaccinations	4	1.6	3	1.2	7	1.4
Blood draw > 42 days after the infant series	6	2.4	5	2.0	11	2.2
Received prohibited vaccines	0	0.0	1	0.4	1	0.2

a. Subjects may have been excluded for more than one reason.

The following table, Table 3-6 (Table 9-7 in the submission), provides the numbers and proportions of subjects achieving a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL and the difference in proportions with 95% confidence interval (CI) for each serotype for the infant series population. Those numbers showed that serotypes 6B (with lower bound of -14.2%) and 23F (with lower bound of -12.1%) from the Prevnar serotypes did not meet the non-inferiority criteria, but all of the new serotypes met the criteria.

Table 3-6. Comparison of subjects achieving a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL after dose 3 of the infant series – evaluable infant immunogenicity population (infant series analysis)

Vaccine Group (randomized)	13vPnC+P80 (N[a] = 238)			13vPnC-P80 (N[a] = 238)				
Serotype	**n[b]**	**%**	**(95% CI[c])**	**n[b]**	**%**	**(95% CI[c])**	**Diff[d]**	**(95% CI[e])**
7vPnC								
4	222	93.3	(89.3, 96.1)	224	94.1	(90.3, 96.7)	-0.8	(-5.4, 3.7)
6B	145	60.9	(54.4, 67.2)	158	66.4	(60.0, 72.4)	-5.5	(-14.2, 3.3)
9V	231	97.1	(94.0, 98.8)	232	97.5	(94.6, 99.1)	-0.4	(-3.7, 2.8)
14	225	94.5	(90.8, 97.1)	232	97.5	(94.6, 99.1)	-2.9	(-6.9, 0.7)
18c	233	97.9	(95.2, 99.3)	233	97.9	(95.2, 99.3)	0.0	(-3.0, 3.0)
19F	228	95.8	(92.4, 98.0)	234	98.3	(95.8, 99.5)	-2.5	(-6.1, 0.6)
23F	205	86.1	(81.1, 90.3)	220	92.4	(88.3, 95.5)	-6.3	(-12.1, -0.7)
Additional								
1	228	95.8	(92.4, 98.0)	220	92.4	(88.3, 95.5)	3.4	(-0.9, 7.9)
3	233	97.9	(95.2, 99.3)	236	99.2	(97.0, 99.9)	-1.3	(-4.1, 1.1)
5	224	94.1	(90.3, 96.7)	220	92.4	(88.3, 95.5)	1.7	(-3.0, 6.4)
6A	206	86.6	(81.6, 90.6)	205	86.1	(81.1, 90.3)	0.4	(-5.8, 6.7)
7F	235	98.7	(96.4, 99.7)	237	99.6	(97.7, 100.0)	-0.8	(-3.2, 1.2)
19A	235	98.7	(96.4, 99.7)	238	100.0	(98.5, 100.0)	-1.3	(-3.6, 0.3)

a. N = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥ 0.35 µg/Ml for the given serotype.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
d. Difference in proportions, 13vPnC+P80 – 13vPnC-P80, expressed as a percentage.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC+P80 – 13vPnC-P80, expressed as a percentage.

The following table, Table 3-7 (Table 9-8 in the submission), provides the geometric mean concentration (GMC) for each serotype and each group, as well as the ratio of the GMCs and its 99.8% CI between the two groups for each serotype.

Table 3-7. Infant Series Analysis – Pneumococcal IgG GMCs (µg/mL) and comparisons after dose 3 of the infant series in the evaluable infant series population.

Vaccine Group (randomized)	13vPnC+P80 (N[a] = 174)	13vPnC-P80 (N[a] = 176)		
Serotype	**GMC[b]**	**GMC[b]**	**Ratio[c]**	**(95% CI[d])**
7vPnC				
4	1.47	1.53	0.96	(0.81, 1.13)
6B	0.51	0.57	0.90	(0.72, 1.14)
9V	1.46	1.51	0.97	(0.85, 1.10)
14	2.37	2.48	0.96	(0.79, 1.15)
18c	1.84	1.87	0.98	(0.86, 1.13)
19F	1.46	1.75	0.84	(0.72, 0.97)
23F	0.93	1.11	0.84	(0.71, 0.98)
Additional				
1	1.39	1.48	0.94	(0.81, 1.10)
3	1.50	1.62	0.93	(0.83, 1.04)
5	1.26	1.30	0.97	(0.83, 1.13)
6A	0.99	1.04	0.96	(0.81, 1.13)
7F	1.98	1.89	1.05	(0.93, 1.18)
19A	2.68	2.94	0.91	(0.80, 1.04)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotypes.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Ratio of GMCS; 13vPnC+P80 to 13vPnC-P80.
d. Confidence intervals (CIs) for the ratio are back transforms of confidence levels based on the Student t distribution for the mean difference of the logarithms of the concentrations (13vPnC+P80 – 13vPnC-P80).

Conclusions of the Infant Series Analysis

For the infant series analysis, the point estimates for the percentages of responders were lower in the 13vPnC+P80 group for most of the 13vPnC serotypes. The non-inferiority criterion (i.e., lower bound of the 95% CI greater than -10%) was met for 11 of the 13 serotypes. Serotypes 6B and 23F did not meet the non-inferiority criterion; for these 2 serotypes the lower bound of the 95% CI was -14.2% and -12.1%, respectively.

Pneumococcal IgG GMCs for the evaluable immunogenicity population in the infant series analysis were similar to those observed in the formulation analysis and were not notably different between vaccine groups. When the ratio of IgG GMCs (13vPnC+P80 to 13vPnC-P80) were computed for each serotype, the lower bound of the 95% CI was greater than 0.5 for all 13 serotypes (i.e., 2-fold non-inferiority criterion was met).

The sponsor provided the following conclusion in the submission:

> "The unexpected diminished responses of serotype 6B contributed to the failure to meet non-inferiority criterion. The percentages of responders to serotype 6B were lower than expected in both groups as both formulations used the same lot of 6B conjugate. Review of the analytic data for this lot of 6B conjugate does not provide any insight into why the 6B responses were low. The percentage of responders to 23F was lower than expected in the 13vPnC+P80 group (86.1%), but closer to the expected value (94.0%) in the 13vPnC-P80 group (92.4%). The reasons for the unexpectedly lower response for serotype 23F in the 13vPnC+P80 group in this study are also not clear at this time. The GMCs for all serotypes except 7F were lower in the 13vPnC+P80 group, but all met the 2-fold criteria for non-inferiority established for comparison of GMCs. The decision was made to include P80 in the 13vPnC formulation and was based on a more robust manufacturing process and supported by the overall similarity in the immunogenicity responses elicited by the 13vPnC+P80 compared with 13vPnC-P80. Minor differences in immunogenicity in the P80-containing formulation are unlikely to be clinically significant and 13vPnC+P80 will likely provide high levels of protection against disease."

3.1.1.6 Reviewer's Comments on Study 009

1. *The study was not conducted under US IND and thus was not subject to regulatory scrutiny. Therefore, the study design and the objectives were not concurred on by FDA/CBER before the study was conducted.*

2. *In general, the trend of the immune responses measured either by the proportion of subjects achieving ≥ 0.35 µg/mL antibody concentration or by GMCs, suggests that the group with P80 produced lower immunogenicity values than did the group without P80, for most serotypes.*

3. *In both interim analyses, serotypes 6B and 23F did not meet the pre-specified non-inferiority criteria with respect to the primary endpoint.*

4. *The sponsor's choice of using the formula with P80 was based on "a more robust manufacturing process and by the overall similarity in the immunogenicity responses elicited by the 13vPnC+P80 compared with 13vPnC-P80."[csr71892-report-body-infant.pdf] Since the choice was not based on statistical evidence, the impact of the lower immunogenicity values for several of the serotypes such as 6B and 23F is not clear.*

3.1.2 Study 6096A1-004 (Study 004)

Study 004 was a pivotal non-inferiority study conducted in the US to compare the immunogenicity of 13vPnC and 7vPnC. This trial was conducted using a 2-, 4-, 6-month infant series schedule. This study also provides information about the immune responses to concomitant antigens in Pediarix®, ActHIB®/PedvaxHIB®, and ProQuad® in the 13vPnC group compared with the 7vPnC group. This study started before the decision

was made to include polysorbate 80 (P80), in the final formulation of 13vPnC. Since the results from study 009 seem to indicate that the immune responses were lower in the group with P80, the results from this study, especially for serotypes 6B and 23F, may be challenging to interpret.

3.1.2.1 Objectives for Immunogenicity

The primary objectives for immunogenicity of this study were as follows:

- To demonstrate that the immune responses to the 7 common pneumococcal conjugates (4, 6B, 9V, 14, 18C, 19F, and 23F) induced by 13vPnC were non-inferior to the immune responses induced by 7vPnC, when measured 1 month after the infant series.
- To demonstrate that the immune responses to the 6 additional pneumococcal conjugates (1, 3, 5, 6A, 7F, and 19A) induced by 13vPnC were non-inferior to the lowest immune response among the 7 common pneumococcal conjugates (4, 6B, 9V, 14, 18C, 19F, and 23F) induced by 7vPnC, when measured 1 month after the infant series.
- To demonstrate that the geometric mean IgG concentrations for the 7 common pneumococcal conjugates (4, 6B, 9V, 14, 18C, 19F, and 23F) induced by 13vPnC are non-inferior to the geometric mean IgG concentrations induced by 7vPnC when measured 1 month after the toddler dose.
- To demonstrate that the geometric mean IgG concentrations for the 6 additional pneumococcal conjugates (1, 3, 5, 6A, 7F, and 19A) induced by 13vPnC were non-inferior to the lowest geometric mean IgG concentration among the 7 common pneumococcal conjugates (4, 6B, 9V, 14, 18C, 19F, and 23F), induced by 7vPnC, when measured 1 month after the toddler dose.
- To demonstrate that the immune responses induced by Pediarix (diphtheria and tetanus toxoids, acellular pertussis adsorbed, hepatitis B [recombinant], and inactivated polio vaccine [IPV]) given with 13vPnC were non-inferior to the immune responses induced by Pediarix given with 7vPnC, when measured 1 month after the infant series. Responses to the following antigens in Pediarix were assessed: diphtheria and pertussis antigens (pertussis toxoid [PT], filamentous hemagglutinin [FHA], and pertactin [PRN]).
- To demonstrate that the immune responses induced by ActHIB (*Haemophilus* b conjugate vaccine [tetanus toxoid conjugate]) given with 13vPnC were non-inferior to the immune responses induced by ActHIB given with 7vPnC, when measured 1 month after the infant series.

The secondary objectives of this study were as follows:

- To demonstrate that the immune responses induced by ProQuad (a combined, attenuated, live-virus vaccine containing measles, mumps, rubella, and varicella viruses) given with 13vPnC were non-inferior to the immune responses induced by ProQuad given with 7vPnC, when measured 1 month after the toddler dose. Responses to the following antigens in ProQuad were assessed: measles, mumps, rubella, and varicella.

