

Meeting Minutes, November 8, 2011 - MenHibrix

Date and Time: November 8, 2011 10:00 am – 12:00 pm
Location: WOC2 – Room 3101
Call-In Information: Toll-Free Number: -----b(4)-----
Passcode: ----b(4)-----
STN #: 125363/0
Sponsor: GlaxoSmithKline Biologicals
Product: Menhibrix, Meningococcal Groups C, and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine

CBER ATTENDEES:

COMMITTEE MEMBERS:

Review Assignment	Committee Member	Supervisor
Chair	Joseph Temenak	Elizabeth Sutkowski
RPM	David Staten	Elizabeth Sutkowski
RPM	Kirk Prutzman	Elizabeth Sutkowski
Clinical Reviewer	Meghan Ferris	Lucia Lee
Product CMC/Serology	Mustafa Akkoyunlu	Willie Vann
Product CMC/Serology	Freyja Lynn	Jay Slater
Product CMC	Willie Vann	Jay Slater
Product CMC	Daron Freedberg	Willie Vann
Product CMC	Drusilla L Burns	Jay Slater
Product CMC	James E Keller	Drusilla Burns
Product CMC	Michael	
Schmitt		
Product CMC	Tina Roecklein	Jay Slater
Clinical Statistical Reviewer	Barbara Kransnicka	Dale
Horne		
Assays Statistical Reviewer	Tsai-Lien Lin	Dale Horne
DPQ/Lot Testing Plan	Rajesh Gupta	Bill McCormick

OTHER CBER ATTENDEES:

Marion Gruber
Phil Krause
Theresa Finn
Wellington Sun
Loris McVittie
Elizabeth Sutkowski
Herb Smith
Jay Slater
Jennifer Bridgewater

GSK ATTENDEES:

Emmanuel Aris (Biologicals, BE), PhD

Senior Specialist, Biostatistics

Angélique Baclin (Biologicals, BE)	Associate, Biostatistics
Gabriel Caliaro (Biologicals, BE)	Senior Manager, QC Analytical
Support	
Carine Capiou (Biologicals, BE)	Vice President, Regulatory Affairs
Francesca Ceddia (Biologicals, BE), MD	Vice President, Vaccine Development
Leader	
Brigitte Cheuvart, PhD (Biologicals, BE)	Director, Clinical Biostatistics
Bartholomew Corsaro, PhD, GVCL	Portfolio Manager and US Lead
Laurent Ferrant (Biologicals, BE)	Validation and Technical Development
Susan Gollon, PhD	Expert Scientific Writer
Jody Gould, PhD	Senior Director, US Regulatory Affairs
Claude Herbiet (Biologicals, BE)	Manager, Quality Control
Barbara Howe, MD	Vice-President and Director, North
American Vaccine Development	
Thomas Jacques (Biologicals, BE), PhD	Scientist, TP ARD (Technological
Platform – Analytical Research and Development)	
Christophe Lenfant (Biologicals, BE)	Senior Manager, TP ARD
Pascal Renaud Lestrade, PhD, (Biologicals, BE)	Senior Manager, Bacterial DU
Pascal Mettens (Biologicals, BE)	Director, DAP
Jacqueline Miller, MD	Senior Director, Global Clinical
Development	
Catherine Poty (Biologicals, BE)	Manager, Quality Control
Norris Pyle, Associate Director	US Regulatory Affairs
Eddie Reilly (Biologicals, BE)	Vice President, Global Regulatory
Affairs	
Catherine Vigano-Wolff (Biologicals, BE), PhD	Manager, Technical Regulatory Unit

BACKGROUND

On September 21, 2011, CBER issued a second CR Letter to GlaxoSmithKline Biologicals (GSK) for STN 125363 MenHibrix for active immunization of infants and toddlers 6 weeks through 15 months of age for the prevention of invasive diseases caused by *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y. The CR Letter had 26 items identified by CBER. On October 13, 2011, and October 21, 2011, GSK emailed preliminary responses/questions to some of the September 21, 2011, CR Letter items. The purpose of this meeting was to discuss CBER's review of GSK's preliminary responses/questions to the September 21, 2011, CR Letter.

DISCUSSION TOPICS

PART 1: CMC/PRODUCT ISSUES (Items 4, 8, 10, 15, 19, 21)

GSK Question for CR Letter Item 4: Does CBER agree that a statistical approach that avoids drift in calibration is an acceptable alternative to the use of primary references for the purpose of reporting changes in reference standards?

