

Date: February 17th, 2010

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To: Julienne Vaillancourt, Chair, BLA Review Committee

File: BLA 125324 / IND ----(b)(4)---

Product: Prevnar 13™ [Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)]

Subject: Review of the Post marketing Plans (PMP) for Prevnar 13™

I have reviewed the following submissions to the IND --(b)(4)--- and BLA 125324, listed by submission dates:

12/12/2008	IND (b)(4)- Amendment 199, serial 190: Original draft pharmacovigilance plan (PVP) with post marketing vaccine effectiveness components.
2/12/2009	IND -(b)(4)- Amendment 211, serial 201: Response to CBER's 1/12/2009 comments on the draft PVP.
3/31/2009	BLA 125324 Amendment 4, module 1.16 (Original Application: submission of final rolling portion): Risk Management Plans, Pharmacovigilance plan and Post Marketing Effectiveness Plan.
6/11/2009	BLA 125324 Amendment 14, module 5.3.5.2: Study 4002- Post-licensure Study: Safety of 13vPnC in Routine Use for Infants and Children-

Synopsis. Study 4010- Post Marketing Study: Effectiveness of 13vPnC in Reducing Acute Otitis Media and Nasopharyngeal Colonization in Young Children- Synopsis.

Note: These were submitted to the IND Amendment 225, serial 215 on 6 3 2009 and resubmitted to the BLA on 6/11/2009.

- 7/22/2009 BLA 125324 Amendment 21, module 1.11.3: Efficacy Information Amendment. Response to Agency June 30, 2009 Comments on Pharmacovigilance Plan.
- 8/07/2009 BLA 125324 Amendment 26, module 5.3.5.2: Study 4002. Post-licensure Study: Safety of 13vPnC in Routine Use for Infants and Children. Draft protocol.
- 10/1/2009 BLA 125324 Amendment 33, module 1.11.3: Efficacy Information Amendment. Response to September 11, 2009 Clinical Questions.
- 10/21/2009 BLA125324 Amendment 46, module 1.11.3: Efficacy Information Amendment. Response to your comments on the post-marketing safety study from October 15, 2009.
- 12/2/2009 BLA 125324 Amendment 57, module 5.3.5.2: Study 4002- Post-licensure Study: Safety of 13vPnC in Routine Use for Infants and Children- Protocol and/or Amendments draft.
- 12/9/09 BLA 125342 Amendment 63, module 5.3.5.2.2: Study 4018- Assessment of national trends in otitis media in infants and children under 5 years of age between years 1997 and 2013 in the USA- Synopsis. Study 6096A1-XXXX- Post marketing observational study of the effectiveness of Prevnar 13 in reducing acute otitis media in young children caused by serotypes in the vaccine
- 12/11/2009 BLA 125324 Amendment 65, module 5.3.5.2: study-4002. Post-licensure Study: Safety of 13vPnC in Routine Use for Infants and Children- Protocol or Amendment.
- 1/14/2010 BLA 125324 Amendment 73, module 1.11.3: Efficacy Information Amendment. Response to Clinical Post Marketing Request 07 January 2010.

- 1/20/2010 BLA 125324 Amendment 75, module 1.11.3: Response to Agency Question from Dec 10, 2009 on Clinical Positive Rechallenge.
- 2/2/2010 BLA 125324 Amendment 77, module 1.11.3: Response to Agency Request from 26 January 2010- Updated list of clinical PMCs.
- 2/15/2010 BLA 125324 Amendment 84, module 5.3.5.2: Study 4002: Post-licensure study: Safety of 13vPnC in Routine Use for Infants and Children- Protocol or Amendment.

Pprevnar 13 Post Marketing Plan (PMP) - Chronology

- 12/12/2008 Submission to IND---(b)(4)--- (amendment 199, serial 190): original draft pharmacovigilance plan (PVP) with post marketing vaccine effectiveness components.
- 1/12/2009 Teleconference: CBER provided comments to the sponsor on the draft PVP and followed up with written comments to the sponsor immediately afterward on the same day.
- 2/12/2009 Submission to IND ----(b)(4)--- (amendment 211, serial 201): response to CBER's 1/12/2009 comments on the draft PVP.
- 3/9/2009 Teleconference: CBER provided comments on the sponsor's 2/12/2009 response. The sponsor agreed to make various changes to the draft PVP, including the phase 4 safety study, based on the discussion.
- 3/31/2009 Original Application (submission of final rolling portion), BLA 125324. Submission included a draft Post Marketing Plan (PMP) with two components: a draft PVP and a draft plan to evaluate vaccine effectiveness post licensure. The components of the draft PMP reflected changes from the 12/12/2008 PVP submitted to IND --(b)(4)---, based on CBER's 1/12/2009 comments, but not CBER's 3/9/2009 comments.
- 6/3/2009 Submission to IND --- (b)(4)--- (amendment 225, serial 215). Response to CBER's 3/9/2009 comments on the draft PMP, i.e., both PVP and vaccine effectiveness components. In addition a revised synopsis of study 6096A1-4002, the proposed phase 4 post marketing safety study,

