Summary Basis for Regulatory Action

Date: August 31, 2016

From: Christina Houck, Review Committee Chair

Through: Jon R. Daugherty, Ph.D., Chief, Regulatory Review Branch 1

BLA/STN#: 125324/1373

Applicant Name: Wyeth Pharmaceuticals, Inc.

Date of Submission: November 12, 2015

PDUFA Goal Date: September 11, 2016

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

Reason for the Submission:

To revise the Prevnar 13 package insert based on safety and immunogenicity data from a Prevnar 13 clinical study to include recipients of Hematopoietic Stem Cell Transplant two years of age and older.

Recommended Action: Approval

Signatory Authorities Action: Approval

Office Signatory Authority: Wellington Sun, M.D., 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.
Prevnar 13, a Pneumococcal 13-valent conjugate vaccine, was licensed in the United States (US) on February 24, 2010, for the active immunization of children 6 weeks through 5 years of age for the prevention of invasive pneumococcal disease (IPD) caused by the 13 serotypes contained in the vaccine and for the prevention of otitis media caused by the seven original serotypes contained in Prevnar (4, 6B, 9V, 14, 18C, 19F and 23F). On December 30, 2011, Prevnar 13 was approved for active immunization for prevention of pneumococcal disease (pneumonia and invasive disease) in adults 50 years of age and older caused by the 13 serotypes contained in the vaccine, based on an immunological surrogate endpoint through the Accelerated Approval regulation [21CFR 601.41]. On January 25, 2013, Prevnar 13 was approved for the active immunization of children 6 through 17 years of age for the prevention of IPD caused by the 13 serotypes contained in the vaccine. As a necessary condition of the accelerated approval Wyeth agreed to a post marketing study 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” to verify and describe clinical benefit. Upon successful verification that the vaccine is safe and effective against community-acquired pneumonia, on May 19, 2015, Wyeth had fulfilled this post-marketing requirement and Prevnar 13 was given traditional approval for the prevention of IPD and pneumonia in adults over 50 years of age. On June 11, 2016, Prevnar 13 was approved for active immunization for prevention of pneumococcal disease in adults 18 through 49 years of age.

In this submission, the Applicant proposes to update the Prevnar 13 package insert with safety and immunogenicity data from a Prevnar 13 clinical study in recipients of Hematopoietic Stem Cell Transplant (HSCT) two years of age and older.

2. Background

*Streptococcus pneumoniae* is a significant cause of morbidity following HSCT, especially after allogeneic HSCT, and particularly when complicated by graft-versus-host disease (GVHD). Invasive pneumococcal disease (IPD) disproportionately affects the very young, the
elderly, certain ethnic groups, and those with underlying conditions. IPD occurs when *S. pneumoniae* invades normally sterile body sites such as blood, cerebrospinal, pleural or peritoneal cavities. The risk for IPD is greater among individuals who have immunodeficiency disease states, including HSCT recipients.

The HSCT population has a 30.2-fold greater incidence of IPD compared to the general population (347 per 100,000 versus 11.5 per 100,000, respectively). HSCT recipients lose immunologic memory associated with prior vaccinations or infections due to conditioning regimens that ablate normal and abnormal hematopoietic cells of the immune system. The transfer of donor immunity is variable and does not necessarily confer long term immunity. As a result, several American and European organizations, including the U.S. Centers for Disease Control and Prevention (CDC), the Infectious Disease Society for America (IDSA), the American Society for Blood and Marrow Transplantation (ASBMT) and the European Group for Blood and Marrow Transplantation (EBMT), developed vaccination guidelines in 2009 for the prevention of infectious complications in recipients of HSCT. IDSA guidelines recommend that 3 doses of Prevnar 13 be administered to adults and children starting 3 to 6 months after HSCT, followed by 1 dose of the 23-valent pneumococcal polysaccharide vaccine (23vPS) given at 12 months after HSCT, if the patient does not have chronic GVHD. For patients with chronic GVHD, a 4th dose of Prevnar 13 should be administered instead of 23vPS.

### 3. Chemistry Manufacturing and Controls (CMC)

#### a) Product Quality

The product formulation used in the study of Prevnar 13 in recipients of HSCT two years of age and older is identical to the formulation described and approved within the original Prevnar 13 Biologics License Application (BLA). Therefore, no new data regarding product quality, facilities inspection or environmental assessment were provided by the applicant or reviewed in support of this supplement.

#### b) CBER Lot Release

There are no pending lots or issues that would preclude approval of this supplement.

#### c) Facilities Review/inspection

There are no ongoing or impending investigations or compliance actions with respect to Wyeth’s facilities or products. Therefore, the Office of Compliance and Biologics Quality, Division of Case Management did not object to approval of this supplement.
4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted as part of this supplement.

5. Clinical Pharmacology

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

6. Clinical/ Statistical

a) Clinical Program

The clinical study submitted to this supplement, Study 6115A1-3003, was an open-label single arm trial to evaluate the safety, tolerability, and immunogenicity of four doses of Prevnar 13 followed by one dose of 23vPS in subjects two years of age and older who had received HSCT 3 to 6 months prior to enrollment. The primary objective of this study in HSCT subjects ≥ 2 years old was to evaluate the immune responses 1 month after 3 doses of 13-valent pneumococcal conjugate vaccine as measured by fold rises of serotype-specific immunoglobulin G (IgG) geometric mean concentrations (GMCs). The study’s secondary objectives were to evaluate: The immune responses 1 month after 3 doses of Prevnar 13 as measured by serotype-specific IgG GMCs; the immune responses 1 month after 4 doses of Prevnar 13 as measured by serotype-specific IgG GMCs and fold rises of IgG GMCs and the immune responses 1 month after 3 doses and 1 month after 4 doses measured by IgG GMCs and fold rise IgG GMCs by serotype in the pediatric subgroup (≥2 to <18 years) and adult subgroup (≥18 years).

