

# Review of Serology Methodology - July 10, 2009 - Hiberix

Department of Health & Human Services

FDA/CBER/OVRR/DBPAP

Memorandum

**Date:** July 10, 2009

**To:** Jay Slater, M.D. HFM-422

Chair, Hiberix BLA Review Team

**From:** Mustafa Akkoyunlu, MD, Ph.D., HFM-428

Willie Vann, Ph.D., HFM-428

**Through:** Chief, Laboratory of Bacterial Polysaccharides

Division of Bacterial, Parasitic, and Allergenic Products

**Subject:** STN 125347 Hiberix: Review of serology methodology used to measure serum PRP antibody and the method used to measure -- b(4)----- in Hib vaccine.

## **New BLA Review**

In this memo, I reviewed the serology assays performed to measure the anti-PRP antibody levels in the sera of toddlers immunized with a booster Haemophilus influenzae type b capsular polysaccharide conjugated to tetanus toxoid (Hiberix) vaccine. Three separate methods were used to measure anti-PRP antibodies in the seven clinical trials submitted in this BLA. These assays are -----b(4)----- assay was used in studies DTPa-HBV-020, DTPa-IPV-13p, DTPa-IPV-026, DTPa-HPV-IPV-010, DTPa-HBV-IPV-012. GSK - b(4)- was used in study DTPa-HBV-032. ---b(4)- ----- was used in clinical study DTPa-HBV-IPV-035.

In all three methods anti-PRP IgG, IgM, and IgA antibody concentration  $\geq 0.150 \mu\text{g/ml}$  is considered as seropositive, while  $\geq 1 \mu\text{g/ml}$  of antibody concentration as seroprotective. Seropositivity suggests that serum contains sufficient antibodies to prevent systemic (invasive) Hib infection. Seroprotectivity on the other hand suggests that the seropositive levels of protective antibodies would last at least one year. These definitions are internationally accepted and they derive from scientific literature reporting experiences with conjugate PRP vaccines.

In addition to reviewing the serology assays used in clinical studies, I also reviewed the -b(4)- method that is used to detect -----b(4)- ----- in PRP-TT bulk conjugate and final container. Initial submission included an SOP for this -b(4)- which was an incomplete translation from French. In addition, the submission did not include proper validation assays for the detection of -b(4)-. The same concerns were voiced by Dr. Rajesh Gupta from DPQ. These concerns were conveyed to the sponsor on a May 12, 2009 letter. The sponsor provided an improved version of the SOP (SOP 9000010114) and a Validation report (Validation 9000001105RVM01). Measurement of -b(4)- ---was done in -b(4)- main steps. ---b(4)- ---- included the -----b(4)- -----

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The documents “GSK -b(4)- SOP” and “PRP ----b(4)---- Performance Characteristics and Validation” provide the methodology to conduct the -b(4)- assay used to measure serum antibodies against PRP antigen in Hib immunized subjects.

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4 Pages determined to be not releasable: b(4)

Recommendations: Serology results presented in this BLA demonstrates that anti-PRP antibody titres induced with GSK Biologicals' Hiberix vaccine is measured with appropriate methods. The validation reports for the -----b(4)----- demonstrate that these methods accurately measure antibodies against PRP in human sera.

The method used to determine the -b(4)- concentration in the bulk conjugate and final container PRP-T vaccine has not been properly validated. It is not clear whether the -----b(4)----- aimed to remove the -----b(4)----- step also removes -----b(4)----- . In the absence of this validation it is not possible to conclude that the method used here correctly measures the -b(4)--- in the Hiberix vaccine. The deficiencies in the methodology used to determine the -b(4)----- concentration in the bulk conjugate and final container PRP-T vaccine has been outlined in Dr. Rajesh Gupta's memo and I concur with his findings.