

Date: August 28, 2009

From: Dr. Eugenia Dragunsky

Through: Dr. Steven Rubin

To: Julianne Vaillancourt, Chair, Review Committee

File: BLA 125324/0.12

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

Subject: Response to the letter from FDA received by the sponsor on May 5, 2009 on "Bioanalytical and Analytical Methods for Human Studies. Polio Neut Sabin"

Reference: BLA 125324, Amendment 0.1, section 5.3.1.4 submitted 10/24/08; Amendment 0.12, section 1.11.3 and section 5.3.1.4.1, submitted 5/19/09

Summary:

The sponsor responds to the following 7 CBER questions. A summary of the sponsor's responses and my assessment of those responses are included.

CBER Question #1: In section 2.1.1 (page 7), you state that all three polioviruses met the acceptance criteria for accuracy recovery ((b)(4) of GMT's being within (b)(4) dilution factor of the expected GMT). However, the data in Table 2-2 indicates that was not achieved for poliovirus type 3. Please clarify

Sponsor's Response:

Addressing this question the sponsor explained that although-(b)(4)-- individual dilutions (high control) of type 3 did not achieve acceptance criteria (b)(4) overall poliovirus type 3 passed the acceptance criteria according to the validation protocol (Am. 0.12, sections 5.3.1.4.1). When the percentage is calculated basing on total number of GMT of all diluted samples it is --(b)(4)---%.

CBER Review of Response:

The response is adequate.

CBER Question #2: In section 2.1.3 (pages 7-8), you list tables 2-3 and 2-4. The data in these tables are difficult to interpret. For both tables, please define all column and row headings. In addition, for Table 2-3, please indicate what the entered data refer to (e.g., numbers 6, 7, 5, 8, 3, 2 etc.).

Sponsor's Response:

Detailed clarifications are presented by sponsor. Such as number 092007 indicates the two numbers month, two number day and two number technician number; number 12 means sample identification; numbers -(b)(4)- mean (b)(4)- independent assays; numbers --- (b)(4)--- indicate test performed in --(b)(4)--; numbers (b)(4) are values correspond to a neutralizing titer as described in SOP (VR-ECD-10011)

CBER Review of Response

The response is adequate.

CBER Question #3: Please provide data demonstrating specificity of your virus stocks used in these assays. We prefer that this is demonstrated by cross-reactivity studies.

Sponsor's Response:

The sponsor used an -----(b)(4)----- method with -----(b)(4)----- specific to one of the three serotypes -----(b)(4)-----
----- was carried out according to details provided by the manufacturer
---(b)(4)----- The results are summarized in the Table below.

[(b)(4)]

CBER Review of Response:

The response is adequate.

CBER Question #4: In regard to Table 2-5 in section 2.1.4 (page 9), we note the failures of the poliovirus types 2 and 3 neutralization assays to meet the prescribed acceptance criteria (----- (b)(4) ----- of the samples having expected titers upon dilution). While we agree that the measured titers were very close to the expected titers, the acceptance criteria were nonetheless not met. Please provide additional data in support of adequate assay sensitivity

Sponsor's Response:

[(b)(4)]

----- (b)(4) -----

CBER Review of Response:
Although some samples did not meet acceptance criteria (2 out of (b)(4) samples for type 3 and 1 out of (b)(4) samples for type 2) the failures were random, and did not have systemic character. Neutralizing antibody titers in failed samples were close to the accepted titers.

It is worth while to take into account also that all type 1 control samples met acceptance criteria (supporting test accuracy). The small inaccuracy of the test could not significantly bias the results (neutralizing antibodies titers) of clinical samples because the vast majority of the volunteers responded with titers well above 1:8. For the most important type 3 the titers were: 98% - between 1:64 and 1:8192, 1% - 1:32, 0.5% - 1:16, 0.5% - 1:8, (study 3005). Therefore, the sponsor's response can be considered acceptable.

CBER Question #5: In regard to Table 2-7 in section 2.1.5.1 (page 12), please describe the set-up of the table and clarify whether the different dilutions of sera shown in the first column were made from a single high titer serum or five distinct sera.

Sponsor's Response:

The sponsor clarified that the dilutions were made from -----(b)(4)-----

CBER Review of Response:

The response is adequate.

CBER Question #6: Please submit the following two documents to the file:

- a. Validation Report of Poliovirus Antibody -----(b)(4)----- Test, Wyeth Vaccines, Research External Contractor Document. VR-ECD-10012, and**
- b. Poliovirus Antibody -----(b)(4)----- Test ((b)(4) Protocol) Wyeth Vaccines Research, External Contractor Document. VR-ECD-10011.**

Sponsor's Response:

The requested documents have been provided (Module 5.3.1.4)

CBER Review of Response:

Please provide your assessment here

CBER Question #7: In Section 6.5.1 (page 27) we note apparent incorrect reference to use of a (b)(4) neutralization assay in measuring poliovirus antibody responses and apparent incorrect reporting of these antibody responses as IgG titers in Table 9.7 in section 9.4.2.1 (page 70). Please confirm these apparent errors and correct them, as follows:

- a. In section 6.5.1, it should be indicated that a -----(b)(4)----- assay (not a (b)(4) neutralization assay) was performed.**
- b. In table 9.7, section 9.4.2.1, the presented titers should be described as neutralization titers in footnote "a".**

Sponsor's Response:

The sponsor corrected these errors

CBER Review of Response:

The response is adequate.