Summary Basis for Regulatory Action

Date: March 24, 2017

From: LCDR Juan Lacayo, Ph.D., Chair of the Review Committee

Biologics License Application (BLA) 125324/1561

Applicant Name: Wyeth Pharmaceuticals Inc.

Date of Submission: May, 26, 2016

Goal Date: March 26, 2017

Proprietary Name/ Established Name:

Prevnar 13®, Pneumococcal 13-valent Conjugate Vaccine (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F [Diphtheria CRM_{197} Protein])

Proposed Label change:

Revise the Prevnar 13 (PCV13) United States Prescribing Information (USPI) sections 7.1 and 14.1 with new information indicating that the antibody responses to PCV 13 and quadrivalent influenza vaccine (QIV) were non-inferior when given concomitantly or individually in Pneumovax 23® (PPSV23)-experienced adults ≥ 50 years of age.

Indication:

- In children 6 weeks through 5 years of age (prior to the 6th birthday), Prevnar 13 is indicated 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.
  - active immunization for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. No otitis media efficacy data are available for serotypes 1, 3, 5, 6A, 7F, and 19A.
- In children 6 years through 17 years of age (prior to the 18th birthday), Prevnar 13 is indicated for:
  - active immunization for the prevention of invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- In adults 18 years of age and older, Prevnar 13 is indicated for:
  - active immunization for the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

Recommended Action:

The Review Committee recommends approval of this labeling change.

Review Office(s) Signatory Authority:

Wellington Sun, MD, Director, Division of Vaccines and Related Products Applications, Office of Vaccines 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.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
Clinical Review(s) • *Clinical*	Tina Mongeau, M.D.
Statistical Review(s) • *Clinical data*	Zhong Gao, Ph.D., February
Pneumococcal Serological Immune Response Assay Review-	Freyja Williams, B.S., August 24, 2016
Quadrivalent influenza vaccine Serological Immune Response Assay Review-	Amy M. Woerner, M.S, December 7, 2016
Labeling Review(s) • *APLB (OCBQ/APLB)*	Loan Nguyen, January 30, 2017

1. Introduction

At the time of this 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, and;
  - otitis media caused by *Streptococcus pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.
- Children 6 years through 17 years of age (prior to the 18th birthday) for the prevention of invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
- Adults 18 years of age and older or the prevention of pneumonia and invasive disease caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.

This supplemental BLA (Submission Tracking Number (STN) 125324/1561) proposes to update the U.S. Prescribing Information (USPI) for PCV 13 to include the results from an agreed upon post-marketing commitment (PMC) study. Study B1851138 was listed as a PMC in the December 30, 2011 approval letter of Wyeth's request to supplement their BLA for PCV13 to include the prevention of pneumonia

and invasive disease caused by the 13 *S. pneumoniae* serotypes in the vaccine formulation in persons 50 years of age or older according to the regulations for accelerated approval of biological products (STN 125324/262).

The original protocol for study B1851138 was submitted to Investigational New Drug (IND) Application 13142. CBER provided feedback and recommendations, which were incorporated into a revised protocol. The Final Study Report for study B1851138 was submitted on January 22, 2016 (STN 125324/1376.1). This study was designed as a Phase 4, randomized, placebo-controlled, multicenter study conducted during the 2014-2015 influenza season to evaluate the immunogenicity and safety of PCV13 when administered concomitantly with seasonal inactivated quadrivalent influenza vaccine (QIV), in adults 50 years and older who had previously received 1 or more doses of 23-valent pneumococcal polysaccharide vaccine, Pneumovax 23®; (PPSV23). The Applicant agreed to this PMC in order to address a concern about the possibility of a more pronounced reduction in antibody response following concomitant administration of PCV13 and inactivated influenza vaccine in PPSV23-experienced adults compared to the data from prior studies demonstrating reductions in antibody responses following PCV13 and trivalent inactivated influenza vaccine (TIV) in PPSV23-naïve adults submitted under STN 125324/262.