- and a synopsis of the proposed phase 4 study to evaluate vaccine effectiveness against otitis media (OM) post licensure, were included.
- 6/11/2009 Submission to BLA 125324 (amendment 14). Submission to the IND (amendment 225, serial 215) was resubmitted to the BLA 125324. See above for details.
- 6/30/2009 CBER comments on information pertinent to proposed safety study 6096A1-4002 in the 6/3/2009 submission to IND ---(b)(4)---and the 6/11/2009 amendment to BLA 125324 were sent to the sponsor via e-mail so that the sponsor might prepare for the teleconference scheduled for the following day.
- 7/1/2009 Teleconference: CBER's 6/30/2009 comments on the sponsor's recent response to the March 9, 2009, comments pertaining to proposed safety study 6096A1-4002 were discussed. [Note: It was agreed that discussion on other aspects of the PMP, e.g., proposed study 6096A1-4010, would be discussed at a later date, in a separate teleconference.]
- 7/22/2009 Submission to BLA 125324 (amendment 21): Wyeth's responses to CBER June 30, 2009 comments on the proposed pharmacovigilance plan.
- 8/07/2009 Submission to BLA 125324 (amendment 26): Wyeth submits a revised draft protocol for their proposed post marketing phase 4 safety study.
- 10/1/2009 Submission to BLA 125324 (amendment 33): Wyeth answers to CBER comments following CBER's review of the July 22 BLA amendment 21 pertaining to Wyeth's pharmacovigilance plan.
- 10/21/2009 Submission to BLA125324 (amendment 46): Wyeth's response to CBER's comments on the post-marketing safety study from October 15, 2009.
- 11/18/2009 The post marketing pharmacovigilance plan and the post marketing effectiveness plan were presented the Vaccine Advisory Committee at the VRBPAC meeting.
- 12/2/2009 Submission to the BLA 125324 (amendment 57). Wyeth submitted the final protocol of the proposed phase 4 safety study.

- 12/9/2009 Teleconference with Wyeth to review the post marketing phase 4 safety study protocol.
- 12/9/2009 Submission to the BLA 125342(amendment 63): Study 4018- Assessment of national trends in otitis media in infants and children under 5 years of age between years 1997 and 2013 in the USA- Synopsis. Study 6096A1-XXXX- Post-marketing observational study of the effectiveness of Prevnar 13 in reducing acute otitis media in young children caused by serotypes in the vaccine.
- 12/11/2009 Submission to the BLA 125324 (amendment 65): Wyeth submitted the revised protocol for the Phase 4 safety study following the teleconference of December 9, 2009.
- 1/14/2010 Submission to the BLA 125324 (amendment 73): Efficacy Information Amendment. Response to Clinical Post Marketing Request 07 January 2010.
- 1/20/2010 Submission to the BLA 125324 (amendment 75): Response to Agency Question from Dec 10, 2009 on Clinical Positive Rechallenge.
- 2/2/2010 Submission to the BLA 125324 (amendment 77): Response to Agency Request from 26 January 2010- Updated list of clinical PMCs.
- 2/15/2010 Submission to the BLA 125324 (amendment 84): Study 4002: Post-licensure Observational Safety Study of 13-valent Pneumococcal Conjugate Vaccine (13vPnC) administered in Routine Use for Infants and Children. Original protocol.

CBER has reviewed the post-marketing plans for BLA 125324 (Prevnar 13™), as submitted by Wyeth as part of the biologics license application (BLA). The review included both the proposed plans to evaluate 13vPnC effectiveness and the pharmacovigilance plan (PVP).

I. PHARMACOVIGILANCE PLAN

A) Summary of ongoing safety issues:

1- Identified risks:

a- Non-clinical studies: Non-clinical studies in rats, rabbits, and/or monkeys demonstrated that 13vPnC was well tolerated and produced an expected reversible local inflammatory reaction with production of anti-13vPnC antibody response without systemic toxicity. Pathological findings of the intestinal system and of the thyroid were observed at higher rates in the vaccine treatment group relative to the saline control group in 3 independent toxicity studies in various species. These findings were considered incidental. There were no corresponding symptoms in humans.

b- Clinical studies: The sponsor evaluated the safety of 13vPnC based on data from 13 infant studies in which a total of 4,729 subjects were randomly assigned to 13vPnC. Control groups (total N=2,760) received Prevnar. Data from an additional study in which 354 older infants and young children 7 months to less than 6 years of age who received 13vPnC were also evaluated.

- The rates of severe adverse events were similar in both the 13vPnC and the Prevnar control groups.
- There were 4 deaths due to SIDS across all studies, 3 in recipients of 13vPnC.
- Overall, the rates of solicited local and systemic adverse events (other than fever) in the 13vPnC group were similar to those in the Prevnar group.
- Tenderness was the most frequently reported local reaction.
- Irritability was the most frequently reported systemic adverse event.
- In the largest U.S. safety study (Study 3005), moderate fever occurred at a statistically significantly higher rate in 13vPnC recipients compared to Prevnar recipients after the 2nd dose. This finding was not observed in the smaller study 004.
- Similar proportions of subjects did not complete the series (22% in the 13vPnC and 17% in the 7vPnC).

Based on the comparative studies with Prevnar, Prevnar 13 does not appear to present safety concerns.

2- Potential/theoretical risks

a- Vaccine failure

Wyeth recognizes that vaccine failure is an important potential risk. Wyeth proposed to evaluate vaccine failure reports by follow-up questionnaire to ascertain whether the serotype was collected. Because serotyping information is not routinely collected even during hospitalization, CBER has questioned the usefulness of the follow-up questionnaire and has advised Wyeth to collect serotyping information as part of a well defined epidemiologic study. Wyeth's response acknowledged that this questionnaire is not intended to measure vaccine effectiveness but rather to improve the quality of the information on individual vaccine failures. Wyeth proposed to rely on IPD surveillance data from the CDC's Active Bacterial Core Surveillance system as a means to monitor the effectiveness of 13vPnC on a population basis (See below).

