Summary Basis for Regulatory Action

Date: December 29, 2011

From: Nicolette deVore, Ph.D., Review Committee Chair

BLA/STN: 125324/262

Applicant Name: Wyeth Pharmaceuticals Inc.

Date of Submission: December 2, 2010

PDUFA Goal Date: January 1, 2012

Proprietary/ Established Name:
Prevnar 13™ / Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)

New indication sought under this BLA supplement: active immunization for prevention of pneumococcal disease (including pneumonia and invasive disease) in adults 50 years of age and older caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

Recommended Action: Approval

Signatory Authorities Action: Approval

Office's Signatory Authority:
Wellington Sun, M.D.
Director Division of Vaccines and Related Products Applications
Office of Vaccine Research and Review

☐√ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Table 1: Review documents used in compiling this SBRA:

Review Category	Reviewer Name
Clinical Review	Rosemary Tiernan, M.D. M.P.H. Tina Khoie, M.D., M.P.H.
Statistical Review	Jingyee Kou, Ph.D. (clinical) Tsai-Lien Lin Ph.D. (assay)
Serological Immune Response Assay Review	Mustafa Akkoyunlu, M.D., Ph.D.
Toxicology Review	Claudia Wrzesinski, D.V.M., Ph.D.
Advertising and Promotional Labeling	Peter Arambula
Bioresearch Monitoring Review	Carla Jordan
Post Marketing Plan Review	Marthe Bryant, M.D., M.P.H., M.H.S.

In addition to the review documents listed above, records of teleconferences and meetings with the applicant, as well as e-mails exchanged internally and with the applicant were referenced. Also, the transcript of the November 16, 2011, Vaccines and Related Products Applications (VRBPAC) meeting, which is available at the link below, was referenced.
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm241549.htm

1. Introduction

At the time of submission, Prevnar 13 (PCV13) was approved for use in children 6 weeks through 5 years of age for active immunization 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,
- otitis media caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

On December 2, 2010, Wyeth submitted Supplemental Biologic License Application (sBLA) 125324/262 seeking approval under the accelerated approval regulations (21 CFR 601.41) for the following additional indication for Prevnar 13:

- active immunization for prevention of pneumococcal disease (including pneumonia and invasive disease) in adults 50 years of age and older caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

The following major issues, which were encountered in the review of this sBLA, are discussed in this document:

- Decreased OPA titers were observed when Prevnar 13 was administered concomitantly with a trivalent Influenza Virus Vaccine (TIV) relative to the titers observed after administration of Prevnar 13 when given one month after TIV. The submission of these data was a major amendment that resulted in a 3 month extension of the review clock and a new Prescription Drug User Fee Act goal date of January 1, 2012.

2. Background

Product description
Prevnar 13 is composed of capsular polysaccharides derived from 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), each of which is individually conjugated to non-toxic diphtheria CRM_{197} protein. This product is identical to that approved for use in children.

Regulatory Background
Streptococcus pneumoniae is a significant cause of morbidity and mortality among infants, young children, the elderly, and persons who have certain underlying medical conditions. Pneumococcal disease can cause both invasive and non-invasive disease. Invasive pneumococcal disease (IPD) is defined by isolation of *S. pneumoniae* from a normally sterile site (i.e. blood, cerebrospinal, pleural or peritoneal fluid). In 2007, the incidence rate of IPD due to all pneumococcal serotypes was 19.8/100,000 for adults 50-64 years of age and 37.9/100,000 in adults ≥ 65 years of age. The most common form of non-invasive disease, non-bacteremic pneumococcal pneumonia, remains a more frequent disease manifestation accounting for approximately 13-34% of pneumonia hospitalizations among adults.

