

Date: February 16, 2009

From: John F. Cipollo, Ph. D.

Through: Willie Vann Ph. D.

To: Julianne Vaillancourt, Chair, Review Committee

File: BLA 125324

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

Subject: Review of manufacturing process

Reference: List of BLA section(s) reviewed: 2.2 Introduction, 2.3 Quality Overall Summary; 2.3.1 Introduction; 2.3.S Drug Substance all Serotypes; 3.2.S Drug Substance all sections for all Serotypes including 3.2.S.1 General Information; 3.2.S.2 Manufacture, 3.2.S.3 Characterization; 3.2.S.4 Control of Drug Substance; 3.2.S.5 Reference Standards and Materials; 3.2.S.6 Container Closure System and 3.2.S.7 Stability; 3.2.P Drug Product, 3.2.P.1 Description of Composition of the Drug Product; 3.2.P.2 Pharmaceutical Development; 3.2.P.3 Manufacture; 3.2.5 Control of Drug Product; 3.2.P.6 Reference Standards of Materials; 3.2.P.7 Container Closure System; 3.2.P.8 Stability; RPT-70303; Amendment 464657/0.10 received 05.13.2009; Amendment 466614/0.15 received 6.11.2009; Amendment 467625/0.19 received 06.26.2009; Amendment 469908/0.23 received 07.30.2009; Amendment 473163/0.30 received 09.21.2009; Amendment 467625/0.31 received 09.21.2009; Amendment 474273/0.35 received 10.06.2009; Amendment 474344/0.36 received 10.07.2009; Amendment 474474/0.37 received 10.08.2009; Amendment 474478/0.38 received 10.08.2009; Amendment 474585/0.40 received 10.12.2009; Amendment 474586/0.41 received 10.12.2009; Amendment 475819/0.47 received 10.28.2009; Amendment 476431/0.48 received 11.05.2009; Amendment 477464/0.41 received 11.23.2009; Amendment 478477/0.61 received 12.08.2009; Amendment 478731/0.64 received 12.11.2009; Amendment 482097/0.83 received 02.10.2010.

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## Executive Summary

Prevnar 13 is a 13-valent pneumococcal vaccine for use in infants and young children for the prevention of pneumococcal disease. The pneumococcal 13-valent conjugate vaccine is a sterile suspension of the capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated by reductive amination to the non-toxic diphtheria CRM197 protein. The vaccine includes the seven serotype conjugates included in the currently licensed Prevnar: 4, 6B, 9V, 14, 18C, 19F and 23F.

Drug formulation has changed from that of Prevnar. Polysorbate 80 has been added to a final concentration of 0.02%. Succinate buffer has been added ---b(4)-----

Issues identified with the Prevnar 13 product are summarized here in the Executive Summary and described in more detail in the subsequent review section. These issues include:

- serotype-5 manufacturing process,
- drug product release testing (---b(4)-----, succinate assessment, and --b(4)-----),
- establishment of a --b(4)----- assay for serotype-b(4)-
- drug product stability testing.
- Serotype --b(4)----- specification

All of these issues can be addressed by completion of a series of post marketing commitments by the firm. The most important of these issues involves the manufacture of serotype-5 conjugate. It should be noted that completion of the post marketing commitments, especially for the type 5 issue, are critical for the long term safety and reliability of the drug product. I also feel strongly that a succinate assay specification should be present for lot release of the drug product. A brief summary of each issue is as follows;

### Serotype 5 Manufacturing Process

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vaccine also contains an additional 6 serotypes with properties that differ from those in Prevnar. -----(b)(4)-----  
----- . In Amendment 474474/0.37, received and submitted to the file on 10/08/2009, Wyeth presented data and proposed the development of a --b(4)----- assay for stability testing. The study design was not optimal but showed an earnest attempt by the sponsor to demonstrate proof of concept that the --b(4)-----  
----- -- Assay may be useful for development as a stability indicating assay for monitoring of the 13 conjugates in the DP. Although evidence was not conclusive, the data presented made ---b(4)--- -----  
----- . However, there are some fundamental obstacles that may prevent progress with this method. Wyeth agrees to a post marketing agreement to develop and implement this assay or another assay if --b(4)----- proves to be problematic.

#### ***Succinate Assay in Final Drug Product***

For Prevnar, monovalent bulk conjugates are formulated in a --b(4)----- solution. For 13vPnC, a succinate buffer has been added in the formulation of all ----- --b(4)----- control and stability. Historically it was observed that some of the less stable serotypes, particularly --b(4)--- ----- This is documented in the file in 3.2.S.2.6. I feel strongly that a succinate assay should be added to release specifications as this buffer is a critical component of the vaccine.

