

# Final Review Memo - Rotarix

## Memorandum

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**To:** File

**Subject:** Final Review Memo

GSK Rotarix (HRV Vaccine) BLA STN 125265/0.0 and Amendments 125265/0.008, 125265/0.009 and 125265/0.017 Concomitant Vaccine Diphtheria and Tetanus Serology

## SUMMARY

In support of the BLA for Rotorix (HRV vaccine) GlaxoSmithKline Biologics (GSK) submitted the standard operating procedures (SOPs) and the validation reports for the Tetanus, Diphtheria, Pertussis, Pneumococcal, *Haemophilus influenza* type b, Hepatitis B ELISAs and the poliovirus ----- assay which were used to demonstrate that co-administration of routine infant vaccines with Rotarix did not impair the immune response to any of these vaccine antigens. This review memo focuses specifically on the Diphtheria (D) and Tetanus (T) serology reports provided.

Five clinical study reports were provided in the BLA to support the conclusion that Rotarix, when given concomitantly, did not adversely affect immune responses to the antigens present in routine infant vaccines. In the phase II trial (Rota-005) Infanrix, OmniHIB, Prevnar and IPOL were co-administered with Rotarix, while in the phase IIb trials, Rota-006 and Rota-007, DTPw-HB-Hib vaccine and OPV or DTPa-IPV/HIB and HBV vaccines respectively were used as the concomitant infant vaccines. Diphtheria and Tetanus serological analyses for these three clinical trials were performed at --- ----- . In a phase IIIb clinical trial (Rota-036), which was conducted in 6 European Union countries, Infanrix Hexa, Infanrix Polio, Hib, Prevnar and Meningitec served as the concomitant infant vaccines while in a phase III trial (Rota-060) conducted in the United States, Rotarix was co-administered with Pediarix, Prevnar and ActHIB. In both phase III trials serological analyses was done at GSK's Biological facilities in Rixensart, Belgium. For both D and T it is considered that antibody levels < 0.01 IU/ml indicate susceptibility to the toxin, levels between 0.01 and 0.1 IU/ml confer basic protection against toxin-mediated disease and antibody concentrations ≥ 0.1 IU/ml provide full protection.

One of the secondary objectives in Rotarix trials Rota-005, Rota-006, Rota-007 and Rota-036 trials was to explore the effect of the HRV vaccine on the immune response to concurrently administered routine infant vaccinations. In all four of these studies the endpoint for the serum concentrations of both D and T, expressed as geometric mean concentrations (GMCs), was ≥ 0.1 IU/ml indicative of seroprotection. The results of studies 005, 007 and 036 all indicate that concomitant administration of Rotarix, be it at two different dosages or with different vaccination schedules (country dependent), did not adversely effect the anti-D or anti-T GMCs compared to placebo controls (infant vaccinations without Rotarix administration). The only exception to this was found in study 006 in which a trend

towards lower anti-D seroprotection rates compared to placebo was found when study groups were administered two different dosages of Rotarix.

In the pivotal phase III Rota-060 trial, the primary objective of the study was to assess the immunogenicity of 3 doses of Pediarix, Prevnar and ActHIB given to healthy infants at 2, 4 and 6 months of age when administered with 2 doses of oral Rotarix given during the same vaccination visit (2 and 4 months of age) or given separately (3 and 5 months of age). With respect to DT, the primary endpoint of the study was anti-D and anti-T antibody concentrations of  $\geq 0.1$  IU/ml (indicative of seroprotection) at Visit 6, one month after dose 3 of the routine infant vaccines with the GMCs calculated by taking the anti-log of the mean of the log concentration transformations. The pre-specified criteria for non-inferiority at Visit 6 was that the lower limits of the standardized asymptotic 95% CIs of the differences (Rotarix co-administration group minus Rotarix separate group) in the percentage of subjects with seroprotective concentrations ( $\geq 0.1$  IU/ml) for each of the anti-D and anti-T antibodies was  $\geq -10\%$  (clinical limit for non-inferiority). The results of this study indicated that the co-administered Rotarix group (n=178) was statistically non-inferior to the separately administered group (n=136) in terms of seroprotection rates of the anti-DT antibodies as the lower limits of the standardized asymptotic 95% CI for the different treatments was  $\geq -10\%$  as pre-specified. The power to meet the non-inferiority criterion for anti-D and anti-T was 100%. At Visit 6 all subjects in each group (100%) showed seroprotective levels ( $\geq 0.1$  IU/ml) for both anti-D and anti-T. The anti-D GMC at Visit 6 was 2.177 IU/ml (95% CI: 1.957; 2.422) in the co-administered group versus 2.453 IU/ml (95% CI: 2.105; 2.859) in the separate administered group. For anti-T, the GMC was 2.012 IU/ml (95% CI: 1.782; 2.272) in the co-administered group and 2.194 IU/ml (95% CI: 1.909; 2.522) in the separate administered group (see table below).