Only one vaccine is currently licensed and available in the U.S. for immunization to protect against pneumococcal disease in adults. Pneumovax®23, the 23-valent pneumococcal polysaccharide vaccine (23vPS), manufactured by Merck and Co., Inc., was licensed in the U.S. in 1983 and is currently approved for use in adults ≥ 50 years of age and persons ≥ 2 years of age who are at increased risk of pneumococcal disease. Each dose contains purified capsular polysaccharide from each of the 23 pneumococcal serotypes found in the vaccine. Pneumovax 23 has 12 serotypes in common with Prevnar 13 (serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) plus eleven additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F). Data suggest that the 23vPS vaccine protects adults and the elderly against IPD; however, no consistent vaccine effect has been observed for prevention of pneumonia. The Advisory Committee on Immunization Practices (ACIP) recommends routine administration of 23vPS in adults 65 years and older.

The clinical development program to support this sBLA for use of PCV13 in adults ≥ 50 years of age was designed with consideration to both the adult age group, for which 23vPS is approved for use (i.e., ≥ 50 years of age), and the adult age group, for which the ACIP recommends routine use of 23vPS (i.e., ≥ 65 years of age).

The initial approval of PCV13 for use in adults will be based on an immunological surrogate endpoint through the Accelerated Approval Regulation [21 CFR 601.41]. This regulation applies to biologics intended to treat serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. The accelerated approval pathway can be granted to biologics "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatment" [21 CFR 601.40]. The "meaningful therapeutic benefit" in this instance is for protection against pneumococcal pneumonia or pneumococcal pneumonia combined with IPD.

Under the accelerated approval regulation, a biological product may be licensed based on adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Opsonophagocytosis, mediated by antibodies and complement, is thought to be the main protective mechanism against pneumococcal disease *in vivo*. Opsonophagocytosis, as measured by the microcolony opsonophagocytic assay (mcOPA), was chosen as the surrogate endpoint for the pivotal studies, as well as other studies that evaluated the immune response following PCV13 and 23vPS.

As a necessary condition of the accelerated approval regulation, the applicant is required to study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Wyeth agreed to perform a confirmatory trial, entitled "A Phase 4, Randomized, Placebo-Controlled Clinical Trial of 13-Valent Pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-Serotype Pneumococcal Community-Acquired Pneumonia and Invasive Pneumococcal Disease" (CAPITA) to verify and describe clinical benefit. This trial is currently under way in the Netherlands and the results are expected in December 2013.

3. Chemistry Manufacturing and Controls (CMC)

a. Product

The formulation intended for use in adults is identical to that currently approved for use in children. A full CMC review of the product was completed at the time of original licensure on February 24, 2010.

b. CBER Lot Release

There were no pending lots or issues that would affect approval of this application.

c. Facilities Review/Inspection

There are no ongoing or pending investigations or compliance actions with respect to Wyeth's facilities or their products. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management did not object to the approval of this supplement.

4. Nonclinical Pharmacology/Toxicology

One reproductive toxicology study, entitled "13-valent pneumococcal conjugate vaccine (PCV13): combined fertility and developmental intramuscular toxicity study in female rabbits (study # ADO00084)," was submitted to this sBLA. In this study, 50 -----(b)(4)---------- rabbits per group received an intramuscular dose of either saline, aluminum phosphate adjuvant, or PCV13. Doses were administered twice prior to mating (17 days and 3 days prior to mating) and twice during gestation (gestation days 10 and 24). Twenty-five rabbits per group underwent Caesarean section on day 29 post-coitum and were submitted for embryotoxicity evaluations. The remaining 25 rabbits per group were allowed to litter. No maternal or developmental toxicity in --------(b)(4)--------- rabbits was observed. Based on the results of this reproductive toxicity study, the pregnancy category in the package insert was changed from C to B.

5. Clinical Pharmacology

No new pharmacology data were requested or submitted in the context of this submission.

6. Clinical/ Statistical

a. Effectiveness

Overview of Phase 3 Immunogenicity Studies to Support the Proposed Indication for Use in Adults ≥ 50 Years of Age

This sBLA includes reports of nine clinical studies, five of which were phase 3 studies evaluating immunogenicity and are discussed below:

- Study 004, was a pivotal study that evaluated the safety and immunogenicity of Prevnar 13 in adults 50 through 64 years of age, who were naïve to vaccination with 23vPS.
- Study 3005, was a pivotal study that evaluated the safety and immunogenicity of Prevnar 13 in adults ≥ 70 years of age who received one prior dose of 23vPS ≥ 5 years prior to enrollment.

