U.S. FOOD & DRUG ADMINISTRATION

March 12, 2020

Allison Lucas, Esq.
C/O Siri & Glimstad LLP
200 Park Avenue
17th Floor
New York, NY 10166

In reply refer to file: F19-6310

Dear Ms. Lucas,

This is in reply to your Freedom of Information Act request dated July 17, 2019, in which you requested "Communication evidencing the last time FDA assessed the warning and precautionary information on the label for Prevnar 13." Your request was received in the Center for Biologics Evaluation and Research on July 18, 2019.

In an email with Ms. Suzann Burk on July 30, 2019, you amended the wording of your request to "The most recent supplement approval for Prevnar 13 (STN 125320) that includes an FDA review of the Warning and Precautions section of the package insert."

Enclosed is the labeling review memorandum dated April 12, 2016 for Prevnar 13.

The following may be included in a monthly invoice:

Review	1.25 Hours	@ $46.00/hr	$57.50
Total			**$57.50**

The above charges may not reflect final charges for this request. Please DO NOT send any payment until you receive an invoice from the Agency's Freedom of Information Staff (HFI-35).

If you are not satisfied with any aspect of the processing and handling of this request, please contact:

Food and Drug Administration (FDA)
Sarah Kotler, Director
Division of Freedom of Information, OES
U.S. Food & Drug Administration
5630 Fishers Lane
Room-1035
Rockville, Maryland 20857
301-796-3900 (main)
301-827-9267 (fax)

You also have the right to contact:

FDA FOIA Public Liaison
Office of the Executive Secretariat
5630 Fishers Lane
Room-1050
Rockville, MD 20857
Email: FDAFOIA@fda.hhs.gov

If you have any questions or if I can be of further assistance, please let me know by referencing the above file number. I can be reached by phone at 240-402-8008 or by e-mail at Ashlee.Eswara@fda.hhs.gov.

Sincerely,

Ashlee L. Eswara -S

Digitally signed by Ashlee L. Eswara -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000803574, cn=Ashlee L. Eswara -S
Date: 2020.03.12 15:07:50 -04'00'

Ashlee L. Eswara, Microbiologist
Access Litigation and Freedom of Information Branch
Center for Biologics Evaluation and Research
Food and Drug Administration

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: April 12, 2016

From: Loan Nguyen, Regulatory Review Officer
OCBQ/DCM/APLB

APPROVED
By Loan Nguyen at 8:28 am, Apr 12, 2016

Through: Lisa Stockbridge, Branch Chief
OCBQ/DCM/APLB

APPROVED
By Lisa Stockbridge at 12:28 pm, Apr 12, 2016

To: Katie Rivers, RPM, OVRR/DVRPA/CMC1
Taruna Khurana, RPM, OVRR/DVRPA/CMC1
Christina Houck, Chairperson, OVRR/DVRPA/CMC1
Elizabeth Valenti, Chairperson, OVRR/DVRPA/CMC1
Jeff Roberts, Supervisory Medical Officer, OVRR/DVRPA/CRB1
Gueorgui Dubrocq, Clinical Reviewer, OVRR/DVRPA/CRB1
Sarah Browne, Clinical Reviewer, OVRR/DVRPA/CRB1
Anuja Rastogi, Clinical Reviewer, OVRR/DVRPA/CRB1

Subject: Labeling Review - Comments on revised prescribing information

Product: **PREVNAR 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein])**
BLA STN: **125324/1358**
125324/1371
125324/1373
Sponsor: Wyeth Pharmaceuticals, Inc.

The sponsor submitted:

☐ Original Application
☐ Major Amendment
☒ Prior Approval Supplement (PAS): Efficacy Supplements
☐ Changes Being Effected (CBE) Supplement

Submission contains:

☒ Prescribing Information (PI) – submitted by the sponsor on September 11, 2015
☐ Patient Package Insert (PPI)
☐ Vial/Carton labels
☐ Other

This labeling review covers three pending efficacy supplements submitted by Wyeth Pharmaceuticals, Inc. (Wyeth) for PREVNAR 13 (Pneumococcal 13-valent Conjugate Vaccine [Diphtheria CRM197 Protein]).

1. 125324/1358: submitted on September 11, 2015 to expand PREVNAR 13 indication to include adults 18-49 years of age.

2. 125324/1371: submitted on November 4, 2015 to include information regarding the use of PREVNAR 13 in subjects infected with human immunodeficiency virus (HIV).

3. 125324/1373: submitted on November 13, 2015 to include information regarding the use of PREVNAR 13 in subjects 2 years of age and older who have received an allogeneic hematopoietic stem cell transplant.

The earliest action due date is July 11, 2016.