CBER Response:

- CBER cannot assess whether the proposed statistical approach is an acceptable alternative to the use of a primary reference without knowing the proposed statistical method and the data to be analyzed.**
- GSK should submit the details of the statistical approach in the Complete Response including, but not limited to, the following.**

- a. It is unclear how the mean change in the trend analysis proposed by GSK will be calculated.
 - b. It is unclear what the “old reference” is referring to (i.e., the original reference or the currently used reference).
 - c. Stability of the primary reference will need to be addressed if all the data in the trend analysis are generated using the primary old reference.
3. It should be noted that Comparability Protocols do not need to be submitted or approved during the original license process. Comparability Protocols could be submitted after approval as a prior approval supplement.

Item 4 Discussion: CBER emphasized that the data indicated in GSK’s preliminary response needs to be submitted in the Complete Response to appropriately review GSK’s response to Item 4. GSK indicated that they have b(4) reference standard and would need to qualify another reference standard. CBER suggested that GSK focus on b(4) reference standard for approval.

GSK Question for CR Letter Item 8: Does CBER concur with the company’s position that the measurement of residual –b(4)-----, and any other by product in final product is not relevant providing that (1) –b(4)- is converted in –b(4)- during the conjugation process and other by-products are not detected, (2) –b(4)-----is not stable in –b(4)- (3) the residual content of –b(4)---- is measured on the conjugate bulks and is well below non toxic doses evaluated in toxicity studies?

CBER Response:

1. CBER does not agree that measurement of residual –b(4)----- and by products is irrelevant.
2. –b(4)- is converted to –b(4)- under the conditions used during conjugation. CBER concurs with the plan to provide –b(4)-data in order to show that –b(4)-is converted to –b(4)--.
3. Residual –b(4)- as measured by –b(4)- and –b(4)----- as measured by b(4)---- has been measured on the b(4) commercial consistency lots manufactured in 2008 and the b(4) clinical consistency lots manufactured in 2004. GSK needs to test enough lots to determine that the residual reagents are gone (or below detectable levels). –b(4)---- lots of MenC-TT and MenY-TT Drug Substance should be a sufficient number of lots to validate that the residual reagents or by products are below detectable levels in the final product.
 - a. How many commercial lots have been manufactured since the commercial consistency lots?
 - b. If at least b(4) lots have been manufactured, then CBER would propose that GSK tests these drug substance lots to show that the residual –b(4)-- are gone or below the detectable level. This data should be submitted in their Complete Response.
 - c. If the firm does not have a substantial amount of drug substance to test, this study may take a long time to conduct and hold up GSK in submitting their Complete Response. At that point, CBER may consider requesting this as a PMC.
4. Residual-b(4)----- is not measured since GSK states that it is not stable in –b(4)-- GSK should clarify the following in their Complete Response

- a. What byproducts are formed when –b(4)---- decomposes under the conditions used during conjugation?
- b. Please provide data to show that these byproducts of –b(4)---- are removed? Please follow the same methodology as discussed for Residual –b(4)- and Residual –b(4)-----

Item 8 Discussion: CBER asked how many lots of MenC and MenY GSK has for testing. GSK indicated they had b(4) lots of MenY and b(4) lots of MenC. The b(4) lots of MenY include the b(4) lots that were already submitted to CBER. GSK asked if this was enough lots to satisfy Item 8. CBER indicated that there should be b(4) lots of each conjugate for testing but GSK should submit all the information they have for every lot and CBER will evaluate it.

Regarding the residual –b(4)-----, and any breakdown products, CBER indicated that the current proposed testing methodology was not sufficient. CBER indicated that GSK needs to account for residual products or any break down products that may be present in the lots and show that they can measure them. GSK should also determine the levels of toxicity for any remaining products. GSK understood.

GSK Question for CR Letter Item 10: Does CBER agree that providing that GSK demonstrates that the performance of the b(4) measurements in terms of accuracy and precision is lower without baseline correction, the current –b(4)- methods should not be modified as requested in item 10d?

