

Validation Report and Standard Operating Procedure (SOP) for Measurement of Total Antibody to *Haemophilus Influenzae* type b Capsular Polysaccharide PRP - Rotarix

MEMORANDUM

DATE: March 10, 2008

TO: File, STN: BL 125265/0

GlaxoSmithKline (GSK), Inc.

Biologics License Application (BLA) for Rotarix® Live Attenuated Human Rotavirus (HRV) Vaccine, Oral, US License No. 1617

Laraine Henschel, MAS, Committee Chair

FROM: Christian D. Lynch

SUBJECT: Validation Report and Standard Operating Procedure (SOP) for Measurement of Total Antibody to *Haemophilus influenzae* type b Capsular Polysaccharide PRP (By ELISA, Human Serology) Final Review Memo

THROUGH: Milan Blake, Ph.D., Acting Director, DBPAP

Willie Vann, Ph.D., Chief, LBP

Summary

GSK submitted a BLA for Live Attenuated HRV, Oral, (Rotarix®) on 1 June 2007.

Rotarix® is supplied as a vial of lyophilized vaccine that is subsequently reconstituted with liquid diluent provided in a prefilled oral applicator. Following reconstitution, each 1 mL dose contains at least $10^{6.0}$ median cell culture infective dose (CCID₅₀) of live, attenuated HRV. Rotarix® is intended for the prevention of rotavirus gastroenteritis caused by G1 and non G-1 types (including G2, G3, G4, and G9) when administered as a 2-dose series to infants 2 to 24 weeks of age.

In support of the BLA, GSK submitted the SOPs and validation reports for the Tetanus, Diphtheria, Pertussis, Pneumococcal, Meningococcal, *Haemophilus influenzae* type b, and Hepatitis B ELISAs, the serum bactericidal assay (SBA) for *Neisseria meningitidis* serogroup C (MenC), and the poliovirus ----- assay. These assays were used in several clinical trials to demonstrate that co-administration of routine infant vaccines with Rotarix® did not impair the immune response to any of the preceding vaccine antigens. Specifically, in the phase II trial (Rota-005), Infanrix, Prevnar, OmniHiB, and IPOL were co-administered with Rotarix®. The phase IIb trials (Rota-006 and Rota-007) were conducted with concomitant administration of DTPw-HepB, Hib, and OPV and DTPa-IPV, Hib and HepB respectively. Prevnar and Hib serological analyses for these trials were performed at ----- . In the phase IIIb clinical trial (Rota-036), Infanrix Hexa, Infanrix Polio, Hib, Prevnar, and Meningitec were concomitantly administered in 6 European Union countries. A second phase III trial (Rota-060) was conducted in the US to evaluate the co-administration of Pediarix, Prevnar, and ActHiB with Rotarix®. The serological analyses of both phase III trials were performed at GSK's Biological facilities in Rixensart, Belgium.

Reference is made to CBER comment #3a (BLA filing letter dated 6 August 2007) regarding the supportive studies and serological analyses conducted at -----.

GSK's response (eBLA amendment 008 dated 9 November 2007) indicated that data from studies Rota-005, Rota-006, and Rota-007 are not considered pivotal for licensure. Moreover, based on recent guidance from CBER regarding the supportive data performed at ----- for GSK's -----), GSK proposed that CBER not consider the validations performed at ----- for licensure. The firm also noted that the results from the Rota-060 co-administration study are considered pivotal for US licensure of Rotarix®.

This memo focuses specifically on the SOP and validation report for the *Haemophilus influenzae* type b ELISA used in the phase III clinical trials (Rota-036 and Rota-060).

Supplement Review

GSK Biologicals

RD_CIB_004: Measurement of Total Antibody to *H. influenzae* type b Capsular Polysaccharide PRP (by ELISA, human serology)

This document is the SOP for the Hib ELISA performed at GSK. CBER has no comments or questions regarding this method.

Validation Report Review (PPPCV01)

Measurement of total antibody to *H. influenzae* type b capsular polysaccharide PRP (by ELISA, human serology): Performance characteristics and validation for the assay performed at SB Biologicals, Rixensart, Belgium, 06 January 1999

This report was submitted to demonstrate the validity of the measurement of total antibody to *H. influenzae* type b capsular polysaccharide PRP in human serum by ELISA. All performance data were obtained using the ELISA procedure outlined in RD_CIB_004.