- Studies 3001 and 3008 evaluated concomitant use of TIV and PCV13 in 23vPS naïve subjects, 50 through 59 years of age and ≥ 65 years of age, respectively.
- Study 3010 evaluated the immune response when PCV13 was given before or after administration of 23vPS in subjects 60 through 64 years of age.

The statistical criteria used in the phase 3 immunogenicity studies, which compared antibody response to each of the 12 serotypes common to PCV13 and 23vPS by mcOPA (i.e., studies 004, 3005, and 3010) is as follows: "Non-inferior" is defined by a lower limit of the 95% CI of the OPA GMT ratio < 0.5.

For comparison of serotype 6A, which is unique to PCV13, the criterion for demonstrating statistically significantly greater responses compared to 23vPS was a lower limit of the 2-sided 95% CI for the difference in proportions of subjects achieving a 4-fold increase in OPA titer (PCV13 – 23vPS) exceeding zero.

Pivotal Studies

Study 004

Study 004 was the pivotal phase 3 study to support licensure of PCV13 in adults aged 50 to 64 years who were naïve to vaccination with 23vPS. Subjects in this study were enrolled into one of two cohorts based on age. In Cohort 1, subjects 60 through 64 years of age were randomized to receive PCV13 (418 subjects) or 23vPS (417 subjects) in a modified, double-blinded design. In Cohort 2, 406 subjects 50 through 59 years of age received PCV13 in an open-label manner. For both cohorts, vaccine effectiveness was evaluated by antibody responses, as measured by serotype specific OPA GMTs, one month after vaccination.

For Cohort 1 (subjects 60 through 64 years of age), the first co-primary objective was to demonstrate that PCV13 is as immunogenic as 23vPS, as measured by OPA GMTs, for the 12 common serotypes contained in both vaccines. This objective was met for all serotypes.

The second co-primary endpoint for this age group was to show that the proportion of subjects who received PCV13 and exhibited a 4-fold increase in serotype 6A OPA titer is statistically significantly greater than the proportion of subjects who received 23vPS and exhibited a 4-fold increase in serotype 6A OPA titer. This objective was also met.

For Cohort 2 (subjects 50 through 59 years of age) the primary objective was to demonstrate non-inferiority of the OPA antibody responses to each of the 13 serotypes in PCV13 in subjects in the cohort compared to that in Cohort 1 subjects (60 through 64 years of age) who received PCV13. This objective was met for all serotypes.

These data show the PCV13 is as immunogenic as 23vPS as measured by OPA for the 13 serotypes contained in PCV13 in adults 60 through 64 years of age, and the OPA titers after PCV13 administration in adults 50 through 59 years of age are non-inferior to the OPA titers after PCV13 administration in adults 60 through 64 years of age.

Study 3005

Study 3005 was a randomized, active-controlled, modified double-blind clinical trial in subjects 70 years of age and older who received 1 dose of 23vPS at least 5 years prior to enrollment. At the initiation of this study (Year 0) subjects were randomized to receive either PCV13 (464 subjects) or 23vPS (474 subjects). One year later (Year 1) all subjects were vaccinated with PCV13. Vaccine effectiveness was evaluated by serotype specific OPA antibody responses one month after each dose of study vaccine.

The first co-primary objective of this study was to demonstrate that PCV13 is as immunogenic as 23vPS for the 12 common serotypes contained in both vaccines as measured by OPA GMTs. This criterion was met for all 12 serotypes. The second co-primary objective was to show that the proportion of subjects, who received PCV13 and exhibited a 4-fold rise in the 6A OPA titer, was statistically significantly greater than the proportion of subjects who received 23vPS and exhibited a 4-fold rise in the 6A OPA titer. This co-primary endpoint was also met. These data show that PCV13 is as immunogenic as 23vPS for the 13 serotypes contained in PCV13 in adults 70 years of age and older as measured by OPA.