#### ***Serotype --b(4)----- Specification***

The --b(4)----- specification for serotype 1 polysaccharide is -b(4)-- as shown in 3.2.S.2.4 Control of Critical Steps and Intermediates. This is much lower than the sponsor's clinical experience. Wyeth should revise this specification to -b(4)- Wyeth has agreed to this revision as a post marketing commitment.

### **REVIEW**

#### **Formulation**

Prevnar 13 is a 13-valent pneumococcal vaccine of use in infants and young children for the prevention of pneumococcal disease. The pneumococcal 13-valent conjugate vaccine is a sterile suspension of the capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F individually conjugated by reductive amination to the non-toxic diphtheria CRM197 protein. Each 0.5 mL dose contains a target of 2.2 µg each of the polysaccharides (except for 6B, formulated at 4.4 µg/dose), approximately 32µg of CRM197, 0.02% polysorbate 80, and 0.125 mg of aluminum as aluminum phosphate adjuvant.

The vaccine includes the seven serotype conjugates included in the currently licensed Prevnar: 4, 6B, 9V, 14, 18C, 19F and 23F with the addition of 6 serotypes; 1, 3, 5, 6A, 7F, 19A. In the United States Active Bacterial Core surveillance data shows that incidence of invasive pneumococcal disease from 6A and 19A has increased. In less developed countries serotypes 1, 5 and 7F are important causes of childhood disease.

Drug formulation has changed from that of Prevnar. Polysorbate 80 has been added to a final concentration of 0.02%. Succinate buffer has been added for additional buffering capacity. --b(4)-----  
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## **Review of Drug Substance Manufacture**

### **Manufacture**

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## Manufacture of Drug Product

Drug product is produced at two sites namely ----b(4)-----  
Wyeth Pearl River. It is formulated as follows:

Names of Ingredients	Unit Formula (0.5 mL dose)	Function	Reference to Standard
Active ingredients:	Nominal Composition		
Thirteen pneumococcal conjugates (saccharides conjugated to CRM <sub>197</sub> )			
Polysaccharide Serotype 1	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 3	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 4	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 5	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 6A	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 6B	4.4 µg	Antigen	Company Monograph
Polysaccharide Serotype 7F	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 9V	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 14	2.2 µg	Antigen	Company Monograph
Oligosaccharide Serotype 18C	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 19A	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 19F	2.2 µg	Antigen	Company Monograph
Polysaccharide Serotype 23F	2.2 µg	Antigen	Company Monograph
CRM <sub>197</sub> protein	~ 32 µg <sup>a</sup>	Carrier protein	Company Monograph
Adjuvant:			
Aluminum Phosphate	0.125 mg Al	Adjuvant	Company Monograph
Other Ingredients:			
(b)(4)	(b)(4)	Excipient	(b)(4)
Succinic Acid	0.295 mg	Excipient	(b)(4)
Polysorbate 80	0.1 mg	Excipient	
Water-for-Injection	qs to 0.5 mL	Excipient	

- a. Vaccine is formulated on the basis of the saccharide content, and the amount of protein is dependent on the polysaccharide/protein ratio of the conjugate.

Specifications are as follows:

Tests	Methods	Specifications Release	Stability
<b>Formulated Bulk Vaccine</b>			
Sterility	(b)(4)	Meets the requirements of the test. No growth observed	N/A <sup>a</sup>
<b>Filled Syringes</b>			
Aluminum	(b)(4)	(b)(4)	N/A <sup>a</sup>
(b)(4)	(b)(4)	(b)(4)	
(b)(4)	(b)(4)	(b)(4)	
Serotype 1	(b)(4)	(b)(4)	(b)(4)
Serotype 3			
Serotype 4			
Serotype 5			
Serotype 6A			
Serotype 6B			
Serotype 7F			
Serotype 9V			
Serotype 14			
Serotype 18C			
Serotype 19A			
Serotype 19F			
Serotype 23F			

The Specifications indicated are acceptable. However, there is no stability indicating assay for the final product to indicate the amount or presence of intact conjugate.

