BLA SUPPLEMENT REVIEW

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FROM: Iryna Zubkova, PhD
SUBJECT: STN# 125363

                   Sponsor: GSK Biologicals
                   Product: Menhibrix

TO: Joseph Temenak. PhD

THROUGH: Stephen Feinstone MD

Summary:
Following is a review of a validation report for an anti-HBs antibody ------(b)(4)------
------------------------------------- developed at GSK to quantitatively determine antibody to
Hepatitis B surface Antigen in human serum samples and to demonstrate that the assay is
adequate for its intended use.

Overview:
In 2002 GSK was informed by -(b)(4)- that the ------(b)(4)----- would be discontinued and
therefore development of an ------(b)(4)---- was favored to ensure long-term supply of an assay
with consistent quality. The Sponsor noted that all test performance data were obtained using the
procedure outlined in the Standard Operating Procedures (SOP) entitled "Measurement of Total
Antibody to Hepatitis B surface Antigen with -----------(b)(4)-----------" and performance
characteristics of -------(b)(4)----- are only valid when testing human serum specimen according
to the SOP.

Immunological principles of a -------(b)(4)-------, reference and calibration standard:

---(b)(4)--

---(b)(4)--

---(b)(4)--

---(b)(4)--

I would suggest that Chapter 5.2.2 of the submission needs to be reviewed by a statistician.

Assay characteristics:

The Sponsor estimated the Limit of Detection (LOD) at ----(b)(4)----, Limit of Quantitation (LOQ) at --(b)(4)-- and set the Cut-off at --(b)(4)--.
The Cut-off of the current assay used at GSK (i.e. ---(b)(4)---) for the determination of -(b)(4)-
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Precision (the extent to which multiple analysis of a sample agree with each other):

Reproducibility was analyzed using -----------------------------(b)(4)-----------------------------
different days, totaling -(b)(4)- observations.
The Sponsor showed good reproducibility of -----------(b)(4)----------, with one note, that the analysis was performed using only ------(b)(4)-------, but the -(b)(4)- was made according to GSK specifications.

Duplicate to single determination:

The laboratory which tests the samples from the clinical trials have to deal with a large number of tests and it is very important to obtain reliable and consistent results over the time. To control the limits of costs and have good productivity the Sponsor decided to proceed to -(b)(4)- instead of -(b)(4)- determinations.
Based on ----(b)(4)---- selections of one of the --------(b)(4)-------- for each sample, computation of the geometric mean and its CI and the intersubjects deviation the Sponsor concluded that the ------(b)(4)------ can be conducted --(b)(4)-- determination on a routine basis.

Linearity:

Linearity, defined as the ability of an analytical process to provide a measurement directly proportional to the analyte concentration, was analyzed within the analytical range of the -(b)(4)-
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*Based on the testing of ---------(b)(4)-------- specimens from vaccinated subjects using different ---(b)(4)--- as a diluents and statistical analysis the Sponsor concluded that linearity of -(b)(4)---------- is very good and ----------------------(b)(4)----------------------- has no impact on the tite*rs.

Specificity:

In order to test specificity the Sponsor conducted an inhibition experiment. The samples were tested using a mixture of ------------------(b)(4)--------------------- or recombinant -----(b)(4)---- subtype before and after inhibition in a reference method and in the ----------(b)(4)----------.
The Sponsor concluded that complete inhibition observed in the samples tested in the -(b)(4)---------------- is specific for both -(b)(4)- and ------------(b)(4)--------------.

Accuracy-Recovery:

In analytical measurement accuracy is defined as how close the average measured value is to the true value.
In order to assess the accuracy of the new assay the Sponsor proceeded to a recovery experiment.
In the recovery experiment -------------------------(b)(4)----------------------------.
Recovery was calculated expressing the measured titer in % of the theoretical titer that should have been measured. The mean recovery and its SD, CV and 95% CI were calculated. Data of the experiment are reported in Tabl.7, p.21.
The mean recovery was 95%.
The Sponsor concluded that recovery observed on the whole analytical range can be considered as very good.

Interferences:

Interference is defined as: Artifactual increase or decrease in apparent concentration of an analyte due to the presence of a substance or a treatment.

The Sponsor studied impact of -----------(b)(4)------------ or --------------(b)(4)------------.
For this purpose --(b)(4)---.
The differences observed between aliquots were not statistically significant and the Sponsor concluded that serum specimens can be ----------(b)(4)----------- without affecting their -(b)(4)------------.