Concomitant Administration with Trivalent Influenza Vaccine (TIV)

Studies 3001 and 3008

Studies 3001 and 3008 were phase 3, randomized, double-blind trials to evaluate the safety and immunogenicity of Prevnar 13 when administered concomitantly with the trivalent inactivated Influenza Virus Vaccine (TIV) Fluarix® (GlaxoSmithKlein) in individuals, who were not previously vaccinated with 23vPS. Study 3001 enrolled 1116 healthy adults 50 to 59 years of age, while study 3008 enrolled 1160 healthy adults ≥ 65 years of age. In these studies subjects were randomized 1:1 to receive either placebo and TIV (Placebo +TIV) concomitantly one month prior to PCV13 administration or PCV13 and TIV (PCV13+TIV) concomitantly one month prior to placebo administration. Sera were tested for immune responses to TIV and PCV13 one month after administration of each vaccine: serotype-specific anti-pneumococcal antibody responses to PCV13 were measured by IgG ELISA and immune responses to TIV antigens (*A/H1N1, A/H3N2, B*) were measured by the hemagglutination inhibition assay (HAI).

The first co-primary endpoint in both studies was to demonstrate that the HAI antibody response to each of the three virus subtypes contained in the TIV were non-inferior after vaccination with PCV13 + TIV as compared to placebo +TIV. PCV13 did not appear to interfere with the immune response to TIV antigens B or A/H1N1. However, in study 3008 the lower limit of the 95% CI for the difference in the proportion of subjects, who achieved at least a 4-fold increase in HAI titer, exceeded -10% for antigen A/H3N2 in the TIV + PCV13 group compared to the TIV + placebo group.

The second co-primary endpoint was to demonstrate that the antibody response to each of the 13 pneumococcal serotypes contained in PCV13 were non-inferior one month after vaccination with PCV+TIV compared to those who received placebo + TIV one month

prior to vaccination with PCV13. In Study 3001 non-inferiority of PCV13 + TIV followed by placebo compared to placebo + TIV followed by PCV13 was met for all 13 serotypes as measured by IgG. However, IgG GMCs after PCV13 + TIV were approximately 60-70% of those achieved in subjects who received placebo + TIV followed by PCV13. In study 3008, non-inferiority was met for 12 of the 13 pneumococcal serotypes (except 19F) when anti-pneumococcal IgG GMCs in the PCV13 + TIV group were compared to those who received placebo + TIV followed by PCV13.

After reviewing these anti-pneumococcal IgG ELISA data, CBER requested submission of OPA data and analyses from studies 3001 and 3008. These data, which were submitted on 21 July 2011, showed a trend of lower immune responses to PCV13 when co-administered with TIV. In study 3001, the lower limit of the 95% CI for the OPA GMT ratio was < 0.5 for five of the thirteen PCV13 serotypes (1, 5, 7F, 9V, and 19F) when the OPA titers of those that received PCV13 + TIV was compared to the OPA titers of those given PCV13 given one month after TIV. In study 3008, the lower limit of the 95% CI for the OPA GMT ratio of the group receiving (PCV13+TIV) compared to the (placebo+TIV) group was < 0.5 for three of the 13 serotypes (4, 7F, and 9V).

Language concerning concomitant administration of PCV13 with TIV was revised in the package insert to reflect these data.

Evaluation of a Subsequent Dose of Pneumococcal Vaccine

<u>Study 004 Extension</u>
Study 004 was revised to include a second study vaccination 3 to 4 years after the initial dose of pneumococcal study vaccine. Of those subjects in Cohort 1 who initially received PCV13, 108 subjects received a second dose of PCV13 (PCV13/PCV13) and 108 subjects received 23vPS as a second dose of pneumococcal vaccine (PCV13/23vPS). All subjects in Cohort 1 who initially received 23vPS and participated in the extension (189) received 23vPS as a second dose of pneumococcal study vaccine (23vPS/23vPS). All 214 subjects in Cohort 2 who participated in the extension study received a second dose of PCV13 (PCV13/PCV13).