-----b(4)-- can not distinguish ----b(4)----- . In meetings with the sponsor this deficiency was discussed. This was a major issue of discussion in the July 28, 2009 and September 1, 2009 face-to-face meetings with the Wyeth. Prevnar had no stability indicating requirement for the conjugate and this was related to CBER by the sponsor in these meetings. However, CBER feels strongly that there should be a stability indicating assay in place for the new product. This issue is covered in detail in another reviewer's memorandum. Although there was no such specification for Prevnar, the Prevnar 13 product is different and it is my opinion that the lack of the specification in the Prevnar product was an oversight. The new product contains succinate and contains an additional 6 serotypes with properties that differ from those in Prevnar. Therefore, as a new product, the request for this requirement is justified.

Wyeth acknowledged this need and has agreed to develop an appropriate assay and is currently developing an assay based on the --b(4)----- . These studies are ongoing. CBER agrees that the development and validation of the appropriate assay may occur as a post marketing commitment.

## **Control and Stability of Drug Product**

Formal stability studies are ongoing. Wyeth is proposing a 24 month expiration dating at the recommended storage conditions of 2-8 °C. In addition to the recommended storage condition of 2-8 °C the stability studies included the following conditions:

- Multiple temperature excursions -b(4)- for a total duration of --b(4)-----, followed by long-term storage at 2-8 °C.
- Multiple temperature excursions to ---b(4)-----, followed by long term storage at 2-8°C.
- Exposure to thermal stress conditions ---b(4)-----  
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- ICH requirements for --b(4)-----

Three clinical and three stability lots were stored at the recommended storage condition and stressed. Product was stored in--b(4)--- orientation. Pearl River conducted stability studies of there validation lots at recommended and stressed conditions --b(4)--- and --b(4)-----. -b(4)----- performed identical tests with three other validation lots. Specifications were met out to 24 months at the recommended storage condition for clinical consistency lots. Validation lots have been evaluated out to -b(4)--- and other time points are pending. Lot --b(4)----- was found to have a non-homogeneous white suspension. The OOS event generated MIR 351153, which determined the suspension to be aluminum phosphate aggregate. All other lots remained within specification. The 24 month expiration dating is appropriate. Stability testing should be continued and reported in annual reporting.

## **List of Meetings and Correspondence**

June 5, 2008: Pre-BLA (CMC) Meeting Minutes

May 19, 2009; Telecon on resolution of serotype 6B --b(4)----- conditions

June 15, 2009; Telecon on CMC Issues, mainly serotype 5 issues

June 19, 2009; Telecon on drug product and drug substance Issues

July 28, 2009; Face-to-Face Meeting on CMC Issues, topics were: serotype 5 assay validation and conjugate in final product

August 6, 2009; the Office of Vaccines Research and Review informed the sponsor about the Agency's decision to cancel the September 10, 2009, VRBPAC meeting to discuss Prevnar 13, because it considered this meeting to be premature, given outstanding CMC issues identified in the review of the Prevnar 13 BLA to date, in particular, information contained in the July 23rd submission.

August 7, 2009; Telecon to inform Wyeth that the July 23rd submission would be deemed a major amendment. Thus, the review clock would be extended by 90 days. Additionally, VRBPAC will be rescheduled to November 18th or 19, 2009.

September 1, 2009; discussion of path forward for outstanding CMC issues.

December 1, 2009; discussion of --b(4)----- Assay

December 3, 2009; discussion on CMC issues

June 12, 2009; e-mail from Mike Smith to Jack Love and Carmel Devlin, titled "RE: Talking points for June 15 teleconference to discuss the -b(4)- of serotype 5."

August 5, 2009; e-mail from Jack Love to Julie Vaillancourt and Mike Smith with attachment, titled "Type 5 -b(4)----- Expts 5Aug2009."

October 6, 2009; Meeting with Wyeth to discuss Testing of Type 1 MBC's for --b(4)-----

October 7, 2009; Telecon w/Wyeth on CBER's request to tighten specs pre-licensure

September 30, 2009; e-mail from Jack Love to Julie Vaillancourt and Mike Smith concerning specifications for ----b(4)-----.

November 9, 2009; Additional items for Prevnar -13

December 1, 2009 Telecon with Wyeth regarding drug substance and drug product validation assays on Prevnar 13

December 9, 2009; Telecon with Wyeth regarding Saccharide ----- --b(4)-----  
----- Procedure

January 15, 2010 Telecon with Wyeth regarding labeling issues

January 22, 2010; Face-to-Face Meeting to discuss CMC PMC validation issues

### **List of Amendments**

Amendment 464657/0.10 received 05.13.2009; Additional clarification of 6B activated saccharide --b(4)----- specification for 13vPnC

Amendment 466614/0.15 received 6.11.2009; Response to SOPs Questions

Amendment 467625/0.19 received 06.26.2009; Response to Serotype 5 Questions from 06.15.2009 Teleconference