In the United States (U.S.), pneumococcal and influenza vaccines may be frequently administered concomitantly in practice. The Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for persons older than 6 months of age to prevent influenza and its complications. The ACIP also recommends PCV13 for all adults ≥ 65 years of age and persons ≥ 2 years of age who are at high risk for pneumococcal disease because of underlying medical conditions. Any potential immunologic interference when PCV13 and influenza vaccinations are administered concomitantly could impact a large portion of the US population. Therefore, this PMC study B1851138 was designed to address the concern of potential additive reductions in pneumococcal antibody responses when PCV13 and influenza vaccines are administered concomitantly to adults with a history of PPSV23 vaccination.

This supplement is to support Wythe's request to revise the PCV13 package insert sections 7.1 and 14.1 with new information indicating that the antibody responses to PCV 13 and quadrivalent influenza vaccine (QIV) were non-inferior when given concomitantly or individually in Pneumovax 23® (PPSV23)-experienced adults ≥ 50 years of age.

2. Background

a. Product Description

PCV 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.

b. Disease 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). The most common form of non-invasive disease, non-bacteremic pneumococcal pneumonia, remains a more frequent disease manifestation accounting for pneumonia hospitalizations among adults.

S. pneumoniae is also a common cause of bacterial co-infection with influenza-A. Bacterial co-infection commonly occurs within the first 6 days of influenza infection and is associated with an increased risk of death. Complex viral, bacterial, and host factors contribute to the pathogenesis of co-infection. Individuals at high risk of developing influenza-related complications including co-infection include adults ≥ 65 years of age and, children < 5 years of age.

c. Regulatory Background

The initial approval of PCV13 for use in adults ≥ 50 years of age was 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 and invasive pneumococcal disease caused by the vaccine serotypes.

The original protocol for study B1851138 was submitted to IND 13142 on September 19, 2012. CBER provided comments regarding the proposed study protocol on March 12, 2013, followed by a teleconference on March 26, 2013. A revised protocol incorporating CBER comments was submitted on November 4, 2013; this protocol also specified use of an inactivated quadrivalent influenza vaccine approved by the Food and Drug Administration (FDA) for the 2014-2015 season. Study enrollment began on September 18, 2014. The final clinical study report was submitted on November 23, 2015 to STN 125324/1376.0. On January 22, 2016, Wyeth submitted an amendment to the final clinical study report due to administrative changes to STN 125324/1376.1.

Under the accelerated approval regulations, 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 functional microcolony opsonophagocytic assay (mcOPA), was chosen as the

surrogate endpoint for the pivotal studies, as well as other serological studies that evaluated the immune response following PCV13 and 23vPS.

Under the Pediatric Research Equity Act (PREA) (section 505B of the Food, Drug, and Cosmetic Act [21 U.S.C. 355B]), PREA requirements do not apply to this application. This supplement does not support approval of a formulation with a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

3. Clinical/Statistical/Pharmacovigilance

The clinical section of the sBLA contains one clinical study report for one clinical study B1851138, conducted in the United States during 2014-2015 influenza season (National Clinical Trial (NCT) 02124161)).

a. Clinical Program

On December 30, 2011, PCV13 was approved in persons 50 years of age and older under the accelerated approval regulations (STN 125324/262) for active immunization for the prevention of pneumonia and invasive disease caused by the 13 *S. pneumoniae* serotypes contained in the vaccine. STN 125324/262 included data from two randomized, double-blind studies (studies 6115A1-3001 and 6115A1-3008) evaluating concomitant administration of PCV13 and TIV (Fluarix, A/H1N1, A/H3N2, and B, Fall 2007/Spring 2008) versus PCV13 alone and TIV alone (non-inferiority comparisons). In study 61151A1-3008 non-inferiority criteria for *S. pneumoniae* serotype 19F and influenza strain A/H3n2 were missed. Both studies evaluated only 23vPS-naïve adults ≥ 50 years of age.