Method Summary

**7 PAGES
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TO BE RELEASABLE**

Validation Report Review (-----)

Measurement of total antibody to *H. influenzae* type b capsular polysaccharide PRP (by ELISA, human serology at -----): Performance characteristics and validation for the assay performed at -----

This report was submitted to demonstrate the validity of the measurement of total antibody to *H. influenzae* type b capsular polysaccharide PRP in human serum by ELISA. All performance data were obtained using the ELISA procedure outlined in PRP- ----PROTOCOL.

The content of this report (i.e., parameters and experiments) is very similar to the Rixensart validation report; however, no data were submitted to demonstrate comparability between the assays performed at these locations. Additional information was requested (see below).

Information Requests

Review of the preceding serology packages indicate that additional information is required to ensure that these assays are sufficiently validated to provide meaningful co-administrative data to support licensure of Rotarix®. CBER's requests regarding the Hib ELISA validations were forwarded to the firm on 6 August 2007 and are listed below in bold. GSK's responses to 3a and 3b were submitted to STN 125265 on 9 November 2007 and 15 November 2007, respectively.

3. **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.**

- a. **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.**

"GSK does not consider the Tetanus, Pertussis and Hib co-administration immunogenicity data from studies 005, 006 and 007 as "pivotal" for licensure of the candidate Rotarix vaccine. Based on recent CBER guidance, received under GSK's -----, -----), GSK proposes that CBER not consider the ----- validations for licensure.

Please note, serology testing (diphtheria, tetanus, pertussis and Hib) for US co-administration study, Rota 060 was conducted on GSK's Rixensart laboratories. GSK considers the Rota-060 co-administration data as pivotal to support US licensure of the candidate RotarixT vaccine."

CBER concurs with GSK's proposal and will not consider the Hib ELISA validations performed at ----- as part of the licensure for Rotarix®. Results obtained with the Hib ELISA in support of co-administration studies 444563/005, 444563/006, and 444563/007 (conducted at -----) will also be excluded. This response is satisfactory.

- b. **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, ----- 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.

*"No significant changes have been implemented for any of these assays since
the validation reports were initially written. The following sections will address
the stability over time of the anti-diphtheria, anti-tetanus, anti-pertussis and
Haemophilus influenzae type b capsular polysaccharide ELISA assays."
Regarding the anti-Pertussis (PW) and Haemophilus influenzae type b (Hib)
capsular polysaccharide (PRP) ELISAs*

*"Once any assay has been validated, the performance and the quality of the
serological results generated by this assay is monitored and validated by
quality control checks. These checks consist of the -----*

----- that are included in -----.

*Briefly, the acceptance criteria are: -----of either of the controls must fall
within its ----- value --- standard deviations, and the titer of the -----
-- must fall within its ----- value--- standard deviations. All the ----
values (-----
-.*

*As an example, Figure 5 to Figure 11 below show the Quality Control charts for
the ----- routinely used in the ELISA tests used to measure
antibody to pertussis (PW) and Hib (PRP) in human serum samples over a 14
month period (April 2006 - May 2007). It is to be noted that for the -- and ---- of
PW, and for the -- of PRP, ----- of positive controls were -----
used during this time period, and ----- was used for the - of PRP ELISA.*

*In addition the CV% was calculated for the titers ----- on valid assay
plates to evaluate the ----- precision of the assays. For all controls
included in the PW and PRP assays the calculated values were well below the
inter-test coefficient of variation ----- as specified in the assay characteristics of
the validation reports.*

*For PW a CV% of 11% and 10% were found for the ----- controls
referred as ----- and ----- . The CV% was 13% and 9% for the--
----- referred as ----- and ----- . For PRP, a CV
of 10% was found for the ----- control referred as -----, and 11%
for both ----- referred as ----- and ----- . Therefore,
the current performance of the PW and the PRP ELISA assays is considered*

consistent with the performance established during the validation of the assays."

The quality control charts provided for the anti-PRP ----- Controls span a 14 month period from April 2006 - May 2007. Data from the --- ----- Control appear to drift slightly above the assigned average in August and September; however, the overall performance of this control is satisfactory. No major drift was noted for ----- of the ----- Control. Moreover, CBER agrees that the performance of the Hib ELISA appears to be consistent with the performance noted in the initial validation. This response is also satisfactory.

Recommendation

Based on the information provided, the ELISA for measurement of total antibody to *Haemophilus influenzae* type b capsular polysaccharide PRP appears to be adequately validated. The results of the initial validation, when combined with the recent control chart data, demonstrate that the Hib ELISA is precise, accurate, linear, specific, and stable. The assay appears to be capable of assessing the immunogenicity of pediatric vaccines given concomitantly with Rotarix® in phase III clinical trials (Rota-036 and Rota-060).