Amendment 469908/0.23 received 07.30.2009; Updated Quality Documents

Amendment 473163/0.30 received 09.21.2009; Cell Bank Notification

Amendment 473247/0.31 received 09.21.2009; Follow-up to CMC questions on June 19, 2009

Amendment 474273/0.35 received 10.06.2009; Response to teleconference of June 19, 2009, face-to-face meetings of July 28, 2009 and September 1, 2009 regarding serotype 5 --b(4)-----

Amendment 474344/0.36 received 10.07.2009; Response to teleconference of June 19, 2009, face-to-face meetings of July 28, 2009 and September 1, 2009 regarding serotype 5 -b(4)-----

Amendment 474474/0.37 received 10.08.2009; Response to teleconference of June 19, 2009, face-to-face meetings of July 28, 2009 and September 1, 2009 regarding drug product stability indicating assay

Amendment 474478/0.38 received 10.08.2009; Response to teleconference of June 19, 2009, face-to-face meetings of July 28, 2009 and September 1, 2009 regarding type 5 characterization

Amendment 474585/0.40 received 10.12.2009; Effect of -b(4)-on free saccharide recovery

Amendment 474586/0.41 received 10.12.2009; Response Regarding Antigenicity of -b(4)--

Amendment 475819/0.47 received 10.28.2009; Responses to --b(4)----- calculation, use of -b(4)--- standard curves, and AOAC International Terms and Definitions

Amendment 476431/0.48 received 11.05.2009; September 1, 2009 meeting minutes

Amendment 477464/0.52 received 11.23.2009; Serotype 1 Conjugation Process Review

Amendment 478477/0.61 received 12.08.2009; Justification of drug product stability; reconciliation of drug product binding to AlPO<sub>4</sub>

Amendment 478731/0.64 received 12.11.2009; Response to agency request for CMC PMC commitments

Amendment 482097/0.83 received 2.10.2010; Response to agency request for revised CMC PMC commitments

## ISSUES SUMMARY

### Issue 1: CMC Issues for Serotype 5 Drug Substance:

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---b(4)----- Specifications for the new serotypes far exceeds Wyeth's Clinical experience. The revised specifications submitted by email on 09/30/2009 in response to CBER's concerns contained considerably more narrow specifications. However, no revised specification met with clinical experience.

--b(4)----- assay is in place to insure consistency of manufacture and that a safe level of --b(4)----- is present in the product after manufacture. Vastly differing amounts of --b(4)---- are allowed in the different serotypes. Wyeth has set the limit for each serotype conjugate based on 3 times standard deviation using a limited number of batches, which places the specification value far outside their clinical experience. Wyeth states that total --b(4)--- per dose based on the current specifications are --b(4)-----  
----- However, such tests do not account for the complex matrix of the drug product.

A CBER statistician, Lev Sirota, reviewed this situation in consultation with Dr. Willie Vann. The narrowed specifications for these three assays are acceptable but Wyeth is to follow up with analysis of -b(4)--- or lots produced by June 2012 and these specifications are to be reevaluated. The sponsor has agreed to these terms in a post marketing commitment.

## **Issue 5**

### **Drug Product Stability Testing**

There is no stability indicating assay for the final product to indicate the amount or presence of intact conjugate. This was a major issue of discussion in the July 28, 2009 and September 1, 2009 face-to-face meetings with the sponsor. Prevnar, the currently licensed product, had no stability indicating requirement and this was related to CBER by the sponsor in these meetings. However, CBER feels strongly that there should be a stability indicating assay in place for the new product. The product is different from the current licensed Prevnar. It contains succinate, polysorbate and contains an additional 6 serotypes with properties that differ from those in Prevnar.

Wyeth acknowledged this need and has agreed to develop an appropriate assay. Wyeth suggested modification of a current assay based on --b(4)-----  
----- It was agreed in a face-to-face meeting on September 1, 2009 that data from two serotypes will initially be submitted as proof of principle. There will be one representative of conjugate prepared in --b(4)-----  
----- These data and plan are to be submitted prior to licensure. CBER agreed that the development and validation of the appropriate assay may occur as a post marketing commitment. Wyeth agreed to submit a plan of action as an amendment to the file. This issue is also covered in detail in another reviewer's memorandum (see Dr. Rajesh Gupta's memo).

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### **Recommendation**

I recommend approval of the Biologic License Application for Prevnar 13 on the basis of the reviewed materials, interactions with the firm, and the post marketing commitments that have been agreed upon.