Study 6115A1-3001 evaluated 23vPS-naïve adults 50-59 years of age and met the non-inferiority criteria for each of the TIV strains and 13 pneumococcal serotypes. Study 6115A1-3008 evaluated 23vPS-naïve adults ≥ 65 years of age and missed, by a small margin, the non-inferiority criteria for the A/H3N2 TIV strain and for pneumococcal serotype 19F. In both studies, pneumococcal immunoglobuin G (IgG) geometric mean concentrations (GMCs) following co-administration of PCV13 with TIV were consistently lower than the values achieved when the two vaccines were administered one month apart. Additionally, post-hoc analyses in a subset of subjects in each study suggested that concomitant administration of PCV13 and TIV generally resulted in lower anti-pneumococcal OPA antibody GMTs compared to administration of PCV13 alone. Due to these results, a statement was added to the PCV13 package insert indicating that antibody responses to PCV13 were diminished when given with inactivated TIV in adults.

In another randomized, double-blind active-controlled study (study 6115A1-3005) submitted to STN 125324/262, prior receipt of PPSV23 within one year of PCV13 vaccination resulted in a diminished immune response to PCV13 compared to corresponding immune responses induced by PCV13 in PPSV23-naïve subjects. Due to these results, a statement was added to the PCV13 package insert describing this finding.

On November 16, 2011, the Center for Biologics Evaluation and Research (CBER) convened a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting to seek input on the immunogenicity and safety data submitted to STN 125324/262. The Committee noted both the diminished antibody responses following concomitantly administered PCV13 and TIV in PPSV23-naïve adults ≥ 50 years of age and the lack of data on the concomitant administration of PCV13 and TIV in PPSV23-experienced adults ≥ 50 years of age. The available data from studies 6115A1-3001, -3008 and -3005 raised a concern that anti-pneumococcal antibody responses following concomitantly administered PCV13 and influenza vaccines might be worse in PPSV23-experienced adults compared to PPSV23-naïve adults. A question arose regarding whether the data in the PPSV23-naïve group could be extrapolated to PPSV23-experienced adults, or if there is a need for a study in PPSV23-experienced adults. There did not appear to be support for extrapolation at the meeting, which ultimately led to the PMC study B1851138.

As specified in the December 2011 approval letter, Wyeth agreed to conduct a study (study B1851138) to evaluate the safety and immunogenicity of concomitant administration of PCV13 and a U.S. licensed inactivated influenza vaccine in adults ≥ 50 years of age who previously received at least one dose of PPSV23 prior to enrollment as a post-marketing commitment.

The original protocol was submitted to IND 13142 on September 19, 2012. CBER provided comments regarding the proposed study protocol on March 12, 2013. CBER comments included the following requests: re-evaluation of the sample size to ensure adequate power to achieve the primary objectives; evaluation of non-inferiority rather than equivalence; addition of HAI GMTs as a primary endpoint in the evaluation of immune response to seasonal inactivated influenza vaccine; increasing recruitment to enable enrollment of subjects in a single influenza season; ensuring all subjects receive the same U.S. licensed inactivated influenza vaccine; and stratification of enrollment based on time since last PPSV23 immunization.

A teleconference was held between CBER and Wyeth on March 26, 2013 to discuss CBER's March 12, 2013 comments. Wyeth submitted responses to CBER's March 2013 comments on August 8, 2013 (IND amendment 316). A revised protocol incorporating CBER comments was submitted on November 4, 2013 (IND amendment 326); this protocol also specified use of an inactivated quadrivalent influenza vaccine approved by the Food and Drug Administration (FDA) for the 2014-2015 season. Study enrollment began on September 18, 2014.