**Table 24 Seroprotection rates and GMCs for anti-diphtheria and anti-tetanus antibodies post-Dose 3 of the routine childhood vaccination (ATP Cohort for immunogenicity)**

				≥0.1 IU/mL				GMC (IU/mL)		
				95% CI				95% CI		
Antibody	Group	Timing	N	n	%	LL	UL	value	LL	UL
Anti- Diphtheria	Co-Ad	PIII (M5)	178	178	100	97.9	100	2.177	1.957	2.422
	Sep-Ad	PIII (M5)	136	136	100	97.3	100	2.453	2.105	2.859
Anti- Tetanus	Co-Ad	PIII (M5)	178	178	100	97.9	100	2.012	1.782	2.272
	Sep-Ad	PIII (M5)	136	136	100	97.3	100	2.194	1.909	2.522

Group Co-Ad = Pediarix, Prevnar and ActHIB at 2, 4 and 6 months of age and HRV vaccine co-administered at 2 and 4 months of age

Group Sep-Ad = Pediarix, Prevnar and ActHIB at 2, 4 and 6 months of age and HRV vaccine administered separately at 3 and 5 months of age

N = number of subjects with available results

n (%) = number (percentage) of subjects with concentration above the cut-off ( $\geq 0.1$  IU/mL)

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PIII (M5) = blood sample taken one month after third dose of routine vaccination (Visit 6)

In addition, the ratio of anti-Diphtheria and anti-Tetanus GMCs between co- and separate administered (ATP Cohort) groups was 0.89 (95% CI: 0.74; 1.06) and 0.92 (95% CI: 0.76; 1.10) respectively, while for the total vaccinated cohort the anti-D and anti-T GMC ratios were 0.94 (95% CI: 0.84; 1.10) and 0.99 (95% CI: 0.84; 1.16).

**Supplement 31      Ratio of anti-diphtheria and anti-tetanus antibodies GMCs  
between groups, one month after the third dose of the routine  
childhood vaccination (ATP Cohort for immunogenicity)**

							GMC ratio		
									95 % CI
Antibody	Group	N	GMC	Group	N	GMC	Ratio order	Value	LL    UL
Anti-Diphtheria	Co-Ad	178	2.177	Sep-Ad	136	2.453	Co-Ad / Sep-Ad	0.89	0.74   1.06
Anti-Tetanus	Co-Ad	178	2.012	Sep-Ad	136	2.194	Co-Ad / Sep-Ad	0.92	0.76   1.10

Group Co-Ad = *Pediarix*, *Prevnam* and *ActHIB* at 2, 4 and 6 months of age and HRV vaccine co-administered at 2 and 4 months of age

Group Sep-Ad = *Pediarix*, *Prevnam* and *ActHIB* at 2, 4 and 6 months of age and HRV vaccine administered separately at 3 and 5 months of age

N = number of subjects with available results

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

**Supplement 55      Ratio of anti-Diphtheria and anti-Tetanus antibodies GMCs  
between groups, one month after the third dose of routine childhood  
vaccination (Total Vaccinated Cohort)**

							GMC ratio		
									95 % CI
Antibody	Group	N	GMC	Group	N	GMC	Ratio order	Value	LL    UL
Anti-Diphtheria	Co-Ad	212	2.318	Sep-Ad	184	2.474	Co-Ad / Sep-Ad	0.94	0.80   1.10
Anti-Tetanus	Co-Ad	212	2.183	Sep-Ad	184	2.204	Co-Ad / Sep-Ad	0.99	0.84   1.16

Group Co-Ad = *Pediarix*, *Prevnam* and *ActHIB* at 2, 4 and 6 months of age and HRV vaccine co-administered at 2 and 4 months of age

Group Sep-Ad = *Pediarix*, *Prevnam* and *ActHIB* at 2, 4 and 6 months of age and HRV vaccine administered separately at 3 and 5 months of age

N = number of subjects with available results

95% CI = 95% confidence interval for the GMC ratio (Anova model - pooled variance across the 2 groups); LL = lower limit, UL = upper limit

Based upon the results from the Rota-060 study, GSK concluded that co-administration of Rotarix with licensed routine infant vaccines recommended in the U.S. did not negatively impact the immune responses to Diphtheria and Tetanus toxoids.

In the original submission (1252650/0.000) GSK provided SOP and validation reports for the Diphtheria and Tetanus ELISAs performed at GSK laboratories in Rixensart, Belgium and the Diphtheria ELISA performed at ----- in -----; however, no validation report or SOP was provided for the Tetanus ELISA carried out at ----- . On August 6, 2007 CBER relayed comments to GSK regarding the Diphtheria, Tetanus, Pertussis and *Haemophilus influenzae* type b capsular polysaccharide ELISAs. The following are the comments that involved Diphtheria and Tetanus serology:

**1. 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 ----- 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.**

- 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---01 and PPPCV01 respectively) are > --- years old. Have any significant changes been implemented for any of these assays? Please provide more recent validation data/ control chart data and any additional trending data to demonstrate assay stability in support of your response.