The IgG GMCs were higher after the 3rd dose of Prevnar 13 when compared to baseline for all subjects for all serotypes. The secondary immunogenicity objectives evaluated the IgG GMCs at 1 month post-4th dose and GMFR 1 month post-4th dose relative to baseline by subjects ≥2 years of age, adults (age ≥18 years), and pediatric/adolescent subjects (age ≥2 to <18 years). The IgG GMCs were higher one month after the 4th dose of Prevnar 13 when compared to baseline for all subjects in all age cohorts and for all serotypes. After the administration of each Prevnar 13 dose, a rise in IgG GMC was demonstrated when compared to the IgG GMC response observed after the prior dose for all serotypes. Additionally, the geometric mean fold-rises (GMFRs) after the 4th dose (relative to baseline) were greater than the GMFR seen after the 3rd dose (relative to baseline) for all serotypes. The observed serotype specific immune responses to Prevnar 13 vaccination followed similar trends when measured either by opsonophagocytic activity (OPA) GMTs compared to enzyme-linked immunosorbent assay (ELISA) IgG GMCs. Following each dose of Prevnar 13, the OPA GMTs increased when compared to the response seen after the prior doses (N=131-195).

In conclusion, this study demonstrated that in a small group of HSCT recipients of varying age and underlying disease pathology, a functional immune response to Prevnar 13 vaccination can be generated. The data do not appear to indicate that there are safety concerns following Prevnar 13 vaccination in HSCT recipients. The benefit of Prevnar 13 vaccination in HSCT
recipients when compared to the associated risks of Prevnar 13 vaccination in HSCT recipients appears to be favorable.

**Bioreresearch Monitoring Review**

Bioreresearch monitoring site inspections were performed for three clinical sites. The inspections of these sites did not reveal significant Good Clinical Practice (GCP) problems that impact data submitted to this sBLA.

**Clinical Serology Assays**

The microcolony opsonophagocytic assay (mcOPA) and the enzyme-linked immunosorbent assay (ELISA) were both used in Study 6115A1-3003. The mcOPA developed by Wyeth was performed at \( b(4) \). The validation report for the mcOPA, not including the Serotype 3 (Pn3) assay, was previously reviewed under supplement STN 125324/950. The assay information for Pn3 reviewed under this supplement support the use of Pn3 mcOPA at the \( b(4) \) facility. The ELISAs used in this study are the \( b(4) \) ELISAs, which were first reviewed by CBER in the original Prevnar 13 application submitted on October 24, 2008, as well as part of subsequent supplements. The ELISAs for Study 6115A1-3003 were performed at \( b(4) \). The validation reports for the \( b(4) \) ELISAs were previously reviewed under supplement STN 125324/950. The assay performance for all ELISAs was deemed adequate for their intended use in this supplement.

**b) 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, as this study was not designed to support approval of a formulation with a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

**7. Safety**

Limited safety data are available on Prevnar 13 administered to recipients of HSCT two years of age and older. For the subjects enrolled (N=247), an e-dairy was used to collect data on solicited local and systemic adverse events for 14 days after each Prevnar 13 dose. All participants who received at least 1 dose of the study vaccine were included in the safety population. The most common solicited local reaction was tenderness, reported in over 70% of all subjects after any dose of the study vaccine. The mean duration of local reactions did not exceed 4.5 days after any dose of Prevnar 13. The most frequently reported systemic reactions, in adults, across all 4 doses included fatigue (49-67%) and headaches (35-45%). For pediatric/adolescent subjects the most frequently reported systemic reactions included fatigue (48-69%), muscle pain (44-58%), and headaches (32-52%). Most unsolicited adverse events (AEs) were infections of mild intensity, with nasopharyngitis reported frequently within one month of any dose. The most frequently reported serious adverse events (SAEs) in the safety
population were infections and benign, malignant, or unspecified neoplasms. Of the reported SAEs, four were considered by the principal investigator to have a reasonable relationship to the vaccine: severe injection site erythema/pyrexia, bilateral pneumonia, bilateral cranial nerve VII paralysis and autoimmune hemolytic anemia and thrombocytopenia. Based on the clinical reviewer’s analysis of these SAEs, the severe injection site erythema event appears to be related to study vaccination, while the others are not considered related to study vaccinations. There were 14 deaths over the course of the study, the causes of which were likely due to each subject’s underlying disease state and not study vaccinations.

8. Advisory Committee Meeting

There were no issues pertaining to this supplement that required input from the Vaccines and Related Biological Products Advisory Committee.

9. Other Relevant Regulatory Issues

No additional relevant regulatory issues were identified during the review of this supplement.

10. Labeling

The package insert (PI) was reviewed by the review committee, including the reviewer from the Advertising and Promotional Labeling Branch. 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 describing the antibody response to Prevnar 13 in recipients of HSCT two years of age and older.

b) Risk/Benefit Assessment

The Prevnar 13 immunogenicity data demonstrate increased IgG and OPA antibody response in HSCT recipients who are vaccinated with a Prevnar 13 as a four dose regimen, with the 1st three doses administered 3-6 months after HSCT, followed 6 months later by a 4th Prevnar 13 dose. The risks associated with use of Prevnar 13 in the study population appeared to be acceptable.

c) Recommendation for Postmarketing Risk Management Activities

No Postmarketing Risk Management Activities are recommended.
d) Recommendation for Postmarketing Activities

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