- To assess the immune response induced by PedvaxHIB given with 13vPnC relative to the immune response induced by PedvaxHIB given with 7vPnC when measured 1 month after the toddler dose.
- To assess the immune response induced by ActHIB given with 13vPnC relative to the immune response induced by ActHIB given with 7vPnC at alternative cutoff levels when measured 1 month after the infant series.
- To assess the immune response induced by PedvaxHIB given with 13vPnC relative to the immune response induced by PedvaxHIB given with 7vPnC at alternative cutoff levels when measured 1 month after the toddler dose.

An exploratory objective of this study was as follows:

- To assess the level of opsonophagocytic activity produced by 13vPnC relative to the level of opsonophagocytic activity produced by 7vPnC in a subset of 200 subjects (100 subjects/group), when measured 1 month after the infant series and 1 month after the toddler dose.

3.1.2.2 Study Design

Study 004 was a phase 3, parallel-group, randomized, active-controlled, double-blind, multicenter trial to evaluate the safety, immunogenicity, and tolerability of 13vPnC compared with 7vPnC when given with routine pediatric vaccinations in healthy infants.

Approximately 640 subjects (320 subjects per group) were to be enrolled in this study at 30 to 40 sites in order to achieve 270 evaluable subjects per group in the infant series and 240 evaluable subjects per group in the toddler dose. Subjects were to be randomly assigned (in a 1:1 ratio prospectively) to receive either 13vPnC + Pediarix + ctHIB/PedvaxHIB + ProQuad + VAQTA® or 7vPnC + Pediarix + ActHIB/PedvaxHIB + ProQuad + VAQTA. A complete medical history was obtained and a complete physical examination was performed at visit 1 before random assignment and administration of any study vaccinations.

Blood samples were to be obtained at 1 month after the third dose (visit 4, at approximately 7 months of age), just before the toddler dose (visit 5, at 12 to 15 months of age), and at 1 month after the toddler dose (visit 6, 28 to 42 days after visit 5). These samples were to be tested for immunoglobulin G (IgG) antibodies against the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) present in 13vPnC. Serum opsonophagocytic assays (OPAs) for the 13 pneumococcal serotypes were to be performed on the post-infant series blood samples in a randomly selected subset of 200 subjects (100 per vaccine group). Serum OPAs for selected serotypes were to be performed using the post-toddler blood samples from the same subset of subjects.

In addition, IgG antibody levels were to be measured in blood samples collected from all subjects, as follows: Hib polyribosylribitol phosphate (PRP) samples collected 1 month after the infant series and 1 month after the toddler dose; pertussis antigens (PT, FHA, PRN [69-kDa outer membrane protein]) and diphtheria toxoid samples collected 1 month

after the infant series; and MMR and varicella virus samples collected 1 month after the toddler dose.

3.1.2.3 Interim Analysis

The following statement is included in the submitted study report:

> "At least one interim analysis was planned after the toddler dose. The interim analysis was performed after all subjects had completed their post-toddler dose visits, their assay data had become available, and the database was considered clean. This interim analysis was to be considered the primary analysis and all type I error (alpha) was to be spent for this analysis. All analyses, except those associated with the 6-month follow-up visit, were performed at this time and were to be considered final. No separate interim analysis was conducted after the infant series."

CBER disagreed with the terminology "interim analysis" during the IND review. The term "interim analysis" usually refers to performing a statistical analysis of the data at a time point prior to the official close of the study with the intention of possibly terminating the study early. In order not to inflate the type 1 error probability, a smaller alpha is used for the interim analysis. Since the "interim" analysis mentioned above used all of the alpha and all the primary objectives were addressed, CBER considers this analysis to be the "primary analysis" and recommended so to the applicant. The applicant agreed to revise the protocol accordingly, but never did.

3.1.2.4 Statistical Methodologies

Statistical analyses were based on the statistical plans outlined in the SAP for the study, dated 14 May 2008.

Endpoints and Statistical Criteria

The primary immunological comparisons are the immune responses in subjects receiving 13vPnC relative to the responses in subjects receiving 7vPnC. The primary endpoint for each of the pneumococcal serotypes is the proportion of subjects achieving a serotype-specific IgG antibody concentration $\geq$0.35 μg/mL measured 1 month after the infant series. This choice of endpoints is based upon the World Health Organization (WHO) Guideline for evaluating new pneumococcal vaccines.

To assess treatment differences for each of the 7 common serotypes, the difference in proportions (13vPnC–7vPnC) was calculated. For each of the 6 additional serotypes, the difference in proportions (13vPnC–7vPnC reference) was calculated using the serotype with the lowest proportion among the 7 common serotypes in the 7vPnC group as the reference group. For each serotype, non-inferiority would be declared if the lower confidence interval (CI) for the difference was greater than –0.10.

The co-primary endpoint for each of the pneumococcal serotypes was the geometric mean concentration (GMC) measured 1 month after the toddler dose.

The co-primary endpoint for each concomitant antigen was the proportion of subjects achieving a predetermined antibody level. The prespecified antibody levels for each antigen were diphtheria ELISA ≥0.1 IU/mL, pertussis (PT, FHA, and PRN) defined levels (at least as large as the observed value achieved by 95% of subjects in the 7vPnC group), and PRP ≥0.15 μg/mL after the infant series.

For the diphtheria, pertussis (PT, FHA, and PRN), and Hib antigens, non-inferiority would be declared if the lower bound of the 2-sided, 95% CI for the difference in proportions was greater than –0.10. For the measles, mumps, rubella, and varicella antigens, non-inferiority would be declared if the lower bound of the 2-sided, 95% CI for the difference in proportions was greater than –0.05 for measles, mumps, and rubella, and –0.10 for varicella.

The secondary endpoints for each of the pneumococcal serotypes were the proportion of subjects achieving a serotype-specific IgG antibody concentration ≥1.00 μg/mL after the infant series and the proportions of subjects achieving serotype-specific IgG antibody concentrations ≥0.35 μg/mL and ≥1.00 μg/mL after the toddler dose. Another secondary endpoint was the serotype-specific geometric mean IgG antibody concentration measured 1 month after the infant series and before the toddler dose. In addition, if any of the pneumococcal serotypes failed non-inferiority at the 0.35-μg/mL level after the infant series, then an additional 0.15-μg/mL level was to be examined. (If all pneumococcal serotypes passed non-inferiority, then the 0.15 μg/mL analysis was not to be performed.).

The co-secondary endpoint for ActHIB was the proportion of subjects achieving an alternative cutoff level measured 1 month after the infant series. The alternative antibody level was PRP ≥1.0 μg/mL.

The co-secondary endpoint for the PedvaxHIB concomitant antigen was the proportion of subjects achieving a predefined PRP level ≥0.15 μg/mL and an alternative PRP level ≥1.0 μg/mL 1 month after the toddler dose.

The co-secondary endpoint for each of the ProQuad concomitant antigens was the proportion of subjects achieving a predetermined antibody level. The prespecified antibody levels for each antigen were measles ≥1.1 index value (I.V.), mumps ≥1.1 I.V., rubella ≥15 IU/mL, and varicella ELISA ≥1.09 I.V.

For the secondary objectives, the following were assessed: alternative antibody levels for PRP level ≥1.0 μg/mL after the infant series; PRP levels ≥0.15 μg/mL and ≥1.0 μg/mL after the toddler dose; and measles ≥1.10 I.V., mumps ≥1.10 I.V., rubella ≥15 IU/mL, and varicella ELISA ≥1.09 I.V. after the toddler dose.

The exploratory endpoint for each of the pneumococcal serotypes was the proportion of subjects achieving a serotype-specific OPA antibody titer ≥1:8 measured 1 month after

the infant series and 1 month after the toddler dose, in a subset of 100 subjects per vaccine group.

Methods of Analyses

Pneumococcal assay values that were reported in the database below the limit of quantification (reported as a text value "BLQ" or reported numeric values below the lower level of quantification) were adjusted to one half the lower level of quantification for analysis. Indeterminate values were not to be assigned a numerical value. Missing values were to be excluded from the immunogenicity analyses; no imputation or estimation of missing values was performed. All analyses were performed using the subject's random vaccine assignment. Subjects who received all vaccinations as randomized were to be included in the evaluable analysis population.

Non-inferiority for the study would be demonstrated only if the lower bounds for the proportions for all 13 pneumococcal IgG comparisons and all 5 concomitant vaccine comparisons were greater than -0.10 and all 13 pneumococcal geometric mean ratio (GMR) comparisons were greater than 0.5.

Analysis Populations

For the immunogenicity analyses, 4 analysis populations were defined: evaluable infant immunogenicity, all-available infant immunogenicity, evaluable toddler immunogenicity, and all-available toddler immunogenicity.

Determination of Sample Size

The details on sample size and power estimations are in section 1.3 of the SAP, dated 14 May 2008, which was submitted in the appendix for study report 004 entitled Statistical Methods.

Sample size estimation was based upon the proportion of responders and the GMCs in each vaccine group. Data from Wyeth study 6096A1-003 were used for the proportion of responders for pneumococcal serotypes. Data from Wyeth study D140-P001 were used for the GMCs for pneumococcal serotypes. Data from Wyeth studies 6096A1-003, D139-P500, and D140-P001 were used for Pediarix, ActHIB, and ProQuad concomitant vaccine antigens.

The study was powered to show both non-inferiority of 13vPnC relative to 7vPnC and non-inferiority of selected concomitant vaccine antigens when routine pediatric vaccines were administered concomitantly with 13vPnC relative to routine pediatric vaccines administered concomitantly with 7vPnC.

Sample sizes of 250 evaluable subjects per group would provide at least 91% overall power to declare non-inferiority for all 13 pneumococcal antigens using a non-inferiority

criterion of -0.10 and a 2-sided type I error of 0.05. Assuming a dropout rate of about 15%, it was determined that an enrollment of 600 subjects would ensure that 500 subjects would be evaluable.

Sample sizes of 240 evaluable subjects per group would provide at least 93% overall power to declare non-inferiority for all concomitant vaccine antigens using a non-inferiority criterion of -0.10 and a 2-sided type I error of 0.05. Assuming a drop out rate of at most 25%, enrollment of 640 subjects would ensure that 480 subjects would be evaluable after the toddler dose.

3.1.2.5 Results and Conclusions

Results of Infant Series

A total of 666 subjects were enrolled in the study at 38 sites in the United States. The following Table 3-8 (Table 9-1 in the submission) provided information on the number of subjects in each group. There were 252 evaluable subjects in each of the 13vPnC and 7vPnC group for immunogenicity evaluation.