APLB reviewed all versions of the proposed revised prescribing information (PI) submitted by the sponsor, taking into consideration comments and edits made to the PI during the labeling meeting on March 14, 2016. The following comments and recommendations are in addition to the changes already made.

OVERALL

- Use a consistent approach for the presentation of sections, subsections, sub-subsections, and sub-sub-subsections throughout the PI. Please note that bolding headers and subheaders are a regulatory format requirement. To create a distinction, refrain from bolding sub-subheadings and other content of labeling unless required by regulations. For example, use **BOLD UPPER CASE** for sections, **Bold sentence case** for subsections, <u>underline</u> for sub-subsections, and *italic* for sub-sub-subsections.

  8 USE FOR SPECIFIC POPULATIONS
  8.1 Pregnancy
  <u>Clinical Considerations</u>
  Disease-associated maternal and/or embryo/fetal risk

- Avoid overuse of subsections.

- Present the proprietary name in UPPER CASE LETTERS (i.e., PREVNAR 13) for consistency with SPL stylesheets.

- Use consistent terminology throughout the PI. For example, consistently use the term, premature infants, infants born prematurely, or preterm infants, not all three interchangeably.

- Use active voice (i.e., command language for directions).

- Group relevant information together.
- Avoid trailing zeros in text. For example, use 5% instead of 5.0%.
- Avoid research jargon, such as Phase I, II, III studies, secondary endpoint, etc. Simply describe the studies and the results.

HIGHLIGHTS (HL)

- Ensure that the HL is limited in length to ½ page (e.g., would fit on one-half page if printed in a two-column format on a standard 8.5" x 11" size paper, single spaced, in 8 point type with ½ inch margins on all sides) unless a waiver is granted (see 21 CFR 201.57(d)(8) and 21 CFR 201.58).
- Add the section RECENT MAJOR CHANGES. Format as follows:

---------- **RECENT MAJOR CHANGES** ----------
Indications and Usage (1.3) xx/2016

- For the INDICATIONS AND USAGE section, include the established pharmacologic class (EPC) in the indication statement. The EPC for *Streptococcus pneumoniae* type 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F capsular polysaccharide diphtheria crm197 protein conjugate antigens is "inactivated pneumococcal vaccine." The list of FDA EPC text phrases can be found using the following link:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM428333.pdf

For example, APLB suggests the following revision:

> PREVNAR 13 is an inactivated pneumococcal vaccine indicated for immunization in the following age-groups:
>
> - Children 6 weeks through 5 years of age (prior to the 6th birthday) for:
> - Prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. (1)
> - 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. (1)
> - 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. (1)
> - Adults 18 years of age and older 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. (1)

Limitations of Use
PREVNAR 13 does not protect against disease caused by *S. pneumoniae* serotypes that are not in the vaccine. (1)

- For the DOSAGE AND ADMINISTRATION section:
    - Add the bold statement "**For intramuscular injection only.**" immediately underneath section heading.
    - Use one bullet to express the dose (one single dose) for children 6 years through 17 years of age and for adults 18 years of age and older. Consider simplifying this bullet to read: Children and adults 6 years and older: one single dose.

For example, APLB suggests the following revision:

---------- **DOSAGE AND ADMINISTRATION** ----------
For intramuscular injection only.
- Dose: 0.5 mL intramuscularly.
- Children 6 weeks through 5 years: primary four-dose series at 2, 4, 6, and 12-15 months of age.
- Children and adults 6 years and older: one single dose.

- For the WARNINGS AND PRECAUTIONS section, consider presenting all the risks. To be conscious of the length of the HL section, APLB suggests the following revision:
    - Hypersensitivity reactions may occur. (5.1)
    - Lower antibody responses in individuals with altered immunecompetence. (5.2)
    - Apnea following intramuscular vaccination in premature infants. (5.3)

- For the DRUG INTERACTIONS section, incorporate the change in the terminology used for inactivated trivalent influenza vaccine. The sponsor suggested "trivalent inactivated influenza vaccine (IIV3)."

- For the USE IN SPECIFIC POPULATIONS section, delete statements relating to the absence of information about the safety and effectiveness of PREVNAR 13 in a specific population (e.g., pregnant women, pediatric patients below the age of 6 weeks, etc.). Instead, present the information relating the use of PREVNAR 13 that differs in high risk populations from that in normal populations.

Please note that:

- For BLA STN 125324/1371, add a bullet for the information about the use of PREVNAR 13 in individuals with HIV.

- For BLAS TN 125324/1373, add a bullet for the information about the use of PREVNAR13 in transplant individuals.

TABLE OF CONTENTS (TOC)

Ensure that the section and subsection headings in the TOC match the section and subsection headings in the revised FPI.