CBER requested that Wyeth insure that serotype information is obtained on any vaccinee who is hospitalized for Invasive Pneumococcal disease (IPD) for the cohort of children included in the Phase 4 Safety Study. Wyeth agreed to assess serotypes of IPD in IPD hospitalized children in a separate study to be conducted in the Northern California Kaiser Permanente (NCKP) population (see below).

b- Adverse events observed with 7vPnC

The following pre-specified events were evaluated as primary outcomes in the Prevnar phase 4 safety study: wheezing diagnoses combined (asthma, bronchiolitis, bronchitis (reactive airway disease), pneumonia, upper respiratory infections), fever, seizure, gastroenteritis, croup, allergic reactions, and breath holding. Secondary outcomes included thrombocytopenia, neutropenia, developmental delays, autoimmune diseases including Kawasaki Syndrome, and diabetes mellitus. In this study, 65,927 children were vaccinated with 235,520 doses of Prevnar. The primary safety outcomes analyses did not demonstrate a consistently elevated risk of

healthcare utilization for croup, gastroenteritis allergic reactions seizures, wheezing diagnoses, or breath-holding across doses, health care settings, or multiple windows. As in pre-licensure trials, fever was associated with Prevnar. In analyses of secondary safety outcomes, the adjusted relative risk of hospitalization for reactive airway disease was 1.23 (95% CI:1.11 1.35). No other outcomes appear to be associated with Prevnar, however, the study may have lacked adequate power to detect small increases in risks, especially for infrequent to rare side effects.

c- Risks in high risk groups

The safety of Prevnar 13 has not been evaluated specifically in infants and toddlers at higher risk of invasive pneumococcal disease, such as children with sickle cell anemia, HIV, and recipients of allogeneic haematopoietic stem cell transplant (HSCT). Wyeth’s plan to include sub analyses for these groups and for children with reactive airway diseases in the final report of the post marketing Phase 4 safety study are described below. Based on recommendations made at the November 18, 2009, meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC), Wyeth will include organ transplant recipients as a high risk group for sub-analyses of data from the phase 4 safety study.

d- Potential off label-use

13vPnC is indicated for infants and children 2 months through 5 years of age. There is a possibility that, once licensed, this vaccine could be used in older children at high risk for pneumococcal infections and in the --b)(4)-. Studies in these groups are ongoing. In particular, Wyeth plans to evaluate the safety of 13vPnC in children with sickle cell disease who were previously vaccinated with 23-v pneumococcal polysaccharide vaccine. Similarly Wyeth proposes to evaluate the safety of 13vPnC in a study of HIV-infected children who have not been vaccinated with 23v pneumococcal polysaccharide vaccine and in recipients of allogeneic HSCT. Wyeth submitted protocols for these studies in high risk groups to IND ----(b)(4)---. -----

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e- Limited pre-licensure clinical safety data:

The addition of 6 antigens to the 7vPnC makes 13vPnC a different vaccine that could elicit different immune responses. Therefore, 13vPnC should be considered as a single entity with its own safety profile. Given the small size of its pre-licensure safety database (N<5,000 infants and toddlers), it is imperative that the PVP further assess the safety of 13vPnC.

f- Potential interference between 13vPnC and other recommended infant and toddler vaccinations

Non-inferiority (NI) criteria were met for all antigens in DTaP-IPV-HepB and Hib, which were all primary study endpoints with a 10% non-inferiority criterion. Immune response to mumps, varicella, and rubella were evaluated as secondary endpoints. Data on responses to these antigens were submitted to the BLA in amendments 28 and 43. Based on review of these data, which CBER viewed as limited, responses to mumps and rubella in Prevnar 13 recipients were considered to be similar to those in Prevnar recipients.

B) Routine pharmacovigilance

Wyeth will continue to comply with the requirements of 21 CFR 600.80. In addition, Wyeth agreed to submit a **monthly** line listing of all non-15 day adverse event reports to the FDA VAERS contractor for the first 3 years, as it did for 7vPnC. Wyeth also agreed to include a description of each individual adverse event report along with frequency distributions of Medical Dictionary of Regulatory Activities (MedDRA) terms for these reports. One listing should identify every MedDRA Preferred Term (PT). Another will group the PT's into higher level categories to facilitate recognition of patterns (System Organ Class (SOC), High Level Group Term (HLGT), and High Level Term (HLT)). Wyeth also agreed to provide the cumulative number of U.S doses distributed with each of these monthly submissions.

Wyeth also agreed with CBER's request to analyze additional safety concerns if they are identified through VAERS, Wyeth, or other data sources during the conduct of the post-licensure safety study (Protocol number 6096A1-4002). The decision of what constitutes a safety concern warranting further investigation in the post-licensure safety study will be based on CBER and Wyeth's judgment in collaboration.

Lot identification

Batch or lot identification codes provide a method to distinguish between 7vPnC and 13vPnC. Because accuracy and completeness of lot tracking in post-licensure safety surveillance has been very challenging for vaccines and other biological products, CBER suggested that Wyeth consider providing valid lot distribution data for 7vPnC and 13vPnC directly to HMO(s) participating in the proposed phase 4 study. These data sets would include product lot identifiers and each final container lot's dates of initial distribution and expiration. The files with these data could be nearly the same as the ones routinely supplied to CBER, excluding only the commercially sensitive lot size variable, or that field could display the number of doses shipped to the HMOs rather than the totals distributed nationwide. Wyeth explained that a system is in place within NCKP to capture Wyeth's vaccine lot numbers upon receipt of the vaccines. Wyeth, now Pfizer, also stated that Pfizer can track lot identification by client and agreed to provide lot identification data for lots distributed to NCKP to FDA if necessary.