Table 3-8. All-available and evaluable immunogenicity population – infant series

Vaccine group (as randomize)	13vPnC		7vPnC		Total	
	n	%	n	%	n	%
Randomized	334	100.0	332	100.0	666	100.0
All-available infant immunogenicity population	266	79.6	263	79.2	529	79.4
Subjects excluded form the all-available infant immunogenicity population	68	20.4	69	20.8	137	20.6
No post-infant series assay result for any pneumococcal serotype or concomitant antigen	68	20.4	69	20.8	137	20.6
Evaluable infant immunogenicity population	252	75.4	252	75.9	504	75.7
Subjects excluded from the evaluable infant immunogenicity population[a]	82	24.6	80	24.1	162	24.3
Not in all-available infant immunogenicity population	68	20.4	69	20.8	137	20.6
Blood draw > 56 days after the infant series	6	1.8	6	1.8	12	1.8
Received prohibited vaccines	4	1.2	1	0.3	5	0.8
Forced randomization	2	0.6	1	0.3	3	0.5
No post-infant assay result for any concomitant antigen[b]	1	0.3	1	0.3	2	0.3
Not eligible for the study	1	0.3	0	0.0	1	0.2
Received vaccine other than randomized	0	0.0	1	0.3	1	0.2
Did not receive all pneumococcal study vaccinations	1	0.3	0	0.0	1	0.2
Did not receive all concomitant study vaccinations	0	0.0	1[c]	0.3	1	0.2
Blood draw < 27 days after the infant series	1	0.3	0	0.0	1	0.2
Did not meet eligibility criteria	1	0.3	0	0.0	1	0.2
Exclusionary adverse event	0	0.0	1	0.3	1	0.2

a. Subjects may have been excluded for more than one reason
b. Subjects with no post-infant assay results for a serotype/concomitant vaccine antigen are not included in this category and are classified as "Not in all-available infant immunogenicity population".
c. Subject 004-010-001056 was not counted among the subjects who received Pediarix at dose 2 due to an error. See section 14.0, Clinical Data Report Errata of the submission.

The following Table 3-9 (Table 9-4 in the submission) provides the number of subjects in each group who achieved a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL after dose 3 of the evaluable infant population and the differences and their 95% CI for each serotype. For the 7 common serotypes, the difference in proportions (13vPnC–7vPnC) was used. For each of the 6 additional serotypes, the difference in proportions (13vPnC–7vPnC reference) was calculated using the serotype with the lowest proportion among the 7 common serotypes in the 7vPnC group as the reference group. For each serotype, non-inferiority would be declared if the lower confidence interval (CI) for the difference was greater than –0.10.

Of the 7 common serotypes, the lower bound for serotype 6B was -10.9% and for serotype 9V was -12.4%. For the 6 new serotypes, serotype 3 had the lowest lower bound, -36.2%. In order to achieve the primary statistical objective, it was stated that all 13 serotypes needed to satisfy the non-inferiority criterion. Therefore, according to this pre-specified success criterion, this objective was not met.

Table 3-9. Comparison of subjects achieving a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL after dose 3 of the infant series – evaluable infant immunogenicity population (infant series analysis)

Vaccine group (Randomized)	13vPnC				7vPnC					
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI[c])**	**N[a]**	**n[b]**	**%**	**(95% CI[c])**	**Diff[d]**	**(95% CI[e])**
7vPnC										
4	252	238	94.4	(90.9, 96.9)	251	246	98.0	(95.4, 99.4)	-3.6	(-7.3, -0.1)
6B	252	220	87.3	(82.5, 91.1)	250	232	92.8	(88.9, 95.7)	-5.5	(-10.9, -0.1)
9V	252	228	90.5	(86.2, 93.8)	252	248	98.4	(96.0, 99.6)	-7.9	(-12.4, -4.0)
14	251	245	97.6	(94.9, 99.1)	252	245	97.2	(94.4, 98.9)	0.4	(-2.7, 3.5)
18c	252	244	96.8	(93.8, 98.6)	252	248	98.4	(96.0, 99.6)	-1.6	(-4.7, 1.2)
19F	252	247	98.0	(95.4, 99.4)	251	245	97.6	(94.9, 99.1)	0.4	(-2.4, 3.4)
23F	252	228	90.5	(86.2, 93.8)	252	237	94.0	(90.4, 96.6)	-3.6	(-8.5, 1.2)
Additional										
1	252	241	95.6	(92.3, 97.8)	250	232	92.8	(88.9, 95.7)	2.8	(-1.3, 7.2)
3	249	158	63.5	(57.1,69.4)	250	232	92.8	(88.9, 95.7)	-29.3	(-36.2, -22.4)
5	252	226	89.7	(85.2, 93.1)	250	232	92.8	(88.9, 95.7)	-3.1	(-8.3, 1.9)
6A	252	242	96.0	(92.8, 98.1)	250	232	92.8	(88.9, 95.7)	3.2	(-0.8, 7.6)
7F	252	248	98.4	(96.0, 99.6)	250	232	92.8	(88.9, 95.7)	5.6	(1.9, 9.7)
19A	251	247	98.4	(96.0, 99.6)	250	232	92.8	(88.9, 95.7)	5.6	(1.9, 9.7)

a. N = Number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥ 0.35 µg/Ml for the given serotype.
c. Exact 2-sided confidence interval based upon the observed proportion of subjects.
d. Difference in proportions, 13vPnC – 7vPnC, expressed as a percentage. For the 7vPnC serotypes, the reference value is the corresponding proportion in the 7vPnC group. For the additional serotypes, the reference value is serotype 6B from the 7vPnC group.
e. Exact 2-sided confidence interval for the difference in proportions, 13vPnC – 7vPnC reference, expressed as a percentage.

In the following Table 3-10 (Table 9-7 in the submission), the geometric mean concentrations, their ratios (13vPnC to 7vPnC) and confidence intervals for each of the 7 common serotypes are given. For the 6 new serotypes, the lowest GMC value from the 7vPnC group, namely serotype 7V, was used as a comparator.

All ratios for the 7 common serotypes were all below 1.00 and the highest value for the upper bounds of the 95% CI was 1.00. The lower bounds of the GMC ratios for the 7 common serotypes were all above 0.5 which was the pre-specified non-inferiority criterion. The lowest ratio of all was 0.52, which was the lower bound for serotype 6B.

Among the 6 new serotypes, when compared to the lowest GMC value of the 7 common serotypes, serotype 3 had a 95% confidence interval of (0.30, 0.41). Note that the upper bound of the 95% CI for serotype 3 is lower than the pre-specified minimum lower bound of 0.5. All other 5 serotypes satisfied the non-inferiority criterion.

Table 3-10. Comparison of pneumococcal IgG GMCs (µg/mL) after dose 3 of the infant series – evaluable infant immunogenicity population

Vaccine Group (randomized)	13vPnC			7vPnC				
Serotype	**n[a]**	**GMC[b]**	**(95% CI[c])**	**n[a]**	**GMC[b]**	**(95% CI[c])**	**Ratio[d]**	**(95% CI[e])**
7vPnC								
4	252	1.31	(1.19, 1.45)	251	1.93	(1.75, 2.13)	0.68	(0.59, 0.78)
6B	252	2.10	(1.77, 2.49)	250	3.14	(2.64, 3.74)	0.67	(0.52, 0.85)
9V	252	0.98	(0.89, 1.08)	252	1.40	(1.27, 1.55)	0.70	(0.61, 0.80)
14	251	4.74	(4.18, 5.39)	252	5.67	(5.02, 6.40)	0.84	(0.70, 1.00)
18c	252	1.37	(1.24, 1.52)	252	1.79	(1.63, 1.96)	0.77	(0.67, 0.88)
19F	252	1.85	(1.69, 2.04)	251	2.24	(2.01, 2.50)	0.83	(0.72, 0.96)
23F	252	1.33	(1.17, 1.51)	252	1.90	(1.68, 2.15)	0.70	(0.59, 0.84)
Additional								
1	252	2.03	(1.78, 2.32)	252	1.40	(1.27, 1.55)	1.45	(1.23, 1.71)
3	249	0.49	(0.43, 0.55)	252	1.40	(1.27, 1.55)	0.35	(0.30, 0.41)
5	252	1.33	(1.18, 1.50)	252	1.40	(1.27, 1.55)	0.95	(0.81, 1.11)
6A	252	2.19	(1.93, 2.48)	252	1.40	(1.27, 1.55)	1.56	(1.33, 1.83)
7F	252	2.57	(2.28, 2.89)	252	1.40	(1.27, 1.55)	1.83	(1.57, 2.13)
19A	251	2.07	(1.87, 2.30)	252	1.40	(1.27, 1.55)	1.48	(1.28, 1.71)

a. n = number of subjects with determinate antibody concentration for the specified serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transformations of a confidence interval based on the Student *t* distribution for the mean logarithm of the concentrations.
d. Ratio of GMCs; 13vPnC to 7vPnC reference. For the 7vPnC serotypes, the reference value is the corresponding geometric mean concentration in the 7vPnC group. For the additional serotypes, the reference value is serotype 9V from the 7vPnC group.
e. Confidence intervals (CIs) for the ratio are back transformations of a confidence interval based on the Student *t* distribution for the mean difference of the logarithms of the measures (13vPnC – 7vPncC reference).

For the secondary endpoint of pneumococcal IgG antibody concentration ≥ 1.00 µg/mL after dose 3 in the evaluable infant immunogenicity population, 6 of the 7 common serotypes and 4 of 6 of the new serotypes did not meet the non-inferiority criterion. As for the secondary endpoint of pneumococcal IgG antibody concentration ≥ 0.15 µg/mL after dose 3, all serotypes met the non-inferiority criterion.

Results of the Toddler Dose

One of the co-primary objectives was to demonstrate non-inferiority of 13vPnC to 7vPnC by meeting the pre-specified criterion for each of the 13 serotypes in terms of the ratio of geometric mean concentrations measured one month after the toddler dose. For this co-primary objective, of all 13 serotypes, serotype 3 did not meet the pre-specified criterion. For the GMC of serotype 3 [0.94 with a 95% CI of (0.83, 1.05)] compared to the GMC of serotype 9V [lowest among 7 common serotypes; 3.63 with 95% CI (3.25, 4.05)], the ratio was 0.26 with 95% CI (0.22, 0.30). The lower bound of the 95% CI of the ratio of the two GMCs was 0.22 which is lower than 0.5, the non-inferiority criterion; therefore, the co-primary objective was not achieved. Also, for the 7 common serotypes, although the lower bounds of the 95% CIs were greater than 0.5, the upper bounds were below 1.00, except for serotype 19F.

For the secondary endpoints, serotype 3 also did not meet the non-inferiority criterion based on the proportion of subjects who achieved antibody concentration ≥ 0.35 μg/mL, the proportion who achieved concentration ≥ 1.00 μg/mL, after the toddler dose, as well as the comparison based on the GMC ratio before the toddler dose.

Besides serotype 3, serotypes 4, 9V, 18C, and 23F of the 7 common serotypes also did not meet the secondary endpoints of antibody concentration ≥ 1.00 μg/mL. None of the lower bounds of the 95% CI of the difference in proportions (13vPnC – 7vPnC) met the non-inferiority criterion, -10%. Furthermore, the upper bounds of the CIs for those serotypes were also below 0.

Results of the Concomitant Immunogenicity Analyses

A co-primary endpoint of study 004 was the proportion of subjects achieving a pre-specified antibody level for each of the concomitant vaccine antigens selected for analysis. These levels were as follows: diphtheria ELISA ≥0.1 IU/mL, pertussis (PT, FHA, and PRN) defined levels (at least as large as the observed value achieved by 95% of subjects in the 7vPnC group), and PRP ≥0.15 μg/mL after the infant series.

Co-secondary endpoints included an alternative pre-specified PRP level ≥1.0 μg/mL after the infant series, pre-specified antibody levels for measles ≥1.10 I.V., mumps ≥1.10 I.V., rubella ≥15 IU/mL, varicella ELISA ≥1.09 I.V., and PRP ≥0.15 μg/mL after the toddler dose, and an alternative PRP level ≥1.0 μg/mL after the toddler dose.

