Mid-Cycle Review, January 12, 2009 - Menveo

- **MID-CYCLE REVIEW BLA 125300**

  January 12, 2009
  Reviewer: Karen Meysick, Ph.D.
  Through: Drusilla Burns, Ph.D.
  Laboratory Chief, LRSP/DBPAP
  Review Focus: Diphtheria and Tetanus Assay Validation (concomitant vaccine)
  Items Reviewed To Date: BLA 125300/0.0 and amendment 125300/0.3
  Study #: V59P18 (pivotal)
  Assays Performed at: --b(4)----------

Brief Summary:

The primary immunogenicity objective of this clinical trial was to demonstrate that the immune response of Tdap given concomitantly with MenACWY was not inferior to the response of Tdap given alone. The secondary objectives related to diphtheria and tetanus serology was to demonstrate that the immune response to Tdap administered alone 1 month after MenACWY was not inferior to the immune response to Tdap administered alone 1 month prior to MenACWY and to assess the immunogenicity of Tdap administered alone or concomitantly with MenACWY and HPV as measured by anti-diphtheria and anti-tetanus GMCs. For these immunogenicity objectives the response to Tdap was assessed as the percent of subjects with anti-diphtheria titers ≥ 1.0 IU/ml and the percent of subjects with anti-tetanus titers of ≥ 1.0 IU/ml. To establish subject titers anti-diphtheria and anti-tetanus -b(4)----- were performed and the data analyzed at --b(4)----------. In the BLA, Novartis provided the validation reports for both the diphtheria and tetanus -b(4)--- done at ---b(4)----------. After initial review of these validation reports there was considered to be insufficient data to adequately assess the validity of each -b(4)-. The additional information required for a complete review of these two validation reports was conveyed to Novartis, via a DI letter, on November 17, 2008 and in response Novartis submitted an information amendment to this BLA (125300/0.3) on December 19, 2008.
The information provided in BLA amendment 125300/0.3 addressed many of the issues that arose during preliminary review of the -b(4)- validation reports; however, several additional questions that concern diphtheria and tetanus -b(4)- validation remain.

Comments to Novartis:
Study V59P18 Diphtheria and Tetanus -b(4)--- Validation

1. In neither Attachment Q1-12 (Section 5.6 “Qualifying a new lot of in-house controls” SOP b(4)003-07 “Qualification of New Reagents and Managing Change for Other Significant Components for -b(4)---- and Other Assays”) nor in Attachment Q9-2 “Reference values and acceptance range for currently used references slopes and controls for diphtheria and tetanus -b(4)-” are the specific concentrations (IU/ml) of the low, medium and high controls given. Please provide the titers of the low, medium and high control samples currently used in the diphtheria and tetanus -b(4)--