In order to evaluate the impact of sample inactivation in the ----------(b)(4)----------, the Sponsor performed the following testing: ----------------------------------(b)(4)---
Statistical analysis showed that the correlation coefficient was very good (-(b)(4)-).
The sponsor concluded that even though ---------(b)(4)------------- samples will not be used in routine conditions, if needed, due to the non availability of the non inactivated samples,

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---(b)(4)------ samples could be used because there is a very limited impact on -----(b)(4)-----
(Tabl.9, p. 24)

To determine if high concentrations of the analyte may lead to underestimation of the titer the Sponsor performed testing of -(b)(4)- samples containing -----------(b)(4)----------.

Based on the results of the testing the Sponsor concluded that high level of ---(b)(4)--- will not lead to incorrect results.

Robustness:
In order to check if results of an assay may be affected by a slight modification of the assay conditions (-(b)(4)- time) the Sponsor tested -(b)(4)- samples ranging from --------(b)(4)------. In this testing time of -(b)(4)- was decreased or increased compared with the recommended time. For statistical analysis data were log transformed and analyzed by linear regression.
The applied condition did not change significantly the results of the test and the Sponsor concluded that samples may be -(b)(4)- in any conditions from ---------------(b)(4)------------------ --.

Comparison with a reference method:

Because ---(b)(4)--- from -(b)(4)- was recognized worldwide as a reference method in the field of -(b)(4)- assessment in human specimens the Sponsor decided to compare ----------(b)(4)-------- assay to this assay.

To test sensitivity and specificity of the ------------(b)(4)------------- serum samples previously tested with ----(b)(4)---- were assayed with the -----(b)(4)------ assay. From --------(b)(4)------- were tested as positive in ----------(b)(4)---------- as negative.
The overall agreement, sensitivity and specificity were calculated for the --------(b)(4)----- assay considering the ----(b)(4)---- as a reference.
The specificity of the -----(b)(4)------ assay is -(b)(4)-, sensitivity -(b)(4)- and overall agreement is -(b)(4)-.

However, I have to note a mistake in the Sponsor's calculations.

Tabl.12, p.30

	--------(b)(4)-------		Total
	-	+	
----(b)(4)---- -	-(b)(4)-	-(b)(4)-	-(b)(4)-
+	-(b)(4)-	-(b)(4)-	-(b)(4)-
total	-(b)(4)-	-(b)(4)-	-(b)(4)-

Sensitivity ------------------------(b)(4)--------------------------

According to the definition "sensitivity = ---b(4)---

---(b)(4)---

My recommendation to the Sponsor is to correct this mistake in the validation report to avoid future misunderstanding.

In order to check and confirm that the conclusion of clinical studies concerning the immunogenicity data of the hepatitis B component based on -----------(b)(4)--------- would not differ from those tested with ---(b)(4)--- the Sponsor proceeded to a more extensive evaluation and applied a linear regression statistical approach. Details of this extensive evaluation is reported in another document entitled "Characterization of the serological immune response against -(b)(4)- in clinical studies using -----------(b)(4)---------- developed at GlaxoSmithKline Biologicals"
The Sponsor used mathematical simulation to predict ----------(b)(4)---------- titer according to linear regression analysis with ---(b)(4)---.

The Sponsor drew the conclusion that there is no evidence that the ---------(b)(4)---------- would lead to different clinical conclusions when compared to ----------------(b)(4)-------------- and to design or sample size issue.

Conclusions:
The Sponsor demonstrated that the -----------(b)(4)------------ showed a high specificity (-(b)(4)-), sensitivity (-(b)(4)-) and overall agreement (-(b)(4)-) compared to ---(b)(4)--- (reference assay).
The Sponsor performed extensive evaluation to determine the possible effect of different factors (---------------------------------(b)(4)--------------------------------------) on the results of the ---(b)(4)---------------------- and show that these factors do not impact test results.
Therefore the ----------(b)(4)----------- developed at GlaxoSmithKline Biologicals can be used for quantitative measurement of ---(b)(4)-- antibodies in human serum samples.

Recommendations:

The data presented confirms that the in-house assay is an acceptable replacement for the -(b)(4)-------, therefore, I recommend approval of this assay for testing human serum samples for -(b)(4)- antibody.

The Sponsor needs to correct a mistake in chapter 14.2, Tabl.12 to avoid future misunderstanding.