C) Post-licensure safety study

Wyeth agreed to conduct a post-licensure observational safety study in collaboration with Northern California Kaiser Permanente (NCKP) using a safety cohort of children who received 13vPnC as part of routine medical care (study protocol 609A1-4002). The overall objective of the study is to expand the understanding of the safety profile of Prevnar 13 in routine use following licensure. Specific objectives are:

1. To assess the incidence rates of all medically attended events from hospitalization and emergency room visits, and pre-specified medically attended events from outpatient clinic settings following vaccination with Prevnar 13.
2. To assess the incidence rates of pre-specified events across all settings.
3. To compare post vaccination incidence rates to corresponding control period rates for each primary series dose separately and for the primary series combined.
4. To compare incidence rates to historical control rates for events of interest from the self control analysis. Pre-specified events include events evaluated in the Prevnar phase 4 study i.e. seizures, thrombocytopenia, neutropenia, autoimmune diseases, including Kawasaki Syndrome, and diabetes mellitus in addition to anaphylaxis/hypersensitivity, apnea, arthralgia/arthopathy, asthma, bronchiolitis, bronchitis (reactive airway diseases), fever, flushing, gastroenteritis, milk/food allergies/intolerance, pneumonia, upper respiratory tract infection (URI), and wheezing diagnoses.
5. To detect medical events to be further evaluated based on a heuristic statistical filter set at a p-value of 0.1 (2 –sided)

The study design incorporates a five-phase approach to safety assessment:

- 1) comparison with self-control periods,
- 2) comparison with historical control cohort
- 3) further statistical analyses, including scan statistics
- 4) Medical chart review and,
- 5) Comprehensive assessment of available data.

The study population will consist of 43,000 infants starting immunization with 13vPnC at 2 months of age who receive 3 doses of 13vPnC as part of the primary vaccination series at NCKP, as well as any children who receive at least one dose of 13vPnC at NCKP during the course of accruing the 43,000 completed primary series vaccinations, analyzing separately children who start immunization with Prevnar 7 and later switch to 13vPnC to complete their pneumococcal vaccine series. The size of the safety cohort, which includes 43,000 children who complete the primary series and children who received at least one dose of Prevnar 13 is estimated as 60,000 children.

The rate of medically attended events will be compared to 2 self control windows, -35 to -5 days prior to vaccination and 31- 60 days post vaccination for the first dose of the primary series and to 1 self control window, 31-60 days post vaccination for all other doses. This analysis will be conducted for each medical setting (ER, hospital, and outpatient clinic) and for all settings combined. Similar comparisons will be performed for each dose (1st, 2nd, 3rd dose) and for the infant series. A comparison will be done after the 4th dose for those children who have received this dose by the end of the study period. An additional risk window will be defined from 0-60 days after vaccination for doses 3 and 4 (when applicable) for events in the ER and hospital settings combined to be compared to a self-control period extending 61 to 120 days as a secondary endpoint. The study follow-up periods (analytic risk windows) will be extended to 6 months following the completion of the infant series for late onset autoimmune diagnoses and agreed upon potential signals of interest.

The interim and final analyses will be done for each utilization setting and all settings combined. All diagnoses will be evaluated for ER and hospital settings separately and for ER and hospital settings combined. Pre-specified events and events for which a signal is detected in other settings will be assessed separately for the ER, hospital, and outpatient clinics and for all 3 settings combined.

Historical controls will be comprised of two distinct groups, a “7v cohort” composed of children who received a complete series of Prevnar 7 before introduction of 13vPnC and a “7v/13v cohort” comprised of children who received any combination of 7vPnC and 13vPnC.

The self-control analyses will be conducted at an alpha of 0.10, 2 sided, and the historical control analyses at an alpha level of 0.05.

Sub-analyses will be conducted for pooled high risk group populations as defined above.

The study has 80% power to detect a 2.5 fold increase over background rates of 1 per 10,000 vaccine doses of a medically attended adverse event for each setting (ER,

hospital, and outpatient clinic). The alpha value for this sample size calculation is defined as 0.05, 2 sided.

The study involves the use of electronic medical records databases maintained by the Kaiser Permanente Health System and based on ICD-9 codes.

Given the limited scale of pre-licensure safety data for this product, both parties (CBER and Wyeth) agreed that the study should start surveillance of the electronic database at Kaiser immediately following licensure and introduction of 13vPnC at the NCKP sites. The duration of the study is estimated at 4 years from the start of the 13vPnC use in routine practice.

This final protocol was submitted on February 15, 2010, and the study is scheduled to start no later than May 2010 as specified in the approval letter.

Time line for submission of study updates:

Wyeth will submit tabulations of ICD-9 codes for ER and hospitalized patients every six months. These tabulations will be submitted within 3 months of the close of each six month period, starting with the first six months of data after study initiation. These preliminary analyses will evaluate grouped diagnoses and explode these groups into individual ICD9 codes in the event of an unexpected “signal.” Wyeth agreed to work with NCKP to develop grouping conventions for the first type of tabulations based on HCUP clinical classifications of ICD9 codes.

