

Review of Pertussis Clinical Serology - Rotarix

DATE: February 25, 2008

FROM: Sandra Menzies, M.S., LMDQC, DBPAP

TO: Laraine Henchal, Chair, Review Committee

SUBJECT: BLA STN 125265 (Rotarix®, GlaxoSmithKline Rotavirus vaccine, live, oral, monovalent) Review of pertussis clinical serology

THROUGH: Drusilla Burns, Ph.D., Acting Lab Chief LMDQC

REFERENCE: STN 125265

SCOPE OF REVIEW:

Product:

Rotarix®, GlaxoSmithKline (GSK) Rotavirus vaccine, live, oral, monovalent

Indication:

Active immunization against rotavirus gastroenteritis caused by G1 and non-G1 (including G2, G3, G4, and G9)

OVERALL CONCLUSION:

The pertussis serological review was limited to assays supporting Rota-060. The immunoassays were found to be adequate for the purposes for which they were used in this application. The PT, PRN, and FHA to *B. pertussis* assays performed at Rixensart, Germany were determined to be stable for the duration of the assays performed to support this submission.

SUMMARY:

GlaxoSmithKline Biologics (GSK) submitted standard operating procedures (SOPs) and the validation reports for the Pertussis ELISAs conducted at their Rixensart laboratories (see appendix A). Six studies evaluated the concurrent administration of DTaP vaccines (Rota-005, Rota-007, Rota-014, Rota-036, Rota-039, and Rota-060) and one study evaluated DTwP vaccine (Rota-006). Study reports for Rota-014 and Rota-039 did not contain data for pertussis components. Study samples from Rota-005, Rota-006, and Rota-007 were performed at ----- . Study samples from Rota-036 and Rota-060 were analyzed at GSK's Rixensart laboratories. See Table 4 in section m2.5 Clinical Overview, pages 18-23, for study details. Based on response to CBER comment #3a (eBLA amendment 008 dated 01/09/2007), data from Rota-005, Rota-006, and Rota-007 should not be considered for licensure. In this same response, GSK indicated that Rota-060 co-administration data are considered pivotal to support licensure of the candidate Rotarix® vaccine in the US. Based on communication with Laraine Henchal, Chair of the review committee for this BLA, CBER agrees with GSK's response. As a result of this information, the pertussis component serological review focused on the methodology and validation of the assays used to measure the antibody response to the pertussis components of vaccines administered concurrently with Rotarix® and data from Rota-060.

The validation packages for measurement of total IgG antibodies to *Bordetella pertussis* for PT, FHA, and PRN by ELISA using human sera are dated ----- . The validation package for measurement of total IgG antibody to *Bordetella pertussis* by ELISA using human sera is dated ----- . The Standard Operating Procedures (SOPs) for these test

methods are ----- . These validation packages and SOPs were reviewed by Bruce Meade on April 26, 2005. To minimize reviewer inconsistencies, the validation packages were reviewed to assure that the validated test methods were stable during the testing of Rota-060 and that Rota-060 endpoints were evaluated during the validation.

For study Rota-060, the pre-specified criteria for non-inferiority (1 month after Dose 3 of routine infant vaccines at Visit 6) required that the lower limit of the standardized 95% CI on the geometric mean antibody concentration (GMC) ratios for each of the anti-pertussis toxoid (PT), anti-filamentous haemagglutinin (FHA) and anti-pertactin (PRN) antibodies are ≥ 0.67 (clinical limit for non-inferiority). The seropositivity rates were calculated with exact 95% CI. The analysis of immunogenicity was calculated for between treatment groups for each antigen by a two-sided asymptotic standardized 95% CIs for the difference between groups in seropositivity/seroprotection rates, as applicable. In addition, the secondary immunogenicity endpoints for seropositivity status at Visit 6 for anti-PT, anti-FHA, and anti-PRN antibody concentration were ≥ 5 EL.U/mL.

The analysis of immunogenicity was calculated for within each treatment group for each antigen. The GMC/GMTs were calculated by taking the anti-log of the mean of the log concentration/titer transformations. The antibody concentrations/titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of GMC/GMT calculation. GMCs/geometric mean titers (GMTs) with 95% CI were tabulated. The 95% CIs of GMC/GMT ratios between groups were computed using an analysis of variance (ANOVA) model on the logarithm10 transformation of the concentration/titers. The ANOVA model included the vaccine group as only fixed effect.

The distribution of antibody concentrations/titers was presented using reverse cumulative curves (RCC).

The validation packages demonstrated that the lower limit of quantitation (LOQ) for PT-ELISA is --- EL.U/mL, for FHA-ELISA is --- EL.U/mL, and for PRN-ELISA is --- EL.U/mL. The LOQ parameter supports the use of the secondary immunogenicity endpoint for seropositivity status.