Because the safety profile of PCV13 when administered concomitantly with TIV and when administered alone to PPSV23 pre-immunized adults was determined by the CBER to be acceptable under STN 125324/262, CBER agreed that daily solicitation of local and systemic adverse reactions daily after vaccination using an electronic diary would not be required. CBER concurred with the Applicant's proposed safety monitoring.

b. Pivotal Study

Study B1851138

A Phase 4, randomized, two-arm, double-blind trial to evaluate the immunogenicity and safety of a PCV13 when administered concomitantly with seasonal inactivated quadravalent influenza vaccine (QIV) in adults 50 years and older who received one or more doses of PPSV23 at least one year prior to study enrollment. This study was conducted during the 2014-2015 influenza season. The study was double-blinded with regards to administration of PCV13 versus placebo; QIV was administered in an open-label manner. Subjects were stratified at randomization by age (50-64 years and ≥ 65 years) and by the time since last PPSV23 vaccination (1-5 years and > 5 years). Within each of the 4 strata created by these 2 factors, subjects were randomized 1:1 into one of two groups.

- Group 1 (PCV13+QIV/placebo) received PCV13 and QIV administered concomitantly (Visit 1), followed 1 month later by placebo (Visit 2).
- Group 2 (placebo+QIV/PCV13) received placebo and QIV administered concomitantly (Visit 1), followed 1 month later by PCV13 (Visit 2).

Approximately 882 subjects were randomized into one of two groups, in a 1:1 ratio. A sample size of 410 evaluable subjects per group was needed to ensure at least 90% power across all 13 serotypes for comparing PCV13 administered concurrently with QIV to PCV13 administered alone, assuming that QIV had no effect on PCV13 OPA in a PPSV23-experinced population. An approximate equal number of subjects were allocated to each age stratum to ensure even distribution of subject ages in the vaccine groups; an allocation target was not set for the time since last PPSV23 vaccination, but the stratified randomization maintained balance in the number subjects in each of the vaccine groups based on the time since last PPSV23 vaccination.

The primary objectives of this study were to:

1. To demonstrate that the immune responses to pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F induced by PCV13 when administered concomitantly with QIV were non-inferior to the immune responses induced by PCV13 administered 1 month after QIV.

2. To demonstrate that the immune responses induced by QIV when administered concomitantly with PCV13 were non-inferior to the immune responses induced by QIV, 1 month after QIV + placebo administration.

The primary immunogenicity endpoints:

1. The primary endpoints for the pneumococcal comparisons were the serotype-specific opsonophagocytic activity (OPA) Geometric Mean Titers GMTs assessed at Visits 2 and 3.

2. The primary endpoints for the QIV influenza stain comparisons were the hemagglutination inhibition assay (HAI) GMTs.

There were also a number of secondary immunogenicity endpoints:

- The percentage of subjects achieving pneumococcal serotype-specific OPA titers ≥ the lower limit of quantitation (LLOQ).
- The pneumococcal serotype-specific OPA geometric mean fold rise (GMFR).
- The proportion of subjects achieving sero-conversion in HAI titers. With seroconversion defined as:
  - Pre-vaccination HAI titer < 1:10 and post-vaccination HAI titer ≥ 1:40; or
  - Pre-vaccination HAI titer ≥ 1:10 and a minimum 4-fold rise in post-vaccination HAI antibody titer with respect to the pre-vaccination titer for influenza virus strains contained in QIV.
- The HAI GMFR for each influenza virus strain.

c. Statistical Methods

Criteria for Study Success

For each of the 13 pneumococcal serotypes, non-inferiority was declared if the lower limit of the 2-sided 95% confidence interval (CI) for the Geometric Mean Ratio GMR of OPA titer was >0.5 (2-fold criterion). Similarly, for each of the influenza virus strains, non-inferiority was declared if the lower limit of the 2-sided 95% CI for the GMR of HAI titer was >0.5.

- Pneumococcal OPA

  For the 13 serotypes contained in 13vPnC, the serotype-specific OPA titers were logarithmically transformed for analysis. OPA GMTs were computed for assay titers collected before Vaccination 1 (Visit 1), 1 month after Vaccination 1 (Visit 2), and 1 month after Vaccination 2 (Visit 3) for each vaccine sequence and serotype. Two (2)-sided 95% CIs were calculated at each time point by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution.