2. In Attachment Q1-7 (SOP b(4)006-08 “Data Acquisition and Analysis”) there is no indication as to the linear range of the --b(4)---------- used in the diphtheria and tetanus -b(4)---. Please comment. Additionally in Appendix 3 and 4 of SOP b(4)006-08 (Dip and Tet SBLCalc Settings) the minimum and maximum -b(4)-- values for the calculation of titers are indicated as --b(4)------; however, in Section 15 “Calculation of Titers” in both the diphtheria and tetanus --b(4)--- validation reports the minimum and maximum b(4) values used for titer calculation are -b(4)--------- Please comment.
3. In response CBER’s question as to the use of pre-determined acceptance criteria (Question #12 in the DI letter), Novartis responded that at the time the -b(4)------were established and validated at --b(4)---------- (1994-1998) it was not common practice to establish pre-set acceptance criteria. However, Novartis did indicate that a CV of 20% was generally applied to evaluate validation parameters and that --b(4)---------- targeted the 20% CV acceptance criteria for all -b(4)---- Later in their response Novartis stated that *“in May 2001, FDA issued a “Guidance for Industry/Bioanalytical Method Validation” that defined acceptance criteria for precision, stating that the coefficient of variation should not exceed 15%, except for the lower limit of quantitation (LLOQ) where a CV of 20% is deemed acceptable and for accuracy, saying that the mean value should be within 15% of the actual value except for the LLOQ where a deviation of 20% is acceptable. Neither FDA nor ICH guidelines specify a general acceptance criterion for linearity but a coefficient of correlation of R2 = 0.99 is generally accepted as indicating a good linearity.”* In the recent re-qualification of the tetanus -------b(4)---------- (Attachment Q1-13, “Qualification of --b(4)---------- for Performance of Tetanus & Pertussis Antibody -b(4)------- dated June 27, 2006) the pre-specified acceptance criteria for precision was indicated as -b(4)-- Please confirm and justify the acceptance criteria for precision currently used by --b(4)---------- for the tetanus --b(4)----.
4. In the original validation report no pre-set acceptance criteria was given for accuracy in the tetanus -b(4)---; however, in the 2006 re-qualification report (Attachment Q1-13) an acceptance criteria of -b(4)-- fold-difference between the measured and nominal concentration was specified for accuracy. As indicated above, Novartis also noted that *“in May 2001, FDA issued a “Guidance for Industry/Bioanalytical Method Validation” that defined acceptance criteria for precision, stating that the coefficient of variation should not exceed 15%, except for the lower limit of quantitation (LLOQ) where a CV of 20% is deemed acceptable and for accuracy, saying that the mean value should be within 15% of the actual value except for the LLOQ where a deviation of 20% is acceptable.”* Please comment and justify the use of a -b(4)-- fold-difference as the acceptance criteria for accuracy in the tetanus -b(4)-. Have any data on the accuracy of high and medium titer serum samples become available since the 2006 re-qualification of the tetanus -b(4)-? Please comment.

V59P18 Clinical Serology Results

5. For the Diphtheria immunogenicity results there appears to be a discrepancy between the GMTs recorded for Groups I and III at Day 31 and Group II at Day 61 (Table 14.2.1.31) and the GMT data presented in Table 14.2.1.18 and Table 14.2.1.25. Please comment.

Study #: V59P11 (supportive)

Assays Performed at: Novartis Clinical Serology Laboratory

Brief Summary:

The primary immunogenicity objective of this supportive trial was to demonstrate that the immunogenicity of a single injection of Tdap vaccine, separately but concomitantly administered with MenACWY, was not inferior to that of a single injection of Tdap vaccine, concomitantly administered with saline placebo. For this primary objective the variables were the percentage of subjects with anti-diphtheria and anti-tetanus titers of ≥ 1.0 IU/ml at 1 month post-immunization. The secondary immunogenicity objective of this study was to compare the immunogenicity of a single injection of Tdap vaccine, when given separately but concomitantly with MenACWY, to that of a single injection of Tdap vaccine, concomitantly administered with saline placebo. For this objective, the immunogenicity response of Tdap was defined as the percentage of subjects with anti-diphtheria and anti-tetanus toxin titers of ≥ 0.1 IU/ml at 1 month post-vaccination, the anti-diphtheria and anti-tetanus geometric mean antibody concentration (GMC; IU/ml) at baseline and at 1 month post-vaccination, and the GMC increase (geometric mean ratio, GMR) from baseline at 1 month post-vaccination. For both objectives anti-diphtheria and anti-tetanus antibody titers were measured by -b(4)-that were performed and analyzed at the Novartis Clinical Serology Laboratory.

Comments to Novartis:
Study V59P11 Diphtheria and Tetanus -b(4)- Validation

6. Please provide details on how the IU/ml of clinical sera samples was calculated and include a sample calculation.
7. Please provide information on the qualification of new reagents used in the diphtheria and tetanus -b(4)-.
8. To confirm that the diphtheria and tetanus -b(4)---- performed in a stable manner over time please provide chart records for each --b(4)-- that includes the time over which the clinical trial was run (April 2006 to May 2007).

Contact FDA

(800) 835-4709
(240) 402-8010
ocod@fda.hhs.gov

Consumer Affairs Branch (CBER)
Division of Communication and Consumer Affairs
Office of Communication, Outreach and Development
Food and Drug Administration
10903 New Hampshire Avenue
Building 71 Room 3103
Silver Spring, MD 20993-0002