Non-inferiority of 13vPnC relative to 7vPnC was demonstrated for the selected antigens in the concomitant vaccines Pediarix (diphtheria and pertussis) and ActHIB (PRP) after the infant series and ProQuad (measles, mumps, rubella, and varicella) and PedvaxHIB (PRP) after the toddler dose.

The results in the all-available toddler immunogenicity population were similar, except that the difference in proportion of subjects in the 13vPnC and 7vPnC groups achieving

an antibody level of 1.10 I.V. for mumps was 1.3% with a lower limit of the 95% CI of -6.6%, which did not meet the non-inferiority criterion of being at least -5%.

Applicant's Conclusion for Study 004 Immunogenicity Evaluation

The applicant has the following conclusion for the pneumococcal immunogenicity evaluations:

> "The study met the primary endpoint for pneumococcal non-inferiority for 10 of the 13 serotypes after the infant series. The exceptions were serotypes 6B, 9V, and 3 which had lower limits for the 95% CI of -10.9%, -12.4%, and -36.2, respectively. Although serotype 3 failed to meet the primary non-inferiority criterion when compared with the 7vPnC serotype having the lowest proportion of responders (6B, 92.8%), the proportion of subjects with an antibody concentration ≥0.35 μg/mL for serotype 3 was much higher in the 13vPnC group than in the 7vPnC group (63.5% versus 4.6%), demonstrating that 13vPnC elicited a substantially greater immune response to this serotype than 7vPnC.
>
> Twelve (12) of the 13 pneumococcal serotypes met the 2-fold non-inferiority criterion for comparison of GMCs. The exception was serotype 3, for which the GMR calculated using the comparison serotype (9V, 1.40 μg/mL) was 0.35 (95% CI, 0.30 to 0.41). However, the GMCs for serotype 3 were 0.49 μg/mL and 0.04 μg/mL in the 13vPnC group and 7vPnC group, respectively. GMCs for the 7 common serotypes were lower in the 13vPnC group than in the 7vPnC group (ie, GMRs were <1, range 0.68 to 0.84 with the upper bounds of most CIs being <1.00), although the differences were within the bounds of the 2-fold non-inferiority criterion."

3.1.2.6 Reviewer's Comments on Study 004

1. *For the primary objective, 2 of the 7 common serotypes (serotypes 6B and 9V) and 1 of the 6 new additional serotypes (serotype 3) did not meet the infant series non-inferiority criterion, based on comparing the proportion of subjects achieving antibody concentration ≥ 0.35 μg/mL.*

2. *For the primary objective, 1 of the 6 new additional serotypes (serotype 3) did not meet the non-inferiority criteria for both the infant series and the toddler dose, based on comparing the GMCs between the two groups.*

3. *Serotype 6B did not meet the non-inferiority criterion by having the lower bound of 95% CI > -10%, based on comparing the proportion of subjects achieving antibody concentration ≥ 0.35 μg/mL. Serotype 6B had a lower bound of 0.52, the lowest of all lower bounds for the GMC ratios between the two groups, barely passing the non-inferiority margin of 0.5. Serotype 6B also did not demonstrate non-inferiority, based on comparing 13vPnC with and without P80 in study 009. Since 13cPnC and 7vPnC used in this trial did not contain P80, this raised a question regarding whether the immunogenicity induced by 6B could be even lower in the final formulation of 13vPnC.*

4. *In comparing the GMCs, among the 7 common serotypes, the upper bounds of the 95% confidence intervals of 6 serotypes were below 1.00, suggesting that the GMCs in general, were statistically lower in the 13vPnC group than in the 7vPnC group.*

5. *It should be noted that if this product is licensed, it will likely replace 7vPnC in the market. Thus, if future pneumococcal vaccines are compared to 13vPnC, there is a potential for the phenomenon of immunogenicity creep to occur, resulting in future vaccines that are even less immunogenic than 13vPnC, if the current non-inferiority criteria are kept the same. This possibility should be considered when determining non-inferiority margins for future pneumococcal vaccines if they will be compared to the 13vPnC vaccine.*

3.1.3 Study 6096A1-3005 (Study 3005)

Study 3005 evaluated 3 lots of 13vPnC, including 2 pilot lots and 1 manufacturing scale lot, to show that different lots produce consistent immune responses and that 13vPnC can be manufactured in a consistent manner. A group of subjects also received 7vPnC to provide additional comparative safety information. In this study, polysorbate 80 was included in the vaccine 13vPnC.

3.1.3.1 Objectives for Immunogenicity

The primary objectives of this study were:

- To demonstrate that the immune responses induced by 3 lots of 13vPnC are equivalent when measured 1 month after the infant series.
- To demonstrate that the immune responses induced by Pediarix given with 13vPnC are non-inferior to the immune responses induced by Pediarix given with 7vPnC when measured 1 month after the infant series. Responses to the following antigens in Pediarix were to be assessed: tetanus; poliovirus types 1, 2, and 3; and hepatitis B. (Responses to diphtheria and acellular pertussis antigens are not assessed in this trial.)

The secondary objective of this study was:

- To demonstrate that the immune responses induced by 3 lots of 13vPnC are equivalent when measured 1 month after the toddler dose.

3.1.3.2 Study design

This was a parallel-group, randomized, active-controlled, double-blind, multicenter trial in which subjects were randomly assigned in a 2:2:2:1 ratio to receive 13vPnC pilot scale lot 1, 13vPnC pilot scale lot 2, 13vPnC manufacturing scale lot, or 7vPnC.

Approximately 1645 subjects (470 subjects in the 13vPnC pilot scale lot 1 group, 470 subjects in the 13vPnC pilot scale lot 2 group, 470 subjects in the 13vPnC manufacturing scale lot group, and 235 subjects in the 7vPnC group) were to participate in this study at approximately 85 sites, to achieve 1400 evaluable subjects (400 subjects in the 13vPnC pilot scale lot 1 group, 400 subjects in the 13vPnC pilot scale lot 2 group, 400 subjects in the 13vPnC manufacturing scale lot group, and 200 subjects in the 7vPnC group).

Each subject was expected to participate from the first vaccination at 2 months of age to a post-toddler dose blood draw at 13 months of age with a follow-up telephone interview 6 months after the toddler dose. The total duration of subject participation was approximately 17 months.

Blood samples (approximately 5 mL) were to be obtained at 1 month (28 to 42 days) after the infant series and 1 month (28 to 42 days) after the toddler dose. Assays performed on these blood samples were to include serotype-specific immunoglobulin G (IgG) concentrations to the 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F).

In addition, the following assays were to be performed on samples collected 1 month after the infant series: serum levels of antibody to poliovirus (strains 1, 2, and 3) were measured using a polio –(b)(4)------ neutralization assay; serum levels of antibody to hepatitis B surface antigen (HBsAg) were measured using an FDA approved in vitro diagnostic kit; and serum levels of IgG antibodies to tetanus toxoid were measured using an antitetanus toxoid enzyme-linked immunosorbent assay (ELISA).

3.1.3.3 Statistical Methodologies

Statistical analyses were based on the statistical plans outlined in the statistical analysis plan (SAP) for this study, version 1 dated 27 May 2008.

Comparisons of Interest and Endpoints

The evaluable infant immunogenicity population was the primary analysis population and included subjects who received the vaccine to which they were randomly assigned at all expected doses, had blood drawn within the protocol-specified time frames, had at least 1 valid and determinate assay result, and had no other major protocol violations. An analysis was also performed for the all-available infant immunogenicity population, which included all subjects with at least 1 valid and determinate assay result.

Missing assay results were not replaced or imputed. All analyses were performed using the subject's randomized treatment assignment. Subjects who received all vaccinations as randomized were included in the evaluable analysis population.

The first primary immunological comparisons were performed using the anti-pneumococcal polysaccharide responses, measured 1 month after the infant series, in subjects receiving the 13vPnC vaccine.

The second primary immunologic comparisons were performed using the immune responses induced by Pediarix given with 13vPnC compared with the responses induced by Pediarix in subjects receiving 7vPnC, measured 1 month after the infant series.

The primary endpoint for evaluation of equivalence among the 3 13vPnC vaccine lots for each of the pneumococcal serotypes was the serotype-specific geometric mean IgG antibody concentration measured 1 month after the infant series.

The secondary endpoints for comparisons of the immune responses among the 3 13vPnC lots were the proportion of subjects achieving a serotype-specific IgG antibody concentration ≥0.35 μg/mL measured 1 month after the infant series and 1 month after the toddler dose; the proportion of subjects achieving a serotype-specific IgG antibody concentration ≥1.00 μg/mL measured 1 month after the infant series and 1 month after the toddler dose; and the serotype-specific geometric mean IgG antibody concentration measured 1 month after the toddler dose.

Analysis Populations

For the 13vPnC immunogenicity analyses, 4 analysis populations were defined: evaluable infant immunogenicity, all-available infant immunogenicity, evaluable toddler immunogenicity, and all-available toddler immunogenicity. If there were no important differences between the evaluable toddler and all-available toddler immunogenicity populations, a single all-available toddler immunogenicity analysis was to be performed. To be included in an evaluable immunogenicity population, the subject must have been eligible, have received the treatment to which they were randomly assigned, have had blood drawn within the protocol-specified time frames, have had at least 1 valid and determinate assay result for the proposed analysis, and have had no major protocol violations. All subjects meeting these criteria were included. To be included in an all-available immunogenicity population, a subject must have had at least 1 valid and determinate assay result related to the proposed analysis.

Methods of Analyses

The pneumococcal IgG serotype antibody concentrations were logarithmically transformed for analysis. Within each lot and for each antibody concentration separately, geometric means of the antibody concentration at each of the visits were calculated and rank ordered from lowest (1) to highest (3). Two-sided, 95% confidence intervals were constructed by back transformation of the confidence intervals for the mean of the logarithmically transformed assay results computed using the Student t distribution. In addition, the ratio of the geometric mean concentrations and corresponding 2-sided 95% confidence intervals were computed to aid in interpretation of results. For the geometric mean ratio, the confidence intervals were computed using the Student t distribution for

the mean difference of the measures on the log scale (lowest relative to middle, lowest relative to highest, and middle relative to highest). To evaluate equivalency among the 3 lots, the equivalence test of Wiens and Iglewicz was used.

For each of the pneumococcal serotypes, the proportion of subjects achieving a serum IgG ≥0.35 µg/mL 1 month after the infant series was calculated. Exact, unconditional, 2-sided 95% confidence intervals on the pairwise difference in proportions were calculated to aid in interpretation of results. The confidence intervals were computed using the non-inferiority procedure of Chan and Zhang, using the standardized test statistics and gamma=0.000001. To evaluate the consistency among the 3 lots, the equivalence test of Wiens and Iglewicz was used.

Interim analysis

The primary analysis for the study was planned to occur before the formal completion of the study (6-month follow-up telephone contact). The primary immunogenicity analysis was planned after the assay results for the infant series were available, and another analysis was to occur after the assay results for the toddler dose were available. In addition, the primary analysis of the safety data collected during the infant series was planned for a regulatory submission before the assay results were available. The immunogenicity analysis after the infant series was the primary analysis and all type I error (alpha) was spent for this analysis.