The final reports of the interim and final analyses will be submitted no later than 9 months after data cut-off. The cut-off dates will be 18 months from the start of the study for the interim analysis and 6 months after the last of the 43,000 children has received his or her third dose.

Draft interim and final study reports will be submitted within 3 months of data cut-off presenting the frequency of each event in the exposed and comparison windows and frequency ratios.

Interim and final study analyses will be presented in two types of tabulations: one with grouped events/ICD-9 codes and the other with more detailed information by individual ICD-9 codes.

- The first set of tabulations would include the numbers and relative rates of events when compared with control windows **for the grouped ICD-9 codes**. For the first dose for those children who start the series with Prevnar 13, the tabulation should include the numbers of events in the pre-vaccination window from -35 to 5 days prior to vaccination, as well as the numbers of events in the post-vaccination control window and the corresponding relative rates. For other doses, tabulations need not include events that occurred in the pre-vaccination control window.
- The second set of tabulations should include the number of events and relative rates at **the detailed ICD-9 code level**. For dose 1, these numbers should be reported for the risk, pre- and post- windows and for other doses for the risk and post-vaccination windows. Additional columns would display the relative rates, as above. These tabulations should be first in order of ICD-9 code, second alphabetic, third in decreasing frequency order, and fourth in decreasing order of relative rate. The third list would only display the 1,000 most frequently occurring ICD-9 codes with relative rates >1. The fourth list would display only the most frequently occurring ICD-9 codes with sufficient numbers for reliable interpretation,

Analysis of data in subpopulations (such as high-risk populations) or of specific outpatient outcomes would only be provided in the final report.

Wyeth agreed to communicate any anticipated delay in the submission of such reports immediately to CBER in the event of unforeseen extenuating circumstances. CBER expects these delays to be rare, and should they become frequent, CBER would wish to discuss the underlying reasons with Wyeth.

In addition, upon CBER's request, Wyeth agreed:

1. To provide causes of mortality for those infants who die within 2 months of vaccination with every six month update submission when data are available. For deaths occurring during hospitalizations, data will be easily identified in the NCKP database, for others, data will be submitted when available.

- . 2. To provide two line listings, including the frequency distribution for:
- i. children who did not complete the 13vPnC series but completed at least one other routine immunization series,
 - ii. children who did not complete 13vPnC or other vaccination at 18 month months and at study completion.

These listing will be provided with the interim analysis and at study completion.

3. To instruct all vaccine providers to submit to VAERS a report for all serious adverse events potentially related to the vaccine regardless whether labeled or unlabelled.

4. To provide a listing of all positive re-challenge with the final study report.

5. To assess serotypes of IPD in IPD hospitalized children in a separate study.

The pharmacovigilance plan including the phase 4 safety study was presented at the November 18, 2009, VRBPAC meeting. The committee agreed that the available data were adequate to support the safety of Prevnar 13 when administered to infants and toddlers at 2, 4, 6, and 12-15 months of age. The committee discussed the proposed phase 4 study and commented specifically on the safety of Prevnar 13 in children at “higher risk” of IPD and asked that infants and toddlers with solid organ transplants be included in the “high risk” groups. The committee also discussed the potential risk of autoimmune diseases with additional doses of CRM197 protein with recommended routine infant and toddler vaccination series. The committee asked that arthralgia be included in the list of pre-specified events of interest and that 6 months of follow-up be considered to assess this potential risk for late onset diagnoses. Wyeth’s agreements to the committee’s requests were included in the revised study protocol (BLA 125324 amendment 56).

II. Post Marketing Effectiveness Study Plan

A- Post Licensure Studies to Monitor and Evaluate Vaccine Effectiveness against IPD

1- CDC Active Bacterial Core (ABC) surveillance study

Prior to submission of the BLA and during a teleconference under IND ---(b)(4)-, the sponsor and CBER discussed how IPD surveillance data from the U.S. Centers for Disease Control and Prevention's ABC surveillance system would likely provide useful data on the impact of Prevnar 13 on the rates of IPD after licensure of Prevnar 13. After being approached by the sponsor in this regard, the CDC contacted CBER and noted that a case-control study was being planned anyway by the CDC to evaluate the post licensure effectiveness of Prevnar 13 on rates of IPD using the ABCs system. CBER advised the CDC to consider submitting a Drug Master File (DMF), which would allow the FDA to review information about the post licensure ABCs case-control study to evaluate the impact of 13vPnC vaccine on serotype-specific rates of IPD, if CDC agreed to allow Wyeth cross-reference the data from this study. This type of regulatory submission would allow Wyeth to cross reference proprietary data in the DMF for CBER review to support the Prevnar 13 application without Wyeth seeing the data, which are considered confidential. The CDC submitted DMF --(b)(4)--- with a draft protocol for the case-control study to FDA/CBER on July 14, 2009. FDA reviewed the draft protocol and provided feedback on it to the CDC, independent of the sponsor. The CDC informed CBER that this protocol was also shared with the sponsor. Also, the study was discussed briefly at the November 18, 2009 VRBPAC meeting. Thus, discussion of this study is brief here, as a more detailed review of this study can be found in DMF ----(b)(4)---.