CBER Comments and Questions for Pertussis components; STN: 125265

CBER Comment #3 from August 6, 2007 Questions

For several of the supportive studies (i.e., 444563/005, 444563/006 and 44563/007), the serological analyses for antibody responses to Tetanus, Pertussis antigens and Haemophilus influenzae type b capsular polysaccharides were conducted at --- -----, while for supportive study 102247/036 all serological analyses were conducted at GSK Biologicals in Rixensart, Belgium.

- i. *(Please submit the ----- assay SOPs and validation data for the Tetanus, Pertussis and Haemophilus influenzae type b capsular polysaccharide ELISAs. Please provide data to demonstrate comparability between the assays performed at ----- -- to those conducted at GSK Biologicals.*

Response found in **Amendment 008 dated 11/9/2007** section m1.11.3 Information
Amendment: Efficacy

GSK did not find studies 005, 006 or 007 to be 'pivotal' for licensure. Based on CBER guidance received under GSK's -----, GSK proposes that CBER not consider the ----- validations for licensure. GSK recommended that US co-administration study, Rota-060 whose serology testing was conducted at GSK's

Rixensart laboratories be considered as pivotal to support US licensure of the candidate RotarixT vaccine.

Conclusion: The response is adequate.

Comment: Review was limited to study Rota-060.

- ii. *The GSK Biologicals validation reports submitted for anti-Diphtheria, anti-Tetanus, anti-Pertussis antigens and Haemophilus influenzae type b capsular polysaccharide ELISAs (i.e., DIPCV01, TEPCV01, PTPCV01, FHPCV01, PRNPCV01, PWPCV01, PRP----- and PPPCV01 respectively) are ----- years old. Have any significant changes been implemented for any of these assays? Please provide more recent validation, control chart data, and any additional trending data to demonstrate assay stability in support of your response.*

Response found in **Amendment 009 dated 11/15/2007** section m1.11.3 Information
Amendment: Efficacy

GSK indicated that no significant changes were implemented for any of the assays since the validation reports were initially written. GSK also provide ---- and ----- control charts for anti-Pertussis ELISAs and ----- control charts for anti-PT, anti-FHA, and anti-PRN.

Conclusion: Anti-Pertussis, anti-PT, anti-PRN, and anti-FHA, control charts appear to be stable. The ----- control chart for PRN ELISA showed a shift between 31 October 2006 and 07 November 2006, a follow-up comment was submitted to try to discern if there was an assignable cause for this shift.

Comments: Rota-060 was initiated on 12 June 2006 and study completed on 08 February 1007. Based on the control charts the assays appear to be stable for this time-frame. The ----- control chart for PRN ELISA lot ----- showed a shift between 31 October 2006 and 07 November 2006. A comment was faxed to GSK on 18 December 2007.

Question 26, page 8 of fax sent 18 December 2007

Regarding Figure 15 PRN ELISA: Quality Control Chart, page 11: The PRN ELISA appears to operate within the --- standard deviation limits. It was observed that between 31 October 2006 and 07 November 2006, the quality control values shifted from the lower portion of the control chart to the upper portion of the control chart. Please provide an explanation for this shift in the control chart.

Response found in **Amendment 0018 Dated 2/6/2008, pages 1 and 2**

Conclusion: This issue is resolved. Even though an assignable cause for the PRN control chart shift could not be identified, the shift did not appear to have an effect on the serum concentrations pre and post shift.

Comment: GSK was not able to identify a cause for the shift in the PRN ELISA control chart. As a result, GSK re-analyzed --- serum samples that were released before and just after the shift, the geometric mean ratio for these samples was -----.

APPENDIX A: LIST OF DOCUMENTS REVIEWED

The following identifies the primary documents covered under this review:

From eBLA STN 125265

Amendment: 0000 Dated: 6/1/2007 Section 5.3.5.4

Document ID	Document Title	Version
SOP RD-CIB-011	Total IgG Antibody to <i>Bordetella pertussis</i> Toxin (By ELISA, Human Serology)	---
Val PTPCV01	Measurement to Total IgG Antibody to <i>Bordetella pertussis</i> – Pertussis Toxin (By ELISA, Human Serology)	-----
SOP RD-CIB-010/E	Total IgG Antibody to <i>Bordetella pertussis</i> Filamentous Hemagglutinin (By ELISA, Human Serology)	---
Val FHPCV01	Measurement of Total IgG Antibody to <i>Bordetella pertussis</i> Filamentous hemagglutinin (By ELISA, Human Serology)	-----
SOP RD_CIB_009_E	Total IgG Antibody to <i>Bordetella pertussis</i> Outer Membrane Protein Pertactin (By ELISA, Human Serology)	---
VAL PRNPCV01	Measurement of Total IgG antibody to <i>Bordetella pertussis</i> outer membrane pertactin (By ELISA, Human Serology)	-----
SOP RD-CIB-030	Measurement of Total IgG antibody to <i>Bordetella pertussis</i> (By ELISA, Human Serology)	---
VAL PWPCV01	Measurement of Total IgG antibody to <i>Bordetella pertussis</i> (By ELISA, Human Serology)	-----

Amendment 001 Dated: 7/13/2007

Section 5.3.5.1.3. Study Report Body (Rota-036)