The following exploratory results were obtained from the second dose of pneumococcal vaccine with regard to the PCV13/23vPS group of Cohort 1

- The lower limit of the 95% CI of the OPA GMT ratio was > 0.5 for each of the 12 common serotypes and >1.0 for 9 of the 12 serotypes in the PCV13/23vPS subgroup when compared to subjects who received a single dose of 23vPS.
- When comparing the PCV13/23vPS subgroup to the 23vPS /23vPS subgroup, the lower limit of the 95% CI of the OPA GMT ratio was >1.0 for each of the 13 serotypes.

These data show that when PCV13 is administered three to four years prior to administration with 23vPS, non-inferiority of OPA titers for all 13 serotypes was observed when compared to either a single dose of 23vPS, or two doses of 23vPS given 3-4 years apart.

Study 3010

Study 3010 was a phase 3 parallel group, modified double-blind, active-controlled trial in which adults 60 through 64 years of age and naïve to 23vPs were enrolled and randomized to receive one of three vaccine regimens. In the PCV13/PCV13 group, 180 subjects received PCV13 as the initial vaccine (year 0) and one year later received a second dose of PCV13. In the PCV13/23vPS group, 302 subjects received PCV13 as the initial vaccine (year 0) and one year later received a dose of 23vPS. In the 23vPS/PCV13 group, 238 subjects received 23vPS as the initial vaccine (year 0) and one year later received a dose of PCV13. Vaccine effectiveness was evaluated by antibody responses, as measured by serotype specific OPA titers one month after vaccination.

For the PCV13/23vPS group, OPA titers of all 12 common serotypes were non-inferior to the OPA titers in subjects who received an initial dose of 23vPS. This was a primary endpoint. Additionally, the lower limit of the 95% CI was > 1.0 for 6 of the 12 common serotypes (serotypes 3, 5, 6B, 7F, 19F, and 23F). The OPA titers in the PCV13/23vPS group were non-inferior for all 12 common serotypes when compared to OPA titers in the 23vPS/PCV13 group. The lower limit of the 95% CI was > 1.0 for 11 of the 12 common serotypes indicating that the PCV13/23vPS group yielded a higher OPA titer than the 23vPS/PCV13 group. However, the group that received 23vPS/PCV13 had lower OPA GMTs for all 12 common serotypes than those that received one dose of PCV13.

Results from study 3010 suggest that OPA GMTs in the PCV13/23vPS subgroup are similar to and higher for some serotypes than the OPA GMTs elicited by a single dose of 23vPS. Additionally, the group that received 23vPS followed one year later by PCV13 had lower OPA GMTs for all 12 common serotypes than the group that received one dose of PCV13.

Clinical Serology Assays

Microcolony Opsonophagocytic Antibody Assay

Opsonophagocytic activity, measured via a microcolony OPA (mcOPA) assay, was selected as a surrogate endpoint for demonstrating the effectiveness of PCV13 in adults. The mcOPA assay for *S. pneumoniae* is designed to assess the ability of functional antibody obtained from heat-inactivated human serum to bind to serotype-specific pneumococcal bacteria in the presence of a functional complement source thereby facilitating bacterial engulfment and death by phagocytic cells. This assay was used to measure OPA response in all phase 3 studies in the PCV13 adult clinical program.

This assay uses bacterial microcolonies for the enumeration of viable bacterial cells. An OPA titer is defined as the titer that results in killing 50% of the bacteria and is calculated by interpolation between the two data points that are immediately below and above the 50% level.

The mcOPA assay was validated for the following parameters: linearity, precision, lower limit of quantitation, limit of detection, and range. Accuracy was not evaluated because

there is no accepted reference standard available for pneumococcal OPA. Overall, the mcOPA was determined to be validated appropriately for the intended purpose. However, it was noted that OPA GMTs were calculated using ½ * LOD (limit of detection) for those titers that fell below the lower limit of quantitation (LLOQ). The applicant was asked to perform a sensitivity analysis in which values below the LLOQ were replaced with the actual titer, 0.5*LLOQ, 0.75*LLOQ, 0.8*LLOQ and 1.0*LLOQ. The sensitivity analysis showed expectedly higher OPA GMTs when compared to the GMTs calculated using ½ *LOD for those titers that fell below the LLOQ. However, there was no impact on non-inferiority comparisons (i.e., all primary endpoints were met regardless of the value that was substituted for the titers that fell below the LLOQ).