In general the CDC ABCs case-control study will measure the effectiveness of Prevnar 13 against IPD caused by Prevnar 13 serotypes in children recommended to receive 13vPnC as part of routine immunization. As a general comment, CBER agrees that a case-control study is a recommended alternative to RCT, but this design has inherent

limitations, such as: the representativeness of the population from which the cases come, similarity between cases and controls in all aspects except disease status (predisposing factors, eligibility for vaccination, likelihood to obtain the same quantity and quality of medical care, and ascertainment of the clinical outcome), selection bias in particular for the controls, and possible differences in exposure assessment and confounding factors.

In addition, CBER is concerned about the ability of the study to assess serotype-specific vaccine effectiveness based on the number of expected IPD cases in the study population after introduction of Prevnar 13. The ABCs is a population-based, national surveillance system for pneumococcal disease in 10 states. According to the 2007 census, about 900,000 children less than 2 years of age and 1.3 million 2-4 year olds reside in the ABCs sites. In 2007, 456 IPD cases were identified through the ABCs among children 3-59 months of age, 288 for those 3-23 months of age, and 168 from 24-59 years of age. Of these 456 cases isolates were available for 87%. Of those, 251 (55%) were 13vPnC serotypes (108 were serotype 19A, 52 serotype 7F, and 16 serotype 3).

2- Surveillance of IPD in Northern California Kaiser Permanente population (Protocol 6009A1-4005)

Wyeth proposed to conduct a study to estimate the annual incidence of IPD in all NCKP members during each of the five years of the surveillance period (2010-2014). The study will compare these rates to those of IPD prior to 7vPnC, during routine use of 7vPnC, and following the introduction of 13vPnC, describe the serotype distribution of IPD cases, and describe the antibiotic susceptibility of vaccine serotype and non-vaccine serotype IPD observed over the five year period. Cases of IPD will be identified through a laboratory-based surveillance system within NCKP.

The annual birth cohort at NCKP is about 36,000 infants. The actual cumulative number of IPD cases at NCKP from April 2001 to March 2005 was 10 for 7vPnC serotypes and 19 for the additional six serotypes contained in 13vPnC. The expected number in a 5 year period is 12.5 for 7vPnC serotypes and 24 for 13vPnC serotypes.

As proposed the study is ecological, and conclusions about vaccine effectiveness would be speculative. CBER suggested that Wyeth consider the possibility of a well-designed case control study within a surveillance system outside the U.S., such as the one for Prevnar (1) or in NCKP potentially expanded to other HMOs where serotyping and vaccine exposure would be better ascertained and in which selection biases might be limited. Wyeth commented that an international study would not be possible, because GlaxoSmithKline recently obtained licensure in Europe and Canada for a similar pneumococcal conjugate vaccine, Synflorix. Although the total number of expected IPD cases in the NCKP population would be too small (2.5 cases per year for 7vPnC serotypes and 5 cases per year for IPD caused by the six additional serotypes), the sponsor noted that expansion to include other HMOs would not be feasible for various logistical reasons.

NCKP is the only HMO that possesses a baseline incidence rate of serotype-specific IPD during the pre- and post- Prevnar era against which to compare incidence rates. Furthermore Group Health Cooperative (Seattle) and United Health Care do not routinely keep data on IPD, and Southern California Kaiser Permanente (SCKP) does not routinely conduct assays to identify the serotype, although it maintains blood culture data for about one year.

A limitation of the NCKP IPD surveillance study is that within the NCKP system assays for serotyping may not be routinely available. CBER suggested that the sponsor further explore collaboration with CDC laboratories and the possibility of forwarding samples from IPD cases to a CDC lab for serotyping. CBER believes that a well designed case control study of adequate size with vaccine exposure and serotyping ascertainment is necessary to evaluate vaccine effectiveness.

B- Additional Post Licensure Studies to Monitor and Evaluate Vaccine Effectiveness against OM

Pprevnar was approved in the U.S. on October 1, 2002, for active immunization of infants and toddlers against otitis media caused by vaccine serotypes. The otitis media indication for PCV7 was supported by (1) data on the effect of PCV7 on all-cause otitis media from the Pprevnar NCKP trial and (2) an acute otitis media efficacy trial that evaluated PCV7 in Finland and involved tympanocentesis.

No data other than those listed above are available to assess the efficacy of each individual serotype contained in Pprevnar 13 or all 13 serotypes combined against OM caused by any of Pprevnar 13 serotypes.

Wyeth planned to assess the effectiveness of Pprevnar 13 for the prevention of AOM caused by vaccine serotypes but recognizes the limitations of the proposed strategies. Wyeth explained that such studies cannot be carried out in Europe or in Canada, because GlaxoSmithKline has recently received approval in these areas for a new conjugate pneumococcal vaccine. Common clinical practices regarding tympanosynthesis and serotyping limits the possibilities of designing a large study in the US population. Nonetheless the sponsor voluntary commits to conduct the post-marketing studies summarized below to evaluate the effectiveness of Pprevnar 13 against otitis media after licensure.