The data collected subsequent to the infant series analysis, and their associated analyses, were secondary and/or exploratory. A final analysis of the 6-month follow-up data was performed after all data had been collected.

Determination of Sample Size

Sample size estimates were based on the geometric mean IgG concentrations for 13vPnC and the proportion of responders in each treatment group. Data from Wyeth studies 6096A1-003 and 6096A1-009 were used for pneumococcal serotypes and from Wyeth studies D139-P500 and D140-P001 for the proportion of responders to the tetanus, polio, and hepatitis B concomitant vaccine antigens.

Overall, a sample size of 400 evaluable subjects per vaccine lot group after the infant series and 200 evaluable subjects in the 7vPnC group after the infant series would provide at least 88% overall power to declare equivalence of the 3 lots of 13vPnC and non-inferiority for all 5 concomitant vaccine antigen comparisons using a 2-sided, type I error of 0.05. Thus, 1645 subjects (470 subjects per 13vPnC group and 235 subjects in the 7vPnC group) were to be enrolled to ensure that the required number of evaluable subjects per group was obtained.

3.1.3.5 Results and Conclusions

Results of Infant Series

The following Table 3-11 (Table 9-1 in the submission), provides the number of subjects in each of the groups. Of 1712 subjects randomly assigned to receive study vaccine, 489 received 13vPnC lot 1, 488 received 13vPnC lot 2, 489 received 13vPnC manufacturing scale lot, and 246 received 7vPnC. For the evaluable pneumococcal immunogenicity population, 413 received 13vPnC lot 1, 404 received 13vPnC lot 2, and 399 received 13vPnC manufacturing scale lot. Of 385 subjects included in the evaluable concomitant vaccine immunogenicity population, 62 received 13vPnC lot 1, 63 received 13vPnC lot 2, 64 received 13vPnC manufacturing scale lot, and 196 received 7vPnC.

Table 3-11. All-available and evaluable immunogenicity populations – infant series

Vaccine group	**13vPnC Pilot Lot 1**		**13vPnC Pilot Lot 2**		**13vPnC Manufacturing Scale Lot**		**7vPnC**		**Total**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**
Randomized	489	100.0	488	100.0	489	100.0	246	100.0	1712	100.0
All-available concomitant infant immunogenicity population	67	13.7	64	13.1	64	13.1	198	80.5	393	23.0
All-available infant immunogenicity population[a]	425	86.9	409	83.8	409	83.6	N/A	N/A	1243	72.6
Subjects excluded form the all-available infant immunogenicity population	422	86.3	424	86.9	426	87.1	48	19.5	1320	77.1
No post-infant series assay result for any concomitant antigen	422	86.3	424	86.9	425	86.9	48	19.5	223	77.0
No post-infant assay result for any pneumococcal serotype[a]	64	13.1	79	16.2	80	16.4	N/A	N/A	393	13.0
Evaluable concomitant infant immunogenicity population	62	12.7	63	12.9	64	13.1	196	79.7	385	22.5
Evaluable pneumococcal infant immunogenicity population[a]	413	84.5	404	82.8	399	81.6	N/A	N/A	1216	71.0

Subjects excluded from the evaluable infant immunogenicity population[b]	427	87.3	425	87.1	426	87.1	50	20.3	1328	77.6
Not in all-available concomitant infant immunogenicity population	422	86.3	424	86.9	425	86.9	48	19.5	1319	77.0
Not in all-available pneumococcal infant immunogenicity population[b]	64	13.1	79	16.2	80	16.4	N/A	N/A	223	13.0
Blood draw > 56 days after the infant series	7	1.4	2	0.4	5	1.0	2	0.8	16	0.9
Received vaccine other than randomized	3	0.6	1	0.2	4	0.8	0	0.0	8	0.5
Subject was vaccinated with another package number	2	0.4	0	0.0	4	0.8	0	0.0	6	0.4
Blood draw < 27 days after the infant series	1	0.2	2	0.4	1	0.2	0	0.0	4	0.2
Not eligible for the study	0	0.0	2	0.4	1	0.2	0	0.0	3	0.2
Did not receive all pneumococcal study vaccinations	0	0.0	2	0.4	1	0.2	0	0.0	3	0.2
Subject was assigned and vaccinated with incorrect package number (wrong subject # engtered)	2	0.4	0	0.0	0	0.0	0	0.0	2	0.1

a. Only applies to the 13vPnC groups.
b. Subjects may have been excluded for more than one reason.

In Table 3-12 (part of Table 9-4 in the submission), the pneumococcal IgG geometric mean concentrations (GMCs) and their corresponding 95% confidence intervals (CIs) for

each serotype and each lot are provided. In Table 3-13 (part of Table 9-4 in the submission), the differences between vaccine lots in log-transformed GMCs are provided. The equivalence criterion for evaluation was that the 95% CIs should be within -0.693 and 0.693, the natural log-transformed value of 0.5 and 2, respectively. Since all 95% CIs were within this interval, the equivalence criterion was met.

Table 3-12. Pneumococcal IgG GMCs after the infant series – evaluable pneumococcal infant population

Vaccine group (randomized)	13vPnC Pilot Lot 1			13vPnC Pilot Lot 2			13vPnC Manufacturing Scale Lot		
Serotype	**N[a]**	**GMC[b]**	**(95% CI[c])**	**N[a]**	**GMC**	**(95% CI[c])**	**N**	**GMC**	**(95% CI)**
7vPnC									
4	411	1.33	(1.24, 1.43)	404	1.34	(1.25, 1.44)	398	1.75	(1.63, 1.88)
6B	409	2.89	(2.58, 3.23)	401	2.15	(1.91, 2.42)	396	2.54	(2.27, 2.85)
9V	411	1.05	(0.98, 1.12)	403	1.11	(1.04, 1.19)	396	1.11	(1.04, 1.19)
14	398	4.97	(4.59, 5.37)	387	5.13	(4.70, 5.59)	387	5.18	(4.72, 5.69)
18c	413	1.30	(1.22, 1.38)	401	1.34	(1.24, 1.44)	398	1.48	(1.38, 1.58)
19F	408	1.85	(1.71, 1.99)	399	2.07	(1.92, 2.24)	398	2.59	(2.40, 2.78)
23F	411	1.24	(1.13, 1.36)	402	1.27	(1.15, 1.40)	399	1.03	(0.94, 1.14)
Additional									
1	411	1.62	(1.50, 1.76)	403	1.81	(1.66, 1.98)	395	1.91	(1.76, 2.07)
3	406	0.52	(0.48, 0.55)	391	0.56	(0.52, 0.61)	393	0.61	(0.57, 0.66)
5	412	1.35	(1.24, 1.47)	402	1.05	(0.96, 1.14)	393	1.35	(1.25, 1.47)
6A	413	2.40	(2.21, 2.61)	402	2.10	(1.92, 2.29)	398	2.12	(1.96, 2.30)
7F	412	2.54	(2.37, 2.71)	401	2.52	(2.35, 2.70)	397	2.67	(2.50, 2.85)
19A	411	1.85	(1.71, 2.00)	403	2.00	(1.85, 2.16)	397	1.88	(1.74, 2.02)

a. n = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. Geometric mean concentrations (GMCs) were calculated using all subjects with available data for the specified blood draw.
c. Confidence intervals (CIs) are back transforms of confidence levels based on the Student *t* distribution for the mean logarithm of the concentrations.

Table 3-13. Pneumococcal IgG GMCs and equivalency assessment (µg/mL) after the infant series – evaluable pneumococcal infant populations

	Log-transformed GMC In each lot of 13vPnC (randomized)			Difference in log-transformed geometric means					
	Lot 1	Lot 2	M[a]	Lot 1 – Lot 2		Lot 1 – M[a]		Lot 2 – M[a]	
Serotype				**%**	**(95% CI)**	**%**	**(95% CI)**	**%**	**(95% CI)**
7vPnC									
4	0.28	0.29	0.56	-0.01	(-0.11, 0.09)	-0.27	(-0.38, -0.17)	-0.27	(-0.37, -0.16)
6B	1.06	0.76	0.93	0.30	(0.13, 0.46)	0.13	(-0.03, 0.29)	-0.17	(-0.33, -0.01)
9V	0.05	0.11	0.11	-0.06	(-0.16, 0.04)	-0.06	(-0.16, 0.04)	0.00	(-0.10, 0.10)
14	1.60	1.63	1.65	-0.03	(-0.15, 0.08)	-0.04	(-0.16, 0.08)	-0.01	(-0.14, 0.12)
18c	0.26	0.29	0.39	-0.03	(-0.13, 0.07)	-0.13	(-0.22, -0.04)	-0.10	(-0.20, 0.00)
19F	0.61	0.73	0.95	-0.11	(-0.22, -0.01)	-0.34	(-0.44, -0.23)	-0.22	(-0.33, -0.11)
23F	0.21	0.24	0.03	-0.03	(-0.16, 0.11)	0.18	(0.04, 0.31)	0.20	(0.07, 0.34)
Additional									
1	0.49	0.59	0.65	-0.11	(-0.23, 0.01)	-0.16	(-0.28, -0.05)	-0.05	(-0.18, 0.07)
3	-0.67	-0.57	-0.49	-0.09	(-0.20, 0.02)	-0.18	(-0.28, -0.07)	-0.09	(-0.20, 0.02)
5	0.30	0.05	0.30	0.25	(0.13, 0.37)	-0.00	(-0.12, 0.12)	-0.25	(-0.37, -0.14)
6A	0.88	0.74	0.75	0.14	(0.01, 0.26)	0.12	(0.01, 0.24)	-0.01	(-0.13, 0.11)
7F	0.93	0.92	0.98	0.01	(-0.09, 0.10)	-0.05	(-0.14, 0.04)	-0.06	(-0.15, 0.04)
19A	0.61	0.69	0.63	-0.08	(-0.19, 0.03)	-0.02	(-0.12, 0.09)	0.06	(-0.04, 0.17)

a. M = 13vPnC Manufacturing Scale Lot

For the secondary immunogenicity endpoint, the applicant provided the number and proportion of subjects achieving a pneumococcal IgG Antibody concentration ≥ 0.35 µg/mL for each of the 13vPnC lots after the infant series. Table 9-5, presented below, illustrates these results submitted by the applicant. However, the reviewer obtained slightly different results of the proportions. The reviewer's results for the proportion are presented in Table 3-14 and the differences between proportions in Table 3-15.