IgG ELISA

Immune response, as measured by IgG ELISA, was a primary endpoint in studies 3008 and 3001. This assay used is identical to that used in support of the original BLA and was reviewed under the original BLA.

b. Labeling considerations

The proposed indication in this sBLA was revised to read as follows:

Prevnar 13 is indicated in adults 50 years of age and older for the prevention of:

- Pneumonia and invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. This indication is based on immune responses elicited by Prevnar 13. There have been no controlled trials in adults demonstrating a decrease in pneumococcal pneumonia or invasive disease after vaccination with Prevnar 13.

c. PMC and PMR

Post Marketing Commitment

Pfizer has committed to conduct a study to evaluate concomitant use Prevnar 13 and a U.S.-licensed inactivated seasonal influenza vaccine among subjects ≥ 50 years of age, pre-immunized with 23vPS. The study will be described as: "A Phase 4, Randomized, Double-Blind Trial to Evaluate the Safety, Tolerability, and Immunogenicity of A 13-Valent Pneumococcal Conjugate Vaccine (13vPnC) When Administered Concomitantly with Trivalent Inactivated Influenza Vaccine in Adults 50 Years and Older Who Received 1 Dose of 23vPS Prior to Study Enrollment." This study will be designed to evaluate immune responses after Prevnar 13+TIV, compared to each vaccine alone. It will also evaluate the safety profile associated with concomitant use. A final protocol will be submitted by September 30, 2012, and the study will begin by September 30, 2013 and conducted during the 2013-2014 and 2014-2015 influenza seasons. The final study report with be submitted by December 31, 2015.

Post Marketing Requirement

As required by the accelerated approval regulations, Pfizer has committed to conducting a study to assess the efficacy of the Prevnar 13 in adults for prevention of community acquired pneumococcal pneumonia caused by the pneumococcal serotypes in the vaccine.

The Phase 4 trial entitled "A Phase 4, Randomized, Placebo-Controlled Clinical Trial of 13-Valent Pneumococcal Conjugate Vaccine Efficacy in Prevention of Vaccine-Serotype Pneumococcal Community-Acquired Pneumonia and Invasive Pneumococcal Disease" (CAPITA) was begun in the fall of 2008. The primary clinical objective of the CAPITA trial is to establish the efficacy of PCV13 in the prevention of a first episode of vaccine serotype-specific pneumococcal pneumonia in community-dwelling adult persons aged ≥65 years. As secondary objectives, the study aims to establish the efficacy of PCV13 in the prevention of a first episode of non-bacteremic non-invasive vaccine-type (VT) pneumococcal pneumonia and a first episode of VT-IPD. In addition, the study will evaluate the safety profile of the vaccine. Based on current case accumulation, it is anticipated that efficacy data will be available in August 2013 with submission of a final study report in December 2013.

d. Bioresearch Monitoring (BiMo)

BiMo inspections were conducted at the following four clinical sites, which participated in the two pivotal phase 3 studies submitted to this BLA efficacy supplement:

Protocol 6115A1-004	site 023	Cary, North Carolina
Protocol 6115A1-004	site 005	Tempe, Arizona
Protocol 6115A1-3005	site 024	Minneapolis, Minnesota
Protocol 6115A1-3005	site 012	Seattle, Washington

The BIMO inspections did not reveal problems that impact the data submitted in the application.

e. PREA Compliance

Under the Pediatric Research Equity Act (PREA) (21 U.S. C. 355c), this application is required to contain an assessment of the safety and efficacy of the product in the pediatric age groups because Wyeth is seeking an indication for pneumonia, which is not an approved indication for Prevnar 13 in children. Wyeth has submitted a request to waive the requirement for all pediatric age groups (birth through 16 years of age). These studies have been waived, because the necessary studies to demonstrate the efficacy of Prevnar 13 for the prevention of pneumococcal pneumonia in the pediatric population are impossible or highly impracticable.