- HAI Titers

  For the influenza virus strains contained in QIV, the strain-specific HAI titers were logarithmically transformed for analysis. HAI GMTs were computed for assay titers collected before Vaccination 1 (Visit 1) and 1 month after Vaccination 1 (Visit 2), and GMFRs (after Vaccination 1/before Vaccination 1) by vaccine sequence for each influenza virus strain. Two-sided 95% CIs were calculated for GMTs and GMFRs for each influenza virus strain by back transformation of the CIs for the mean of the logarithmically transformed assay results computed using the Student t distribution. For the HAI GMRs, the 2-sided 95% CIs were computed using the Student t distribution for the mean difference of the measures on the log scale (13vPnC+QIV, Visit 2, relative to placebo+QIV, Visit 2).

  The proportion of subjects achieving seroconversion in HAI titers was defined as the proportion of subjects with either a pre–Vaccination 1 HAI titer <1:10 and a post–Vaccination 1 HAI titer ≥1:40, or a pre–Vaccination 1 HAI titer ≥1:10 and a minimum 4-fold rise in post–Vaccination 1 HAI antibody titer

with respect to the pre–Vaccination 1 titer for influenza virus strains. For the influenza virus strains contained in QIV, the proportion of subjects achieving a seroconversion in HAI titers from before Vaccination 1 (Visit 1) to 1 month after Vaccination 1 (Visit 2) was computed, respectively, for each group (Group 1 (PCV13+QIV/placebo) and Group 2 (placebo+QIV/PCV13)) To assess vaccination difference (13vPnC+QIV – placebo+QIV), 2-sided 95% CIs on the difference in proportions were calculated using the procedure of Chan and Zhang.

Immunogenicity analyses were performed on two analysis populations:

- All-Available Immunogenicity Population: subjects who had at least one valid and determinate assay result related to the proposed analysis.

- Evaluable Immunogenicity Population: subjects who met the following criteria:
  - Were eligible for the study and randomized;
  - Were ≥ 50 years of age on the day of vaccination;
  - Received the vaccine sequence to which they were randomized;
  - Received all study vaccinations;
  - Received expected study concomitant vaccination (QIV);
  - Had at least one valid and determinate assay result for antibody response to any pneumococcal serotype or concomitant vaccine (QIV) antigen;
  - Had pre-vaccination blood drawn on same day as vaccination;
  - Had post-vaccination blood drawn within 27 to 56 days after vaccination;
  - Received no prohibited vaccines; and
  - Had no other major protocol violations.

- Safety Population: All subjects who received at least 1 dose of investigational product. For the safety analyses, subjects were analyzed according to the vaccine sequence received. Subjects who lacked any safety data were excluded from that analysis.

- Missing assay results were excluded from the immunogenicity analyses; no imputation or estimation of missing values was attempted. All immunogenicity analyses were performed according to the vaccination sequence assigned to the subject as per the study design.

CBER agreed that Wyeth would not have to adjust for baseline pre-vaccination titers. Randomization and stratification and large sample size would be sufficient. Adjustment for baseline titers would probably have little impact on the post-vaccination GMT comparisons.

d. Study Results

Study B1851138 met its two pre-specified co-primary study objectives. The primary analysis for the co-primary objectives used the evaluable

immunogenicity population. When PCV13 and QIV were administered concomitantly, PCV13 induced non-inferior pneumococcal immune responses compared to PCV13 alone. Likewise QIV induced non-inferior immune responses when administered concomitantly with PCV13 when compared to QIV + placebo. The lower limit of the 2-sided 95% CI for the geometric mean ratio [(PCV13+QIV)/PCV13)] exceeded 0.5 for each of the 13 serotypes. Although the non-inferiority criterion was met for each vaccine serotype, pneumococcal OPA antibody GMTs generally appeared to be lower one month after concomitant PCV13+QIV compared to one month after PCV13 alone. For each of the QIV vaccine strains, the lower limit of the 2-sided 95% CI for the geometric mean ratio [(PCV13+QIV)/QIV] exceeded 0.5. The HAI GMT directed against the A/H3N2 strain induced by QIV appeared to be higher after concomitant PCV13+QIV compared to after QIV+Placebo. The HAI GMTs directed against the other 3 vaccine strains appeared to be similar following concomitant PCV13+QIV and following QIV+placebo.