(Applicant provided) Table 9-5: Subjects Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL for Each 13vPnC Group After the Infant Series - Evaluable Pneumococcal Infant Population

	Vaccine Group (as Randomized)												Difference (95% CI) in Percentage		
	13vPnC Pilot Lot 1				13vPnC Pilot Lot 2				13vPnC Manufacturing Scale Lot						
Serotype	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	N[a]	n[b]	%	(95% CI[c])	13vPnC Pilot Lot 1 - 13vPnC Pilot Lot 2	13vPnC Pilot Lot 1 - 13vPnC Manufacturing Scale Lot	13vPnC Pilot Lot 2 - 13vPnC Manufacturing Scale Lot
7vPnC															
4	411	401	97.6	(95.6, 98.8)	404	386	95.5	(93.0, 97.3)	398	392	98.5	(96.7, 99.4)	2.0 (-0.51, 4.75)	-0.9 (-3.09, 1.10)	-2.9 (-5.58, -0.58)
6B	409	388	94.9	(92.3, 96.8)	401	359	89.5	(86.1, 92.3)	396	374	94.4	(91.7, 96.5)	5.3 (1.55, 9.19)	0.4 (-2.77, 3.66)	-4.9 (-8.82, -1.10)
9V	411	392	95.4	(92.9, 97.2)	403	385	95.5	(93.0, 97.3)	396	382	96.5	(94.1, 98.1)	-0.2 (-3.13, 2.83)	-1.1 (-3.97, 1.73)	-0.9 (-3.81, 1.88)
14	398	395	99.2	(97.8, 99.8)	387	383	99.0	(97.4, 99.7)	387	380	98.2	(96.3, 99.3)	0.3 (-1.27, 1.95)	1.1 (-0.60, 3.01)	0.8 (-1.04, 2.76)
18C	413	404	97.8	(95.9, 99.0)	401	384	95.8	(93.3, 97.5)	398	390	98.0	(96.1, 99.1)	2.1 (-0.38, 4.74)	-0.2 (-2.33, 1.99)	-2.2 (-4.89, 0.23)
19F	408	399	97.8	(95.9, 99.0)	399	389	97.5	(95.4, 98.8)	398	395	99.2	(97.8, 99.8)	0.3 (-1.93, 2.60)	-1.5 (-3.46, 0.28)	-1.8 (-3.87, 0.02)
23F	411	375	91.2	(88.1, 93.8)	402	354	88.1	(84.5, 91.1)	399	348	87.2	(83.5, 90.3)	3.2 (-1.03, 7.46)	4.0 (-0.27, 8.39)	0.8 (-3.75, 5.46)
Additional															
1	411	402	97.8	(95.9, 99.0)	403	391	97.0	(94.9, 98.5)	395	389	98.5	(96.7, 99.4)	0.8 (-1.48, 3.18)	-0.7 (-2.78, 1.34)	-1.5 (-3.77, 0.67)
3	406	278	68.5	(63.7, 73.0)	391	283	72.4	(67.7, 76.8)	393	311	79.1	(74.8, 83.0)	-3.9 (-10.27, 2.45)	-10.7 (-16.80, -4.57)	-6.8 (-12.76, -0.74)
5	412	388	94.2	(91.5, 96.2)	402	363	90.3	(87.0, 93.0)	393	371	94.4	(91.6, 96.5)	3.9 (0.15, 7.69)	-0.2 (-3.52, 3.09)	-4.1 (-7.92, -0.36)
6A	413	405	98.1	(96.2, 99.2)	402	384	95.5	(93.0, 97.3)	398	391	98.2	(96.4, 99.3)	2.5 (0.12, 5.23)	-0.2 (-2.22, 1.86)	-2.7 (-5.39, -0.27)
7F	412	411	99.8	(98.7, 100.0)	401	397	99.0	(97.5, 99.7)	397	396	99.7	(98.6, 100.0)	0.8 (-0.47, 2.30)	0.0 (-1.12, 1.18)	-0.7 (-2.30, 0.52)
19A	411	403	98.1	(96.2, 99.2)	403	399	99.0	(97.5, 99.7)	397	392	98.7	(97.1, 99.6)	-1.0 (-2.91, 0.80)	-0.7 (-2.69, 1.19)	0.3 (-1.40, 2.04)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype.
b. n = Number of subjects with an antibody concentration ≥0.35 µg/mL for the given serotype.
c. Exact 2-sided confidence interval based on the observed proportion of subjects.

Program ID: Study 6096A1-3005/CP IMM_PNEUM_IGG_RESP_POP_PT35.SAS. Runtime ID: 15AUG2008 13:38.

Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/6096A1 13VPNC (INFANT)/3005/Reports, Tables, and Figures/Immunogenicity/6096-3005 imm_pnc_elisa_cmp_resp_aft_inf_35_eval_i.htm.

Table 3-14. Subjects achieving a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL for each 13PnC group after the infant series – evaluable pneumococcal infant population

	Vaccine Group (as randomized)											
	13vPnC Pilot Lot 1				13vPnC Pilot Lot 2				13vPnC Manufacturing Lot			
Serotype	**N[a]**	**n[b]**	**%**	**(95% CI[c])**	**N[a]**	**n[b]**	**%**	**(95% CI[c])**	**N[a]**	**N[b]**	**%**	**(95% CI[c])**
7vPnC												
4	411	401	97.6	(95.6, 98.8)	401	386	95.5	(93.0, 97.3)	398	390	98.0	(96.1, 99.1)
6B	409	387	94.6	(92.0, 96.6)	401	358	89.3	(85.8, 92.1)	396	374	94.4	(91.7, 96.5)
9V	411	387	94.2	(91.4, 96.2)	403	385	95.5	(93.0, 97.3)	396	381	96.2	(93.8, 97.9)
14	398	394	99.0	(97.4, 99.7)	387	383	99.0	(97.4, 99.7)	387	380	98.2	(96.3, 99.3)
18c	413	403	97.6	(95.6, 98.8)	401	382	95.3	(92.7, 97.1)	398	390	98.0	(96.1, 99.1)
19F	408	399	97.8	(95.9, 99.0)	399	389	97.5	(95.4, 98.8)	398	394	99.0	(97.4, 99.7)
23F	411	374	91.0	(87.8, 93.6)	402	351	87.3	(83.7, 90.4)	399	345	86.5	(82.7, 89.7)
Additional												
1	411	401	97.6	(95.6, 98.8)	403	390	96.8	(94.5, 98.3)	395	389	98.5	(96.7, 99.4)
3	406	269	66.3	(61.4, 70.8)	391	278	71.1	(66.3, 75.5)	393	306	77.9	(73.4, 81.9)
5	412	385	93.4	(90.6, 95.6)	402	361	89.8	(86.4, 92.6)	393	368	93.6	(90.8, 95.8)
6A	413	405	98.1	(96.2, 99.2)	402	384	95.5	(93.0, 97.3)	398	390	98.0	(96.1, 99.1)
7F	412	411	99.8	(98.7, 100.0)	401	397	99.0	(97.5, 99.7)	397	396	99.7	(98.6, 100.0)
19A	411	403	98.1	(96.2, 99.2)	403	399	99.0	(97.5, 99.7)	397	392	98.7	(97.1, 99.6)

a. N = number of subjects with a determinate IgG antibody concentration to the given serotype
b. n = number of subjects with an antibody concentration ≥ 0.35 µg/mL for the given serotype
c. Exact 2-sided confidence interval based on the observed proportion of subjects.

The reviewer's Table 3-15 provides the difference in proportions and the corresponding 95% CI for the pair-wise comparisons among the 3 lots of 13vPnC. The values are slightly different from those in Table 9-5 submitted by the applicant. Only serotype 3 did not meet the secondary immunogenicity criterion. Although the reviewer's conclusions are the same as the applicant's, the confidence intervals are wider for several of the serotypes. For serotype 6B, the upper bound of the difference between lot 1 and lot 2 calculated by the reviewer is 9.25 and the lower bound of the difference for lot2 and the manufacturing scale lot is -9.09%. Both results for lot 1 and lot 2 for serotype 6B are very close to the 10% equivalence margin that was pre-specified.

Table 3-15. Subjects achieving a pneumococcal IgG antibody concentration ≥ 0.35 µg/mL for each 13vPnC group and their paired-wise differences after the infant series – evaluable pneumococcal infant population

	L1	L2	M	Diff (L1 - L2)		Diff (L1 – M)		Diff (L2 – M)	
Serotype	**%**	**%**	**%**	**%**	**(95% CI)**	**%**	**(95% CI)**	**%**	**(95% CI)**
7vPnC									
4	97.6	95.5	98.0	2.02	(-0.51, 1.75)	-0.42	(-2.66, 1.77)	-2.45	(-5.14, 0.04)
6B	94.6	89.3	94.4	5.34	(1.52, 9.25)	0.18	(-3.05, 3.44)	-5.17	(-9.09, -1.31)
9V	94.2	95.5	96.2	-1.37	(-4.54, 1.74)	-2.05	(-5.15, 0.95)	-0.68	(-3.58, 2.18)
14	99.0	99.0	98.2	0.03	(-1.65, 1.73)	0.80	(-0.96, 2.78)	0.78	(-1.04, 2.76)
18c	97.6	95.3	98.0	2.32	(-0.27, 5.11)	-0.41	(-2.63, 1.78)	-2.73	(-5.48, -0.21)
19F	97.8	97.5	99.0	0.30	(-1.93, 2.60)	-1.20	(-3.25, 0.62)	-1.50	(-3.66, 0.36)
23F	91.0	87.3	86.5	3.68	(-0.61, 8.05)	4.53	(0.17, 8.98)	0.85	(-3.87, 5.58)
Additional									
1	97.6	96.8	98.5	0.79	(-1.59, 3.28)	-0.91	(-3.08, 1.14)	-1.71	(-4.09, 0.45)
3	66.3	71.1	77.9	-4.84	(-11.3, 1.61)	-11.6	(-17.8, -5.40)	-6.76	(-12.9, -0.64)
5	93.4	89.8	93.6	3.65	(-0.18, 7.58)	-0.19	(-3.67, 3.30)	-3.84	(-7.78, 0.02)
6A	98.1	95.5	98.0	2.54	(0.12, 5.23)	0.07	(-2.01, 2.21)	-2.47	(-5.18, 0.03)
7F	99.8	99.0	99.7	0.75	(-0.47, 2.30)	0.00	(-1.12, 1.18)	-0.75	(-2.30, 0.52)
19A	98.1	99.0	98.7	-0.95	(-2.91, 0.80)	-0.69	(-2.69, 1.19)	0.27	(-1.40, 2.04)

Conclusions for the Infant Series

The applicant has the following statements and conclusion for the immunogenicity analysis based on study 3005:

- "The pneumococcal IgG GMCs were highly similar among the 3 13vPnC vaccine lots. The differences between paired comparisons of the 3 lots, expressed as natural log-transformed GMC values, ranged from -0.27 to 0.30 across all 13 serotypes. The three 13vPnC lots were considered to be equivalent as the 95% confidence intervals for the difference between each paired combination of lots was less than the absolute value of 0.693 for each of the 13 serotypes.
- Pneumococcal IgG GMCs expressed by the 13vPnC recipients, combined across all 3 vaccine lots, ranged from 1.09 for serotype 9V to 5.09 for serotype 14 for the 7 common serotypes and from 0.56 for serotype 3 to 2.57 for serotype 7F for the additional serotypes.
- With the exception of serotype 23F, the percentage of responders in the evaluable pneumococcal infant immunogenicity population with antibody concentrations ≥0.35 µg/mL for the 7 common serotypes ranged from 94.9% to 99.2% for lot 1, 89.5% to 99% for lot 2, and 94.4% to 99.2% for the manufacturing scale lot. For serotype 23F, the percentage of responders was 91.2% for lot 1, 88.1% for lot 2, and 87.2% for the manufacturing scale lot. For the 6 additional serotypes, the percentage of responders was at least 90% in each of the three 13vPnC groups for

all but serotype 3. For serotype 3, the percentage of responders was 68.5% for lot 1, 72.4% for lot 2, and 79.1% for the manufacturing scale lot."