1- Upstate NY study with M. Pichichero as PI (Study number 4010)

Wyeth proposed to conduct a post-marketing observational study to demonstrate the effectiveness of 13vPnC in reducing AOM and nasopharyngeal colonization in young children caused by vaccine serotypes. Children presenting with AOM will undergo tympanocentesis, be recruited prospectively beginning at 2 months of age and followed until 30 months of age. Pprevnar 13 will be given to all children along other recommended infant vaccines as part of routine care. Nasopharyngeal (NP) and oropharyngeal (OP) samples will be obtained at 6, 9, 12, 15, 18, 24, and 30 months of age, and middle ear fluid (MEF) will be obtained by tympanocentesis for every child presenting with a first and second episode of AOM, and children who are identified as “otitis prone” and experience recurrent (AOM) with treatment failure throughout the study. Exclusion criteria include hypersensitivity to a vaccine component, HIV infection,

malignancy, receipt of immunosuppressive drug, any condition associated with a known predisposition to AOM, such as congenital anomaly, and children who did not begin the infant immunization series with 13vPnC. The number of subjects to be enrolled is 360. Effectiveness of the vaccine will be assessed by estimating the difference in rate of each serotype and overall to a pre- 13vPnC baseline period. CBER indicated that the sample size was too small to adequately represent the general U.S. population. Therefore, CBER suggested that Wyeth seek other clinical centers in order to obtain an adequately sized and representative sample of the population. Wyeth and Dr. Pichichero agreed to expand the study by adding a satellite site located in urban Rochester, NY. CBER recognizes that this addition will contribute to diversify the ethnic and socio-economic status of the study population. However, reservations about the adequacy of sample size and the generalization of the results to the US population remain.

2- Shelly Kaplan Study (Protocol 6096A1-XXXX)

In addition, Wyeth proposes to conduct a prospective observational study to monitor the impact of Prevnar 13 routine use in reducing AOM caused by serotypes in the vaccine using the United States Pediatric Multicenter Pneumococcal Surveillance Group (USPMPSG). The USPMPSG is a laboratory-based surveillance network of eight pediatric hospitals across the United States. The study population will consist of children living in the catchment areas of each of the 8 USPMPSG hospitals and who have middle ear fluid (MEF) obtained during the course of standard medical care at these sites. Cases will be identified through a laboratory-based surveillance system and include children with MEF isolates identified as *S. Pneumoniae*. MEF isolates obtained at USPMPSG sites are not generally obtained from primary tympanocentesis of first- or second- episode of acute otitis media, but more likely to represent isolates of spontaneous drainage during an episode of AOM, during myringotomy and/or tympanocentesis tube placement, or during tympanocentesis performed for children who did not respond to clinical treatment. The distribution of the observed serotypes will be summarized for each year of this study as well as for the years of the baseline period. Trends will be estimated using Poisson regression.

As currently described, this study would only allow ecological inference of vaccine effectiveness. If vaccine history can be collected, a case control or a case only study design may be possible. The main limitations of the study include a selection bias of the study population, the lack of ascertainment of vaccination exposure, and the lack of a control group. Despite these limitations, this analysis may contribute to a better understanding of the evolution of trends of AOM caused by *S. Pneumoniae* specific serotypes among US children with recurrent ear infections.

3- National Administrative Database Study (Protocol 6096A1- 4018)

Wyeth proposes to analyze national trends in office visits for otitis media in US infants and children under 5 years of age between calendar years 1997 and 2013 using two national medical cares surveys, the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Care Survey (NHAMCS). Both surveys are observational, cross sectional surveys conducted annually by the National Center for Health Statistics. Findings from NAMCS are based on a national sample of physician office visits while findings from NHAMCS are based on a national sample of visits to the emergency departments and outpatient departments of non-institutional hospitals. The strength of the surveys is their ability to produce national estimates. The main limitations are that the estimates are based on physician office visits and not on the overall occurrence of OM in the population, the diagnosis of OM includes all causes of OM combined and there is no assessment of vaccine exposure.

As proposed this analysis is ecological and conclusions about vaccine effectiveness would be speculative.

CONCLUSION:

Product and product indications: Wyeth has submitted a Biologic License Application for 13-valent conjugate pneumococcal vaccine for the prevention of invasive disease (including sepsis, meningitis, bacteremia, bacteremic pneumonia, and empyema) and otitis media caused by streptococcus pneumoniae serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14,

18C, 19A, 19F, and 23F for children <5 years old as part of the infant routine immunization series. The 13vPnC is expected to replace 7vPnC in the U.S. population upon licensure of 13vPnC.

Summary of pertinent safety issues: No safety concerns beyond those that exist for Prevnar have been identified in pre-clinical studies and pre-licensure clinical trials and studies. However the whole clinical data from US and non-US studies encompassed fewer than 5,000 children who received 13vPnC and about 2,700 who received 7vPnC. CBER agrees with the sponsor's plan to conduct a large post-marketing observational study to assess the general safety of 13vPnC.

Summary of post licensure plans to monitor vaccine effectiveness against IPD and evaluate vaccine effectiveness against OM: Wyeth proposes to rely on the results of a case control study planned by CDC using the ABC surveillance system. Limitations inherent to the study design include the representativeness of the population from which the cases come, similarity between cases and controls in all aspects except disease status, selection bias for the controls, and possible differences in exposure assessment and confounding factors. In addition, CBER is concerned about the ability of the study to assess serotype-specific vaccine effectiveness based on the number of expected IPD cases in the study population after introduction of Prevnar 13. Wyeth also proposes to conduct a study to estimate the annual incidence of IPD in all NCKP members during each of the five years of the surveillance period (2010-2014). As described, the study is ecological and inference of vaccine effectiveness would be speculative.

To evaluate the effectiveness of Prevnar 13 against AOM caused by the serotypes contained in the vaccine in young children, Wyeth proposes to voluntarily conduct three post-marketing studies. CBER sees no problem with Wyeth's plan to conduct these studies, but all parties should understand that their results will be ecologic comparisons that would not directly provide evidence on the field effectiveness of Prevnar 13 overall nor for individual antigens.