Although the sero-conversion rates of the influenza strains were similar between 13vPnC+QIV and placebo+QIV, the sero-conversion rates were low for both vaccine groups. The sero-conversion rates after administration of 13vPnC+ QIV compared to those after administration of QIV alone were 29.3% and 24.2% for A/H1N1; 27.9% and 31.6% for A/H3N2; 21.3% and 22.3% for B/Brisbane; and 23.2% and 24.7% for B/Massachusetts, respectively. In post-hoc analyses, the proportion of subjects with a baseline HAI titer ≥ 40 for QIV vaccine strains was evaluated. Although a larger proportion of subjects in each study group had baseline titers ≥ 40 for each of the A strains compared to the B strains, sero-conversion rates to the A and B vaccine strains were similarly low. The high pre-vaccination titers against the A strains observed in this study may explain the low sero-conversion rates against the A strains in QIV

e. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the Food, Drug, and Cosmetic Act [21 U.S.C. 355B]), PREA requirements do not apply to this application. This application does not support approval of a formulation with a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

4. Chemistry Manufacturing and Controls (CMC)

The formulation used 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.

a. Product Quality

No new data regarding product quality, facilities inspection or environmental assessment were provided by the Applicant or reviewed in support of this supplement.

b. Assay Validation

1. opsonophagocytosis assays
   The clinical serology and bioassay reviewer for pneumococcal assays evaluated the current validation status of the pneumococcal opsonophagocytosis assays and the clinical serologic data from study B1851138. 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).

   The reviewer concluded that the assay performance for all vaccine serotypes appears adequate for use in support of this study and no unusual or aberrant data were noted that would confound study conclusions. The reviewer noted that each serotype-specific mcOPA lower limit of quantitation (LLOQ) was acceptable, was the same as those reported by Wyeth in the original mcOPA assay validation files, and was used in STN 125324/262. Subsequent to the completion of this study, Wyeth updated the LLOQs for serotypes 7F and 9V. The assay reviewer reviewed the immunogenicity data from study B1851138 with regard to the effect of the use of the original LLOQs on the study outcomes. The use of the original LLOQ versus the new LLOQs for serotypes 7F and 9V did not appear to affect the outcome of the study. Please refer to the clinical serology and bioassay review for more information.

2. 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.

3. Hemagglutination inhibition assays (HAI)
HAI is used to detect the presence of antibodies that bind to influenza hemagglutinin (HA) protein. HA is on the surface of the influenza virus and it binds to turkey RBCs forming a lattice, a process called hemagglutination.

The clinical serology and bioassay reviewer for HAI assays evaluated the validation of the HAI assay for the 4 influenza strains present in the vaccine used in study B1851136 and the clinical serologic data from study B1851136.

The assay was validated by (b) (4) for each strain of influenza present in the quadrivalent vaccine used in the clinical trial (Fluzone®, Sanofi Pasteur, for the 2014-2015 season). The strains in this QIV were: A/California/7/2009 (H1N1); A/Texas/50/2012 (H3N2); B/Brisbane/60/2008; and B/Massachusetts/2/2012.The reviewer concluded that no aberrant or unusual data were noted and that the data supports the approval of this supplement.

c. CBER Lot Release
There were no pending lots or issues that would affect approval of this application

d. 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.

5. Nonclinical Pharmacology/Toxicology
No new pharmacology/toxicology data were submitted as part of this supplement.

6. Clinical Pharmacology
No new pharmacology data were submitted as part of this supplement.

7. Safety
The safety population includes all subjects who received at least 1 dose of investigational product. For the safety analyses, subjects were analyzed according to the vaccine sequence received. Subjects who lacked any safety data were excluded from that analysis. Subjects were observed for at least 20 minutes after vaccination for any acute reactions. The safety endpoints were the proportions of subjects with AEs and SAEs. Evaluation of the safety endpoints was descriptive in nature.