3.1.3.6 Reviewer's Comments on Study 3005

1. *The study has demonstrated lot consistency through GMC comparisons.*

2. *Serotype 3 did not meet the equivalence criterion based on comparison of proportions of subjects achieving an antibody concentration ≥ 0.35 µg/mL.*

3. *The 95% CIs for serotype 6B are (1.52, 9.25), (-3.05, 3.44), and (-9.09, -1.31) for pilot lot 1, pilot lot 2, and the manufacturing scale lot, respectively. One upper bound and one lower bound are very close to the pre-specified equivalence margin, 10%.*

3.2 Evaluation of Safety

For safety analysis, the applicant submitted a Clinical Summary of Safety and Integrated Summary of Safety (ISS) report that included 13 of the 15 studies submitted. The only two studies not included are study 002, which was a phase 1 adult study conducted in the US, and study 3002, which was a catch up study conducted in Poland in children older than 15 months. Since many of the 13 studies were conducted outside the US and followed different vaccination schedules, this review focuses mostly on the US studies.

Studies reviewed here are the 3 studies conducted in US infants and toddlers, namely, 003, 004, and 3005. The safety population consists of subjects who received at least one dose of either of the pneumococcal vaccines. Safety analyses compared the proportion of subjects reporting any of the adverse events between the subjects who received 13vPnC and the subjects who received 7vPnC. In this review, the term "increased risk" means that the difference between the proportions of the adverse events between the two groups resulted in a p-value < 0.05 (not adjusted for multiple testing). Since interest is in the 13vPnC, only the increased risks for 13vPnC recipients compared to the recipients of the vaccine currently licensed, 7vPnC (Prevnar) are reported in this review; that is, decreased risks for 13vPnC are not reported here. However, it should be noted that a type 1 error adjustment was not made for multiple tests in these evaluations; thus, the potential for false positive findings should be considered in interpreting results with small p-values.

3.2.1. Study 003

This was a phase 1/2 study. Data from subjects who received at least one dose of study vaccine were included in the infant series safety analysis. Data were analyzed according to the pneumococcal vaccine the subject received. The numbers of subjects included in the safety population for each dose are shown in the following Table 3-16.

Table 3-16. Number of subjects randomized and included in safety analysis by dose

	13vPnC	7vPnC	Total
Randomized	122	126	249
Dose 1	121	122	247
Dose 2	115	118	237
Dose 3	109	119	228
Toddler Dose	86	103	189
6 Month Follow-up	86	103	189

For local reactions, data on erythema, swelling/induration, and tenderness were collected. For systemic reactions, data were collected on fever, decreased appetite, irritability, increased sleep, decreased sleep, as well as medication used to prevent symptoms and to treat symptoms. No statistically significant increases were found in the number of subjects with reports of local reaction, systemic events, or antipyretic medication use among the subjects who received 13vPnC compared to the subjects who received 7vPnC after any of the 3 infant doses or the toddler dose.

For the summary of adverse events (AEs) in the infant series, one subject who was randomized to receive 13vPnC but received 7vPnC at dose 3 in error was excluded. For the AE analysis, no statistically significant increase was found in the subjects who received 13vPnC compared to the subjects who received 7vPnC in the infant series, toddler dose, and the 6-month follow up after the toddler dose. However, in the infant series, a p-value of 0.055 was observed for immune system disorders due to 4 subjects (3.3%) reported in the 13vPnC recipients compared to 0 in 7vPnC recipients. Also, a p-value of 0.055 was observed for oral candidiasis due to 8 subjects (6.7%) reported in the 13vPnC recipients compared to 2 subjects (1.6%) in the 7vPnC recipients. It should be noted that there was no type 1 error adjustment for multiple tests in these evaluations; thus, the potential for false positive findings should be considered in interpreting results with small p-values.

3.2.2. Study 004

For study 004, 670 subjects were screened, and 666 subjects were randomized. The following Table 3-17 shows the number of subjects who received either one of the pneumococcal vaccines at each infant dose and toddler dose.

Table 3-17. Number of subjects randomized and received either one of the pneumococcal vaccines at each infant dose and toddler dose.

	13vPnC	7vPnC	Total
Randomized	334	332	666
Dose 1	332	331	663
Dose 2	309	305	614
Dose 3	298	300	598
Toddler Dose	272	265	537

In evaluation of local reactions and systemic reactions, the denominators were based on the number of subjects reporting "yes" at least one day or "no" for all days. Local reactions included tenderness, induration, and erythema at the site of the pneumococcal vaccine injection. The systemic events specified in the protocol were fever (rectal temperature ≥38°C or 100.4°F) and use of antipyretic medications to treat and to prevent symptoms, as well as decreased appetite, irritability, increased sleep, decreased sleep, and hives (urticaria). Severity of local reactions and fever was also assessed and reported in the e-diary.

There was no statistically significant increase in risk for local reactions observed. However, for systemic reactions, a p-value of 0.026 was observed for fever > 39°C but ≤ 40°C in the subjects who received 13vPnC compared to the subjects who received 7vPnC within 7 days after receiving the first infant dose. There was no type 1 error adjustment for multiple tests in these evaluations; thus, the potential for false positive findings should be considered in interpreting results with small p-values.

For adverse events (AEs), the infant series included 332 subjects who received 13vPnC and 331 subjects who received 7vPnC. The toddler dose included 267 subjects who received 13vPnC and 258 subjects who received 7vPnC. There was no statistically significant increased risk observed in any of the AEs for both the infant series and the toddler dose in the group who received 13vPnC compared to the group who received 7vPnC.

For the 6-month follow-up, 330 subjects who received 13vPnC and 329 subjects who received 7vPnC were included in the safety analysis. There was no increased risk observed in the 13vPnC group compared to the 7vPnC group.

3.2.3. Study 3005

This was a lot consistency trial; therefore, the 13vPnC group consisted of 13vPnC Pilot Lot 1, 13vPnC Pilot Lot 2, and the 13vPnC Manufacturing Scale Lot. A total of 1712 subjects were randomized in a 2:2:2:1 ratio into one of the three 13vPnC lots, or the

7vPnC group. The following Table 3-18 provides the number of subjects who received each of the infant doses.

Table 3-18. The number of subjects randomized and the actual lot for 13vPnC or 7vPnC received in this study.

	13vPnC			7vPnC	Total
	Pilot Lot 1	Pilot Lot 2	Manufacturing Scale Lot		
Randomized	489	488	489	246	1712
Dose 1	487	485	483	244	1699
Dose 2	454	448	455	228	1585
Dose 3	441	437	437	225	1540
Toddler Dose	415	398	406	209	1428

Subject 3005-092-008935 was randomized and received 13vPnC Pilot Lot 2 but was excluded from the safety study at the investigator's request due to the need of referral to a cardiologist for a heart murmur. There should be a total of 1698 subjects included in the safety series analysis for the infant series. However, it is not clear exactly how many were included because the local and systemic reactions are based on the number of subjects reporting "yes" for at least one day or "no" for all days. The analysis of adverse events included 486 subjects from 13vPnC Pilot Lot 1, 484 subjects from 13vPnC Pilot Lot 2, 483 from the13vPnC Manufacturing Scale Lot, and 244 from the 7vPnC group.

Local reactions included tenderness, induration, and erythema at the site of the pneumococcal conjugate injection. No statistically significant increase in risk, except a p-value of 0.055, was observed for any induration for subjects in the 13vPnC group compared to the 7vPnC group within 7 days after dose 2.

The systemic events included fever, decreased appetite, irritability, hives (urticaria), increased sleep, decreased sleep, as well as the use of antipyretic medications to treat and to prevent symptoms. There was a statistically significant increase of risk (p-value of 0.038) for fever ($39°C < \text{temperature} \leq 40°C$) in the 13vPnC group compared to the 7vPnC group within 7 days after dose 2 in the infant series. Overall, a p-value of 0.009 was observed for increased risk of any systemic event in the 13vPnC group compared to the 7vPnC group within 7 days after dose 2. Again, it should be noted that there was no type 1 error adjustment for multiple tests in these evaluations; thus, the potential for false positive findings should be considered in interpreting results with small p-values.

For any adverse events, among 486 subjects who received the 13vPnC Pilot Lot 1, 483 who received 13vPnC Pilot Lot 2, 483 who received 13vPnC Manufacturing Lot, and 244 who received 7vPnc, no increased risk was observed among the 13vPnC groups compared to the 7vPnC group for the infant series.

For the toddler dose and the 6-month follow-up, no statistically significant increased risk was observed for the 13vPnC group compared to the 7vPnC group regarding local reactions, systemic reactions, and adverse events.

3.2.4. Combined Results

At CBER's request, the applicant submitted a combined safety analysis for the 3 US studies, 003, 004, and 3005 [amendment 60 submitted on December 4, 2009]. Only data for the infant series were included for study 3005. No statistically significant (p-value < 0.05) increase in risk was observed in any of the three infant doses or the toddler dose for systemic events, fever, antipyretic medications, and adverse events. However, when comparing the adverse events in the infant series, between the infant series and the toddler dose, and the toddler dose, a p-value < 0.05 was found for the 13vPnC infant series group compared to the 7vPnC group for the system organ class of injury, poisoning, and procedural complication.

The applicant provided the Summary of Clinical Safety and the Integrated Summary of Safety that included safety evaluations on 13 studies conducted in the US and other countries. The 13 studies included 4729 subjects in the 13vPnC group and 2760 in the 7vPnC group. For local reactions, increased risks (p-value < 0.05) for the 13vPnC group compared to the 7vPnC group were observed for moderate induration and moderate erythema for dose 1. For systemic events, an increased risk for 13vPnC group was observed for fever between 38°C and 39°C [both inclusive] for dose 1.

The adverse events, for which an increased risk (p-value < 0.05) was observed for the 13vPnC group compared to the 7vPnC groups are: anaemia, eye discharge, gastrointestinal inflammation, injection site bruising, oral candidiasis, fungal skin infection, viral rash, injury, poisoning and procedural complications, food intolerance, and nasal congestion in the infant series. For between infant series and toddler dose, an increased risk was observed for the following AEs: gastrooesophageal reflux disease, pharyngitis, laryngitis, dermatitis atopic, and dermatitis allergic. For the toddler dose, the following increased risks were observed: lower respiratory tract infection, psychiatric disorders, restlessness, and eczema infantile.

3.3 Gender, Race, Age and Other Special/Subgroup Populations

The applicant did not plan for any subgroup statistical analysis either on the immunogenicity or on safety evaluations. Since there was no pre-planned subgroup analysis and provisions for adequate power, any such analysis may lack statistical validity as well as sufficient power to detect meaningful differences.

For the two pivotal US trials, studies 004 and 3005, the age of the subjects ranged from 1.3 months to 3.3 months old. For the racial composition, 70%-80% of the subjects were white. Thus, subgroup analysis based on age or race will not produce any meaningful

results. The reviewer performed subgroup analysis on the immunogenicity data from studies 004 and 3005 based on gender, and the results are as follow.

