

Record of Telephone Conversation - September 11, 2009 - Prevnar 13

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RECORD OF TELEPHONE CONVERSATION
Submission Type: Original Application Submission ID: 125324/0 Office: OVRR
Product:
Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)
Applicant:
Wyeth Pharmaceuticals Inc.
Telecon Date/Time: 11-SEP-2009 11:01 AM Initiated by FDA? Yes
Telephone Number:
Communication Category(ies):
Information Request
Author: MICHAEL SMITH
Telecon Summary:
email: Additional comments on phase 4 study 6096A1-4002
FDA Participants: Julie Vaillancourt, Michael Smith, Colleen Sweeney, Marthe Bryant and Wise, Robert
Non-FDA Participants: Jack Love and Carmel Devlin
Trans-BLA Group: No
Related STNs: None
Related PMCs: None
Telecon Body:
Email:

From: Vaillancourt, Julianne
Sent: Friday, September 11, 2009 11:01 AM
To: 'Jack Love'; 'Carmel Devlin'
Cc: Smith, Michael (CBER); Sweeney, Colleen; Bryant, Marthe; Wise, Robert
Subject: additional comments on phase 4 study 6096A1-4002
Reference: BLA 125324, section 1.11, Document, titled "Information Amendment, Pharmacovigilance Plan –June 30, 2009"

Dear Jack and Carmel,

Dr. Marthe Bryant has reviewed the July 22, 2009, amendment to your BLA, which contains a response to our June 30 comments on your proposed pharmacovigilance plan, and has the following requests, which pertain to your proposed phase 4 safety study, protocol # 6096A1-4002, titled "Post-licensure Observational Safety Study of 13-valent Pneumococcal Conjugate Vaccine (13vPnC) Administered in Routine Use to Infants and Children":

- 1. With regard to your July 22, 2009, response to specific request #2 in our June 30, 2009, comments on your draft pharmacovigilance plan:**

We originally requested that you provide a tabulation of incidence rates with self-control comparative rates for pre- and post- vaccination windows for all medically attended events for each setting and for all settings combined every three months.

In response you noted that provision of this information on a quarterly basis would not be possible and would limit the investigative site's ability to be responsive to additional requests that might derive from this surveillance.

Therefore you proposed to provide counts for grouped events in the exposure and post-vaccination observation windows for the ER and hospital settings, without statistical significance tests and without confidence limits. These reports would be considered provisional "pulse checks" or snapshots that would allow detection of a previously unsuspected safety signal of potential importance. The first report would include the first 6 months of data and would be available 12 months after the start of the study. Subsequent cumulative reports would be provided bi-annually, and they would be separate from an interim report. The official interim analysis (after about 18 months using the first 12 months of data) would include rates and statistical tests, as well as selected pre-specified outpatient outcomes. Analysis of data in subpopulations (such as high-risk populations) or of specific outpatient outcomes would only be provided in the final report.

In response, we agree with your proposed timeline for reporting the tabulations of ICD-9 codes from ER and hospitalized patients, i.e., every six months rather than every 3 months. However, we have the following additional requests:

- a. Please provide the "every six month" cumulative tabulations within three months after the close of each six month period, starting with the first six months of data after study initiation.
- b. We advise you to consider conducting the official interim analysis using the first 18 months of data, rather the first 12 months of data, in order to allow for accumulation of more experience with this new product. This interim analysis should include outpatient settings and not be restricted to hospital and ER settings.
- c. It would be helpful for us to receive the interim and final analysis results of this study in a timely manner. Therefore, please consider submitting a preliminary or draft interim analysis report within three months of the interim analysis cut-off point followed by the final analytic report no more than six months later (i.e., 24 months after the study initiation). Likewise, please consider submitting a similar expedited submission of the final study analysis to CBER within three months of study end, followed by submission of the final study report within another three months.
- d. Please submit two types of tabulations: one with grouped events/ICD-9 codes and the other with more detailed information by individual ICD-9 codes, as follows:
 - o The first set of tabulations should 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 13vPnC, the tabulation should include numbers of events in the pre-vaccination window from -35 to -5 days prior to vaccination, as well as the number of events in the post vaccination control window and the corresponding relative rates. Please note that we recommend expanding the pre-vaccination interval by 5 days, in order to have the same amount of person time before and after the vaccinations. Alternatively, the comparative rates could be adjusted for a shorter pre-vaccination window, e.g., (30 day numerator divided by (25 day

denominator multiplied by 30/25)). For other doses, tabulations need not include events that occurred in the pre-vaccination control window. (See sample format below).

**Grouped ICD-9 codes for ER and Hospital Settings, number and relative rates
Dose 1 in children starting the infant series with 13vPnC**

ICD-9 codes	Pre-vax window -35 to -5 days	Risk window 0-30 days	Post-vax window 31-61 days	Relative rate N1/N1-0	Relative rate N1/N1-1
287 Purpura and other hemorrhagic conditions	N1-0	N1	N1-1	N1/N1-0	N1/N1-1
493 Asthma					
490 bronchitis, not specified as acute or chronic					
786 symptoms involving respiratory system and other chest symptoms					

All other doses

ICD-9 codes	Risk window 0-30 days	Post-vax window 31-61 days	Relative rate N1/N1-1
287 Purpura and other hemorrhagic conditions	N1	N1-1	N1/N1-1
493 Asthma			
490 bronchitis, not specified as acute or chronic			
786 symptoms involving respiratory system and other chest symptoms			

- The second set of tabulations should include the number of events 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 detailed tabulations should first be 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, because infrequently occurring codes will give rise to instability of the apparent relative rates.

2. With regard to your July 22, 2009, response to specific request #6 in our June 30, 2009, comments on your draft pharmacovigilance plan:

In our original request we noted that high risk groups are defined as infants with sickle cell anemia, HIV, and constrictive airway diseases and that selections of such groups could be based on diagnoses and corresponding medications. We suggested that the high risk group definition be expanded to patients with steroid or other immunosuppressive medications. In response, you agreed to include separate sub analyses of groups at specific increased risk of invasive pneumococcal disease ("high risk groups"), but proposed that identification of these groups would be based on diagnoses alone, as pharmacy information is housed in a separate database and would not be readily available to allow for expansion of the definition of "high risk" to include patients receiving steroids or other immunosuppressive agents.

In response, we understand the challenges that this particular analysis might present. However, due to the limited safety data in these high risk groups, we request that high risk patients be identified for the final study report analyses on the basis of diagnoses as well as pharmacy data. In addition to a primary analysis that pools all identified high risk patients, their data could be presented separately for two mutually exclusive subsets:

- a. Patients with diagnoses consistent with increased risk for invasive pneumococcal infections, regardless of pharmacy information.
- b. Patients without diagnoses consistent with increased risk for invasive pneumococcal infections but with prescriptions or medication administration records for steroids or other immunosuppressive medications.

We look forward to your response to these additional requests and, if you would like, we can discuss them with you via teleconference soon.

Regards,

-Julie

Julienne Vaillancourt, R.Ph., M.P.H.

Captain, US Public Health Service

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