Safety monitoring consisted of the following:

- Close observation of subjects for at least 20 minutes for acute reactions

- Collecting and recording unsolicited adverse events (AEs) and serious adverse events (SAEs) from signing of the informed consent document to the final telephone contact 6 months after the last study vaccination.
- Newly diagnosed chronic medical conditions (including autoimmune and neuroinflammatory disease) were collected at the last study telephone contact 6 months after the last study vaccination.

Of the 876 subjects in the safety population The majority (93.3%) of subjects had 1 previous dose of 23vPS. The mean time from the subjects' most recent previous dose of 23vPS to the first study vaccination was 5.8 years. There were no notable differences in the percentages of demographic characteristics between the vaccine groups.

- Adverse Events
  AEs were reported for similar proportions of subjects in both vaccine groups (15.3% in Group 1 [13vPnC+QIV/placebo] and 11.9% in Group 2 [placebo+QIV/13vPnC]) after Vaccination 1 and before Vaccination 2. The most frequently reported AEs for both vaccine groups were those categorized as infections and infestations and general disorders and administration site conditions, reported for similar proportions of subjects in Group 1 (6.4% and 2.7%, respectively) and in Group 2 (4.1% and 2.5%, respectively).

  AEs were reported for similar proportions of subjects in Group 1 (13vPnC+QIV/placebo) and Group 2 (placebo+QIV/13vPnC) after Vaccination 2, and before the 1-month blood draw after Vaccination 2 (i.e., placebo compared with 13vPnC alone) (10.4% in Group 1 and 12.5% in Group 2). Most AEs were mild or moderate in severity. Approximately 1% of subjects in each study group reported severe AEs after each vaccination.

  The Applicant also reported AEs after 13vPnC vaccination (i.e., the proportion of subjects with AEs after 13vPnC+QIV compared with 13vPnC alone). The proportions of subjects with AEs were similar in both vaccine groups (15.3% in Group 1 and 12.5% in Group 2). The most frequently reported AEs were those categorized as infections and infestations and general disorders and administration site conditions in Group 1 (6.4% and 2.7%, respectively) and infections and infestations and musculoskeletal and connective tissue disorders in Group 2 (4.9% and 1.9%, respectively)

- Death
  One subject (Subject 1138-10661003) in Group 1 (13vPnC+QIV/placebo) died from cardiogenic shock (b) (6) after Vaccination 2. The investigator and the Applicant considered the event of cardiogenic shock to be not related to 13vPnC, placebo, QIV, or the protocol procedures.

- Nonfatal Serious Adverse Events
  In group 1, serious adverse events (SAEs) were reported by 6 (1.4%) subjects after PCV13+QIV and by 7 subjects after Placebo (1.6%). In group 2, SAEs were

reported by 0 subjects after QIV+Placebo and 6 subjects (1.4%) after PCV13 alone. Eleven subjects reported SAEs at the 6 month follow up (5 (1.1%) in group 1 and 6 (1.4%) in group 2). None of the reported SAEs were considered related to vaccination.

Similar proportions of subjects with SAEs were reported in both vaccine groups (1.4% in Group 1 and 1. % in Group 2) after Vaccination 2 and before the 1-month blood draw after Vaccination 2.

SAEs were reported for 1.4% of subjects in both vaccine groups after 13vPnC vaccination.

- Dropouts and/or Discontinuations
  Two subjects in Group 1 were withdrawn from the study because of an AE after 13vPnC vaccination, specifically after Vaccination 1 and before Vaccination 2. One had a non-related AE of colitis; the other had a related mild injection site pain for 30 days. No subjects were withdrawn from the study because of AEs after Vaccination 2 and before the 1-month blood draw after Vaccination 2 or at the 6-month follow-up telephone contact.

The safety profile of PCV13 when administered concomitantly with seasonal quadrivalent influenza vaccine to PPSV23 pre-immunized adults ≥ 50 years of age was generally consistent with the known safety profile of PCV13 described in the package insert.