FULL PRESCRIBING INFORMATION (FPI)

1 INDICATIONS AND USAGE

See comment above about the EPC and consider omitting the subsections. APLB suggests the following revision:

1 INDICATIONS AND USAGE

PREVNAR 13 is an inactivated pneumococcal vaccine indicated for immunization in the following age groups:

- Children 6 weeks through 5 years of age (prior to the 6th birthday) for
  - Prevention of invasive disease caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F.
  - 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.
- 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 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.

Limitations of Use

PREVNAR 13 does not protect against disease caused by *S. pneumoniae* serotypes that are not in the vaccine.

2 DOSAGE AND ADMINISTRATION

- The section currently has too many subsections. For readability, consider the following outline:

2 DOSAGE AND ADMINISTRATION
For intramuscular injection only.

2.1 Dose and Vaccine Schedule

2.2 Administration

- For the above proposed subsections, consider the following to improve comprehension:
    - For the subsection 2.1 Dose and Vaccine Schedule, present the vaccine schedule by age groups, preferably in table format.
    - For the subsection 2.2 Administration, use bullet format and command language. For example,

2.2 Administration

- PREVNAR 13 is a suspension containing an adjuvant in a prefilled syringe that must be shaken vigorously immediately prior to use to obtain a homogenous white suspension in the vaccine container.
    - Do not use if vaccine is not re-suspended.
    - Do not use if vaccine is discolored.
- Do not mix PREVNAR 13 with other vaccines/products in the same syringe.
- Inject intramuscularly using the sterile needle attached to the supplied prefilled syringe.
- Preferred sites for injection are the anterolateral aspect of the thigh in infants and the deltoid muscle of the upper arm in toddlers, children and adults. Do not inject in the gluteal area or areas where there may be a major nerve trunk and/or blood vessel.

5 WARNINGS AND PRECAUTIONS

- For readability and consistency in terminology used across CBER products, consider revising the 5.1 section:

5.1 Hypersensitivity Reactions

Hypersensitivity reactions may occur. Epinephrine and other appropriate agents used to manage immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur following administration of PREVNAR 13.

- Use consistent terminology for premature infants.

6 ADVERSE REACTIONS

- Consider revising the section to present only "adverse reactions (AR)" as defined in 21 CFR 201.57(c)(7). An AR is an undesirable effect, reasonably associated with the use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

- Consider grouping clinical trials experience into one subsection (see 21 CFR 201.57(c)(7)(ii)(A) and *Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*). Please note the following:

    - Subsection 6.1 usually is reserved for Clinical Trials Experience with the following verbatim presented right underneath the subheading:

      Because clinical trials are conducted under widely varying conditions, adverse-reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

    - Subsection 6.2 usually is reserved for Postmarketing Experience with the following verbatim presented right underneath the subheading:

      The following adverse reactions have been identified during post approval use of PREVNAR 13. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to PREVNAR 13 exposure.

7 DRUG INTERACTIONS

- Use active voice when possible.

- Delete "Do not mix PREVNAR 13 with other vaccines/products in the same syringe" because the same information is already included in section 2.

- For the **7.3 Antipyretics** subsection, please consider the following:

    - Provide the reference for the postmarketing clinical study.

    - Clarify whether or not other antipyretics were used or only acetaminophen was used in the study.

8 USE IN SPECIFIC POPULATIONS

- Revise subsections 8.1, and 8.2 to conform to the PLLR.

- Consider grouping all pediatric information, including high risk pediatric subpopulations (such as preterm infants and children with sickle cell), into one subsection, 8.4 Pediatric Use.

- Consider presenting each subpopulation as a separate subsection. For example, revise subsection 8.6 for individuals with HIV infection (for BLA STN 125324/1371) and create subsection 8.7 for individuals received hematopoietic stem cell transplantation (for BLA STN 125324/1373).

14 CLINICAL STUDIES

This section currently is very lengthy with too many subsections and sub-subsections. Please consider revising the entire section for comprehension and readability.

15 REFERENCES

Only include a reference to the source of the information when the labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions (see 21 CFR 201.57(c)(16)).

16 HOW SUPPLIED/STORAGE AND HANDLING

- Add subheadings, How Supplied and Storage and Handling for readability.

- Move latex information to How Supplied.

- Use bullet format to improve readability.

If you have any questions regarding this review please contact Loan Nguyen, Pharm.D., Regulatory Review Officer at 240-402-9030.

Firm: Wyeth

STN: 125324/1358
125324/1371
125324/1373

Document type: Review Memorandum

Bcc: L. Nguyen
APLB Chronologic File
APLB Historical File

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Concurred: L. Stockbridge 4/11/16
Finalized: L. Nguyen 4/12/16

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Concurrence box:

MailCode or Office	Name Date
APLB	APPROVED By Loan Nguyen at 8:28 am, Apr 12, 2016
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