COMMENTS

1- Phase 4 study requirement or commitment: CBER recognizes the demonstrated safety profile for 7vPnC as a foundation for evaluating the safety profile of 13vPnC, because the two products share common vaccine components. CBER acknowledges 7vPnC's large pre-marketing safety database and vast post-marketing experience. However, CBER also recognizes that, because 13vPnC is a new and different vaccine, new and unexpected AEs could emerge with widespread use after licensure. Although no safety concerns have been identified pre-licensure, the safety data for 13vPnC are limited. Wyeth has agreed to voluntarily conduct a large post-marketing observational safety study and has discussed details with CBER.

The study population will consist of a cohort of 43,000 children who will have completed the Prevnar 13 infant series plus all children who receive at least one dose of Prevnar 13 during the time of accrual, about 60,000 children total. The details of the post-marketing safety study have been discussed and agreed upon during the July 1 teleconference and subsequent communications described above.

The phase 4 safety study was presented at the VRBPAC meeting for comments on November 18, 2009. Wyeth updated the study protocol to include the recommendations of the committee regarding the unknown risk of autoimmune diseases that could be potentially associated with increasing doses of CRM protein component with routine vaccination in U.S. children. These recommendations included the addition of arthralgia in the list of pre-specified events, the extension of the post-vaccination observation window for late onset diagnoses, and the extension of follow-up to six months after the completion of the primary series. CBER and the applicant both reached agreement on the final study protocol.

Of note, the pre-specified events of interest will be assessed in the context of routine pharmacovigilance and do not trigger any of the 3 FDAAA criteria for a post marketing

requirement. Therefore, CBER considers this phase 4 safety study to be a post-marketing commitment.

2- Vaccine failure: CBER requests that Wyeth insure that serotype information is obtained on any vaccinee hospitalized for Invasive Pneumococcal Disease (IPD) for the cohort of children included in the Phase 4 Safety Study.

3- High risk populations: Wyeth noted its intention in the PVP 1) to evaluate the safety of 13vPnC in children of ages 6 to 18 years with sickle cell disease who were previously vaccinated with 23-v pneumococcal polysaccharide vaccine, 2) to evaluate the safety of 13vPnC in HIV-infected children of ages 6 years and older who have not been vaccinated with 23v pneumococcal polysaccharide vaccine. Protocols for these studies have been submitted to IUND ----(b)(4)--- for CBER review.

4- Effectiveness Studies: The efficacy of Prevnar 13 against IPD caused by all 13 serotypes and against OM caused by the 7 original Prevnar serotypes is inferred based on demonstration of non-inferiority immunogenicity. Serotype 3 failed to meet these criteria in the pivotal non-inferiority study. However, a functional antibody response was observed for serotype 3, based on opsonophagocytic activity (OPA) data. To monitor the effectiveness of 13vPnC against IPD post licensure, Wyeth plans to rely on CDC ABC surveillance data in particular by means of a case-control study to be initiated immediately after market introduction of Prevnar 13.

- The proposed study design is a case-control study. While CBER recognizes the benefits of such a study, CBER also recognizes the limitations inherent in the case-control design, most importantly non-randomization of subjects, vulnerability to selection biases, potential differences in case ascertainment and vaccination status between cases and controls and between ABC sites and ELC sites, and possibly incomplete vaccine exposure ascertainment.
- Also, because of the low incidence of IPD caused by some serotypes, it is unlikely that the assessment of effectiveness can be completed for each individual serotype, in particular serotype 3.

CBER reviewed the protocol for this study under DMF-(b)(4)--. CBER comments on this study were provided directly to the CDC.

As part of its plan to evaluate vaccine effectiveness, Wyeth proposes to analyze IPD trends within the NCKP population before and after introduction of 13vPnC. A separate study to assess the IPD trends in Alaskan native children is ongoing. CBER recognizes that both studies are ecologic. Without a proper control group, interpretation of the results will be limited. Furthermore, since the sample size is likely to be small, effectiveness for each individual serotype, especially serotype 3, will be hard to demonstrate. CBER recommended that the NCKP study be expanded to other HMOs. However, according to the sponsor this would not be feasible for logistical reasons.

In addition, Wyeth also proposes to conduct three post-marketing studies to assess the impact of Prevnar 13 on reducing AOM caused by the serotypes contained in the vaccines in young children. CBER recognizes the challenges of designing a study to evaluate the effectiveness of Prevnar 13 against OM caused by the serotypes in the vaccine in the US. However, each of these proposed studies presents major limitations, including small sample size, potential selection bias, lack of control group, lack of vaccine exposure ascertainment, that will preclude conclusion of vaccine effectiveness against OM. CBER believes that a well designed case control study of adequate size with vaccine exposure and serotyping ascertainment is necessary to evaluate vaccine effectiveness. Nonetheless, CBER sees no problem with Wyeth's plan to conduct these studies, but all parties should understand that their results will be ecologic comparisons that would not directly provide evidence on the field effectiveness of Prevnar 13 overall nor for individual antigens.

RECOMMENDATION

Based on her review of the proposed pharmacovigilance plan, this Office of Biostatistics and Epidemiology reviewer recommends approval of Prevnar 13 and concurs with the post-marketing studies as stated in the approval letter.

Marthe G. Bryant-Genevier, MD, MPH, MHS
VSB/DE/OBE/CBER

Reference:

- 1- Whitney, G. Cynthia et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 2006; 368:1495-502