8. Advisory Committee Meeting

There were no issues pertaining to this supplement that required input from the Vaccines and Related Biological Products Advisory Committee. However, On November 16, 2011, the Center for Biologics Evaluation and Research (CBER) convened a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting to seek input on the immunogenicity and safety data submitted to STN 125324/262. The Committee noted both the diminished antibody responses following concomitantly administered PCV13 and inactivated TIV in Pneumovax 23 (PPSV23)-naïve adults ≥ 50 years of age and the lack of data on the concomitant administration of PCV13 and inactivated influenza vaccine in PPSV23 pre-immunized adults ≥ 50 years of age. The concern was whether the data in the PPSV23-naïve group could be extrapolated to PPSV23 pre-immunized adults, or if there is a need for a study in PPSV23 pre-immunized adults. There did not appear to be support for extrapolation at the meeting.

9. Other Relevant Regulatory Issues

There were no additional relevant regulatory issues identified during conduct of the various reviews.

10. Labeling

The package insert (PI) was reviewed by the review committee, including the reviewer from the Advertising and Promotional Labeling Branch.

The list below reflects the major labeling revisions made to the Prevnar 13 package insert based on the data included in this sBLA.

a. In the Highlights section of the PCV13 package insert, the statement indicating that "antibody responses to PCV13 were diminished when given with inactivated influenza vaccine, trivalent (IIV3)" was deleted. This statement was deleted because in light of the results from study B1851138 there is no clear evidence of clinically significant interference when PCV13 is administered concomitantly with an inactivated influenza vaccine in PPSV23 experienced persons.

b. The following revisions were made in the full prescribing information section of the PCV13 package inserts:
   i. Section 6.2 was updated to include safety data from study B1851138.
   ii. Section 7.1 [Concomitant Immunizations] was updated in order to mention study B1851138.
   iii. Section 14.3 was updated in order to mention study B1851138.
   iv. Section 14.4 was updated to include results from study B1851138.

c. Section 2.5 [Vaccination Schedule for Children 15 months through 5 years of age Previously Vaccinated with Prevnar (PCV7)] was deleted, because few (if any) children ≤ 5 years of age are considered completely immunized with PCV7 since the approval of PCV13 in 2010.

All issues were acceptably resolved after exchange of information and discussions with the Applicant.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The Committee recommends approval of the Applicant's BLA supplement, which contains data supporting a labeling change to revise the PCV13 package insert sections 7.1 and 14.1 with new information indicating that the antibody responses to PCV 13 and quadrivalent influenza vaccine (QIV) were non-inferior when given concomitantly or individually in Pneumovax 23® (PPSV23)-experienced adults ≥ 50 years of age.

b) Risk/ Benefit Assessment

Both pneumococcal disease and influenza are important causes of morbidity and mortality in adults. Bacterial co-infection commonly occurs within the first 6 days of influenza infection and is associated with an increased risk of death in adults ≥ 65 years of age. Because the ACIP recommends that adults ≥ 65 years of age receive PCV13, many adults may receive PCV13 concomitantly with their annual influenza vaccine. Therefore, it is important to show that both vaccines could be administered concomitantly without significantly diminishing the immune response to either vaccine and without adversely affecting safety.

The safety profile of PCV13 when administered concomitantly with QIV to PPSV23-experienced adults ≥ 50 years of age is generally consistent with the known safety profile of PCV13 described in the package insert. Therefore, the overall favorable benefit/risk of vaccination with PCV13 and QIV is unchanged by concomitant administration of the two vaccines in preventing pneumococcal and influenza disease and influenza in elderly individuals. The results from this study are particularly relevant, because pneumococcal and influenza vaccines are often administered concomitantly, especially in PPSV23-experienced individuals.

c) Recommendation for Postmarketing Activities

No safety signals have been identified to date that would justify a post marketing requirement. Based on a review of the submitted clinical data and the proposed pharmacovigilance plan, the Committee concurs with continued routine safety surveillance for Prevnar 13, i.e., careful monitoring for any unanticipated risks in ongoing clinical trials, surveillance systems of various countries, and post-marketing adverse reaction reports.