Gender Analysis

Study 004

The following table depicts the results of comparing the proportions of subjects who achieved immune response ≥ 0.35 µg/mL between male and female per-protocol subjects who received 3 doses of 13vPnc in study 004. The p-values were obtained from performing t-tests on the differences between the two gender groups. Using the conventional 0.05 as the significance level (that is, with no alpha adjustment for multiple testing), these results showed no significant difference between male and female responses to the 13 serotypes included in 13vPnC vaccine.

Table 3-19. Proportion of subjects ≥ 0.35 µg/mL post dose 3 in male and female per-protocol subjects who received 13-valent in study 004.

Serotype	Female	Male	Difference	p-value
4	116/123 = 0.943	122/129 = 0.946	- 0.003	0.927
6B	107/123 = 0.870	113/129 = 0.876	- 0.006	0.886
9V	113/123 = 0.919	115/129 = 0.891	0.027	0.464
14	119/122 = 0.975	126/129 = 0.977	- 0.001	0.945
18C	120/123 = 0.976	124/129 = 0.961	0.144	0.517
19F	120/123 = 0.976	127/129 = 0.984	- 0.009	0.615
23F	112/123 = 0.911	116/129 = 0.899	0.011	0.760
1	118/123 = 0.959	123/129 = 0.953	0.006	0.821
3	82/122 = 0.672	76/127 = 0.598	0.074	0.229
5	107/123 = 0.870	119/129 = 0.922	- 0.052	0.172
6A	118/123 = 0.959	124/129 = 0.961	- 0.002	0.939
7F	120/123 = 0.976	128/129 = 0.992	- 0.017	0.293
19A	121/123 = 0.984	126/128 = 0.984	- 0.001	0.968

The following table depicts the results of comparison between male and female subjects who received 4 doses of 13vPnC in terms of the geometric mean concentration (GMC) from study 004. The results show that for serotypes 9V, 14, and 19F, the female group had a significantly higher response than the male group.

Table 3-20. Comparisons of the geometric mean concentrations (GMCs) post dose 4 for male and female subjects who received 13vPnC in study 004.

Serotype	Female (N) GMC	Male (N) GMC	Difference (in logarithm)	p-value
4	(112) 3.981	(123) 3.512	0.125	0.335
6B	(112) 12.394	(122) 10.782	0.139	0.338
9V	(111) 3.051	(123) 2.290	0.287	0.013+
14	(112) 10.554	(123) 7.970	0.281	0.043+
18C	(112) 3.047	(124) 3.352	- 0.095	0.462
19F	(112) 7.576	(123) 5.816	0.264	0.030+
23F	(111) 5.152	(123) 5.002	0.030	0.835
1	(111) 5.194	(124) 4.952	0.048	0.728
3	(111) 0.986	(121) 0.891	0.101	0.397
5	(111) 3.882	(124) 3.577	0.082	0.490
6A	(112) 8.169	(123) 8.220	- 0.006	0.958
7F	(112) 5.784	(123) 5.570	0.038	0.764
19A	(112) 9.311	(124) 7.912	0.163	0.154

+: The female group had statistically significantly higher geometric concentration than the male group.

Study 3005

Study 3005 was a lot consistency trial. There were 3 lots for the 13vPnC: Pilot Lot 1, Pilot Lot 2, and the Manufacturing Scale Lot. The following table presents the results of comparing the male and female subjects who received 3 doses of one of the 3 lots of 13vPnC. There is no significant difference for all 13 serotypes for the Pilot Lot 1. For Pilot Lot 2, serotypes 6B, 9V, 19F, 23F, 1, 3, 5, 7F, and 19A, the female subjects showed significantly higher GMC compared to the male subjects. For the Manufacturing Scale Lot, the female group showed higher GMC for serotype 9V.

Table 3-21. Comparisons of the geometric mean concentrations between male and female subjects who received 3 doses of one of the 3 lots of 13v in study 3005.

	Pilot Lot 1			Pilot Lot 2			Manufacturing Scale Lot		
	Female	Male	p-value	Female	Male	p-value	Female	Male	p-value
N[§]	188-194	210-219		174-182	213-222		172-177	215-220	
Serotype									
4	1.354	1.307	0.625	1.417	1.282	0.182	1.868	1.660	0.106
6B	3.091	2.719	0.266	2.474	1.916	0.033+	2.561	2.530	0.916
9V	1.046	1.052	0.929	1.264	1.004	0.001+	1.214	1.036	0.024+
14	4.893	5.032	0.724	5.358	4.944	0.368	5.227	5.145	0.869
18C	1.290	1.305	0.860	1.443	1.260	0.078	1.487	1.470	0.874
19F	1.884	1.818	0.649	2.414	1.838	0.000+	2.746	2.464	0.145
23F	1.326	1.164	0.166	1.448	1.142	0.020+	1.103	0.984	0.253
1	1.604	1.642	0.777	2.000	1.668	0.045+	1.996	1.847	0.354
3	0.540	0.494	0.218	0.652	0.499	0.001+	0.607	0.621	0.768
5	1.315	1.383	0.555	1.159	0.968	0.042+	1.385	1.329	0.623
6A	2.442	2.368	0.715	2.235	1.995	0.212	2.221	2.044	0.307
7F	2.596	2.489	0.538	2.835	2.292	0.003+	2.664	2.672	0.962
19A	1.938	1.772	0.262	2.178	1.864	0.044+	1.984	1.795	0.200

§: N: range of the sample size

+: The p-value is < 0.05 and the females had higher GMC than the males in that lot.

The following table presents the results of comparing the male and female subjects who received 4 doses of one of the 3 lots of 13vPnC. For Pilot Lot 1, the female group had a significantly higher GMC than the male group for serotypes 19A and 19F. For Pilot Lot 2, serotypes 6B, 9V, 19F, 23F, 1, 3, 5, and 19A, the female subjects showed significantly higher GMC compared to the male subjects. For the Manufacturing Scale Lot, the female group showed higher GMC for serotypes 4, 9V, and 19F.

Table 3-22. Comparisons of the geometric mean concentrations between male and female subjects who received 3 doses of one of the 3 lots of 13v in study 3005.

	Pilot Lot 1			Pilot Lot 2			Manufacturing Scale Lot		
	Female	Male	p-value	Female	Male	p-value	Female	Male	p-value
N§	168-171	194-197		153-155	187-189		156-158	197-200	
Serotype									
4	2.465	2.142	0.086	2.415	2.115	0.110	3.446	2.779	0.022+
6B	12.01	10.43	0.098	10.69	8.344	0.006+	10.51	9.468	0.206
9V	2.016	1.818	0.193	2.240	1.735	0.001+	2.229	1.826	0.012+
14	6.635	6.596	0.948	7.484	6.716	0.257	7.373	6.566	0.208
18C	2.052	1.859	0.262	2.354	2.082	0.185	2.732	2.299	0.061
19F	5.480	3.816	0.001+	5.471	4.098	0.004+	7.396	5.890	0.023+
23F	3.720	3.061	0.063	3.875	3.159	0.040+	3.274	2.973	0.344
1	2.830	2.680	0.524	3.388	2.629	0.008+	3.087	2.951	0.630
3	0.802	0.704	0.115	0.788	0.646	0.028+	0.828	0.784	0.496
5	3.289	2.965	0.200	2.994	2.371	0.006+	2.881	2.740	0.512
6A	8.103	7.055	0.100	7.568	6.523	0.088	7.164	6.582	0.308
7F	4.420	4.296	0.731	4.469	4.065	0.321	4.468	4.667	0.612
19A	9.588	7.501	0.004+	9.122	7.713	0.047+	8.819	8.437	0.607

§: N: range of the sample size
+: The p-value is < 0.05 and the females had statistically higher GMC than the males in that lot.

Although study 004 and 3005 were not powered to detect differences between male and female subgroups, both studies show that female subjects have statistically significantly higher geometric mean concentrations than the male subjects for many serotypes. The impact of multiple testing and type1 error inflation should be considered, in addition to the likely clinical relevance of the differences observed.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

1. Of the 13 serotypes contained in the test vaccine, 10 serotypes met the primary objectives in pivotal study 004; in this study 3 serotypes, namely 6B, 9V, and 3, did not meet the primary objectives.

2. The safety evaluation of 13vPnC was based on comparisons with the licensed 7-valent vaccine, Prevnar. Therefore, the safety profile described in the submission and

in this review is that of relative safety rather than absolute safety (i.e., vaccine compared to placebo).

3. There were no data on the efficacy for prevention of otitis media for 13vPnC submitted in this application. Therefore, the effectiveness of 13vPnC against otitis media cannot be evaluated statistically at this time.

4.2 Conclusions and Recommendations

Conclusions

1. Study 009 showed that the antibody concentrations of the group receiving the vaccine with P80 were lower in general. Serotypes 6B and 23F did not meet the primary objectives for both interim analyses.

2. Study 004, the pivotal trial, showed that Serotypes 6B, 9V, and 3 did not meet the non-inferiority criterion of the primary objective. Since the study was designed without alpha adjustment, statistically non-inferiority is claimed only if all 13 serotypes meet the pre-specified criterion.

3. In study 3005, only serotype 3 did not meet the equivalence criterion on the primary endpoint. However, serotype 6B had a confidence bound very close to the equivalence margin.

Recommendations

The reviewer recommends that OVRR take into consideration the following points in making the decision on licensing this product:

1. Pre-specified non-inferiority criteria were not met for three of the *Streptococcus pneumoniae* serotypes in the US pivotal trial (study 004); however, pre-specified non-inferiority criteria were met for the remaining ten serotypes in this trial.

2. Serotype 6B either did not meet or narrowly met the primary immunogenicity objectives in all 3 trials reviewed in the efficacy section. Since a serologic correlate of protection has not been established, the clinical significance of this result is not clear.

3. In general, the antibody concentrations appear to be lower in the 13vPnC group than in the 7vPnC group for the seven common serotypes. The product and clinical reviewers may wish to comment on the potential for interference as a result of the additional serotypes in the 13vPnC vaccine.

4. For the six new serotypes not included in Prevnar, comparisons of the 13vPnC vaccine were made to the lowest response rate observed among the Prevnar serotypes in Prevnar recipients. Because all serotypes in Prevnar are considered effective in preventing invasive pneumococcal disease, the lowest serotype response was still considered a comparison to an effective serotype. With regard to licensure criteria for future pneumococcal conjugate vaccines, consideration should be given to whether this non-inferiority criterion used in study 004 for the six additional serotypes should be redefined given the low antibody response observed by serotype 3.

5. The WHO's recommendation states that failure of some serotypes to meet the pre-specified acceptance criteria may not necessarily preclude licensure of a product with multiple serotypes.

APPENDICES (IF NEEDED)

None

DISTRIBUTION LIST

cc:
Original/HFM-481/Michael Smith
DCC/HFM-99
HFM- 215 /Chron
HFM-485/Tina Khoie
HFM-485/Douglas Pratt
HFM-217/Jingyee Kou
HFM-217/A. Dale Horne
HFM-215/Henry Hsu
HFM-210/Steve Anderson
HFM-210Bob Ball