**3. We request that you submit the SOPs for "Qualification of new lots of reference and control sera for use in ELISAs", "Qualification of new lots of antigen for use in ELISAs", and "Qualification of new lots of reagents for use in ELISAs".**

GSK's responses to CBER's comments on D&T serology test methods were received on November 9, 2007 (125265/0.008) and November 15, 2007 (125265/0.009) and are summarized below.

In response to comment #1(i) (125265/0.008) regarding Diphtheria and Tetanus co-administration immunogenicity data obtained from ----- in support of phase II trials Rota-005, 006 and 007, GSK indicated that they do **not** consider these studies as "pivotal" for the licensure of Rotarix. Furthermore, based on the guidance GSK received from CBER regarding supportive data performed at ----- for GSK's -----, GSK proposed that CBER **not** consider the --- ----- validations for licensure.

With regard to comment #1(ii) (125265/0.009 Module 1.11.3) GSK indicated that no significant changes had been made to the assays since the validation reports were initially written and supplied data to support assay stability. The Quality Control charts, which spanned April 2006 to May 2007, for the Diphtheria and Tetanus ----- IU/ml) and ---- Positive Controls ----U/ml) were included and covered the period of the pivotal phase III clinical trial (June 2006 to February 2007). The acceptance criteria for assay stability is that the titer of ----- the controls must fall within its assigned ----- standards deviation while the titer of the ---- control must fall within its assigned ----- standards deviation. All the ---- values of each control (valid or not) are plotted in the control charts in order to evaluate drift over time and no major drifts were apparent over time (Figures 1-4 solid points represent valid data points). The CV% was also calculated for the control titers on valid assay plates to assess intermediate precision. The CV% for ----- Diphtheria controls was found to be 9% while the --- control CV% for Tetanus was 7% and the ---- control 11%. As the assay characteristics specified that the inter-test CV% acceptance criterion was ---- all quality control charts met the required specifications.

In response to comment #3 (125265/0.008), GSK provided the SOPs for "Qualification of new lots of reference and control sera for use in ELISAs", "Qualification of new lots of antigen for use in ELISAs", and "Qualification of new lots of reagents for use in ELISAs" (125265/0.008, Module 5.3.5.4.3). Qualification of new lots of reference sera ----- current reference sera in order to establish its concentration of specific antibodies with at least ----- from ----- runs to establish the average concentration. Once the concentration of the new reference lot has been established -----

----- to ensure that no bias has been introduced. New lots of control sera are qualified by first establishing the -----

----- The concentration of the control sera is then established from -----from -----

----- assays ----- control value. The procedure for the qualification of new lots of antigen and conjugate for use in ELISAs is ----- and consists of ----- assays. -----  
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On December 18, 2007 CBER relayed a second information request to GSK regarding the Diphtheria and Tetanus serological data. This request is provided below.

1. **In regard to the Diphtheria and Tetanus serology assays, we have the following requests. We note that this information was provided to ----- on -----, so the information provided there can be cross referenced, if applicable, for this STN:**
  - a. **For each critical reagent used in the Diphtheria and Tetanus ELISAs, please submit a summary of the data generated to qualify the batch(es) used in the assays presented in this submission.**
  - b. **Please submit data which supports the precision of the Diphtheria and Tetanus ELISAs over their entire working ranges and indicate the specific GMC/GMT range of samples used to determine assay precision.**

GSK's response to the information request was received on January 8, 2008 (125265/0.17, Module 1.11.3) and is summarized below.

With regard to comment #1(a), GSK provided a Table (see below) that contained the lot number of the antigen, reference standard and conjugate used over the course of the phase III clinical trial (Rota-060) for the D and T ELISAs. Also included in the table was a summary of the qualification data for each reagent and the geometric mean ratio (GMR) of the titer of clinical samples evaluated with the new reagent lot and the reference lot of the reagent. The specification of the GMR was between ----- and all reagents used met the acceptance criteria.

In response to comment #1(b), GSK provided a table which summarized the titer ranges used to evaluate intermediate precision of the D and T ELISAs. In addition, this table contained the number of samples analyzed and the averaged %CV across all samples calculated from the %CV value of each sample obtained from ----- technicians. The averaged %CV across all samples (i.e., -----) for both D and T ELISAs was below the ---CV acceptance criteria.

#### **RECOMMENDATION:**

With regard to the Diphtheria and Tetanus serology comments raised in review of 125265/0.0 and 125265/0.008, 125265/0.009 and 125265/0.017 GSK's responses and the data provided are considered adequate. Based on all the information provided, the Diphtheria and Tetanus ELISAs used to evaluate the immune responses to D and T antigens in pediatric vaccines when co-administered with Rotarix in the phase III clinical trial (Rota-060) are acceptable and there are no outstanding concerns.