7. Safety

A total of 6198 subjects, aged 50 through 95 years, participated in the five immunogenicity studies and one safety study, 5667 of whom received PCV13. The 5,667 PCV13 recipients included 2,616 adults who were aged 50 through 64 years and 3,051 adults aged 65 years and older. Of the 5,667 PCV13 recipients, 3,751 adults had not previously received 23vPS and 1,916 adults were previously vaccinated with 23vPS at least 3 years prior to enrollment.

The commonly reported local adverse reactions after PCV13 vaccination in 23vPS unvaccinated and 23vPS previously vaccinated adults were redness, swelling and pain at the injection site, or limitation of arm movement. The commonly reported systemic adverse reactions in 23vPS unvaccinated and 23vPS previously vaccinated adults were fatigue, headache, chills, rash, decreased appetite, or muscle pain and joint pain.

An increase in some solicited systemic reactions within 14 days post-vaccination was noted when PCV13 was administered concomitantly with TIV compared with TIV given alone (headache, chills, rash, decreased appetite, muscle and joint pain) or with PCV13 given alone (fatigue, headache, chills, decreased appetite, and joint pain).

Across the 6 studies, serious adverse events within 1 month of vaccination were reported after an initial study dose in 0.2%-1.4% of 5055 persons after an initial study dose of PCV13 and in 0.4%-1.7% of 1124 persons after an initial study dose of 23vPS. From 1 month to 6 months after an initial study dose, serious adverse events were reported in 1.2%-5.8% of persons vaccinated during the studies with PCV13 and in 2.4%-5.5% of persons vaccinated with 23vPS.

Twelve of 5,667 (0.21%) PCV13 recipients and 4 of 1,391 (0.28%) 23vPS recipients died. Deaths occurred between day 3 and day 309 after study vaccination with Prevnar 13 or 23vPS. Two of 12 deaths occurred within 30 days of vaccination with PCV13 and both deaths were in subjects >65 years of age. One death due to cardiac failure occurred 3 days after receiving PCV13 administered with TIV and the other death was due to peritonitis 20 days after receiving PCV13.

No imbalances in deaths or serious adverse events were detected in subjects who received PCV13 when compared to 23vPS. No major safety issues were identified with administration of PCV13, as a single dose, to 23vPS vaccine-naïve or 23vPS pre-immunized adults aged ≥ 50 years of age. However, the safety database is not large enough to detect rare events that could occur at a frequency lower than 0.1%. When PCV13 was concomitantly administered with TIV, systemic reactogenicity was increased in subjects 50 through 59 years of age and in subjects ≥ 65 years of age when compared to administration of PCV13 alone or TIV alone.

8. Advisory Committee Meeting

The Vaccines and Related Biologic Products Advisory Committee (VRBPAC) convened on November 16, 2011, to hear presentations, discuss the accelerated approval pathway for Prevnar 13, and review the available safety and immunogenicity data. There were 15 voting members in attendance. The following questions were presented to the committee:

1. Are the immunogenicity data adequate to support the effectiveness of Prevnar 13 under the accelerated approval regulations for the prevention of pneumococcal disease caused by serotypes in the vaccine in adults ≥50 years of age? Please vote yes or no.

2. Are the available data adequate to support the safety of Prevnar 13 when administered to adults ≥ 50 years of age? Please vote yes or no.
3. Given that a confirmatory clinical endpoint study is ongoing, are there any additional studies needed to further evaluate the safety or effectiveness of PCV13? Please discuss.

The first two questions were voted on and each received fourteen votes for 'yes' and one vote for "no". Discussion of the third question included a suggestion to determine what OPA titers are predictive of protection against pneumonia and IPD, an appeal to evaluate the persistence of the immune response following PCV13 vaccination, as well as a recommendation for a study to gather additional data regarding the concomitant administration of TIV and Prevnar 13 in adults who have been previously vaccinated with 23vPS.

9. Labeling

Package Insert
All issues were acceptably resolved after exchange of information and discussions with Wyeth.

10. Recommendations

Recommended Regulatory Action: Approval