CBER Response:

1. CBER does not agree with GSK's proposal. The b(4) assay is not valid for its intended use in that correcting baselines prior to analysis may give rise to quantification errors. In their proposed method GSK is using incorrect acquisition parameters resulting in rolling baselines which are then arbitrarily corrected. CBER requests that GSK acquire data with flat baselines so that arbitrarily correcting the rolling baselines is not required.
2. CBER suggests that a flat baseline can be obtained by changing the data acquisition mode to remove the roll in the baseline. This can be performed by setting the parameter ---b(4)----- and by setting the ----b(4)----- to avoid artifacts from pulses. If additional technical information is needed, we could propose either a technical meeting with CBER, or alternatively, discussions with –b(4)--- In summary, the data will need to be recollected and not just reanalyzed.
3. The following should be submitted as part of their Complete Response.
 - a. Please repeat the analysis on b(4) lots of commercial production material using both the CBER suggested b(4) method (data acquired with flat baselines) and the original –b(4)----- method submitted in the BLA. The original BLA contained data bridging the –b(4)----- method (used for the release of the clinical trial and commercial consistency lots) and the GSK proposed b(4)-- method (using baseline correction).
 - b. If the material is available for testing, this should be relatively simple. If there is no material, then discussion will be needed to determine if we approve the original s –b(4)----- method and request

the change to the b(4)--- method be in a post approval supplement or whether there is enough data to allow this request as a PMC.

Item 10 Discussion: CBER emphasized that GSK's approach to use --b(4)- content testing---b(4)----- testing, -b(4)--- content, -b(4)-content, --b(4)----- content and identity testing by ---b(4)----- assays was not acceptable. Specifically, CBER reiterated their concern that GSK's method for baseline correction may induce up to 10% errors. GSK stated that --b(4)--- representative advised them that baseline correction as indicated by CBER was not possible using their --b(4)-----. CBER indicated that they also spoke with a --b(4)--- representative who indicated it was possible to correct for baseline errors with specific collection parameters. It was decided that this discussion was better suited for a technical meeting. CBER indicated that the current --b(4)--- was still valid and GSK could proceed if they continued to use it. The --b(4)----- can be validated and implemented post approval.

GSK Question for CR Letter Item 15: Does CBER agree that GSK can submit the development plan for the --b(4)----- assay in the Complete Response and that the full data package including validation data and proposed acceptance criteria can be submitted within 2 months of the Complete Response submission without impacting the review clock?

CBER Response:

1. **CBER accepts this approach.**
2. **EMPHASIS that the data MUST BE SUBMITTED WITHIN 2 MONTH OF COMPLETE RESPONSE**

Item 15 Discussion: CBER emphasized that data needed to be submitted within 2 months of the complete response. Failure to do so may lead to a CR Letter. GSK understood.

GSK Question for CR Letter Item 19: Does CBER agree that the --b(4)----- stability data can be submitted within 2 months of submitting the Complete Response without impact on the review clock?

CBER Response:

1. **CBER accepts this approach.**
2. **EMPHASIS that the data MUST BE SUBMITTED WITHIN 2 MONTH OF COMPLETE RESPONSE**

Item 19 Discussion: CBER emphasized that data needed to be submitted within 2 months of the complete response. Failure to do so may lead to a CR Letter. GSK understood.

GSK Question for CR Letter Item 21: Does CBER agree that a commercial stability program on each drug substance and on the drug product is sufficient and that a commercial stability program on ----b(4)----- is not required?

CBER Response:

1. **CBER does not agree with this approach.**
2. **GSK should place b(4)lot of each -----b(4)-----
--. Please revise your procedures to include placing b(4) lot of each -----
b(4)----- All we need to see pre-approval is a study design, not data on specific lots. Please note that this is a standard request for polysaccharide vaccines.**

Item 21 Discussion: GSK indicated that they understood CBER's concerns. GSK asked why CBER was asking for stability data for the free polysaccharides. CBER responded that it was important to be certain of the quality of the starting materials and that the polysaccharides are stable over their shelf life.

PART 2: SEROLOGY ISSUES (Items 1-3)

CBER communicated the following to GSK:

General Serology Comments:

We accept that we will likely not know the cause of the decrease in sample values when the sera from study -005 were reassayed.

But other data submitted to the BLA indicate that the assay may be more variable than expected. If the assays are not reliable, increased uncertainty is introduced into the assessments of efficacy. If the data are unreliable at the cutoff, then the efficacy may be overestimated or underestimated.

If the assays have been trending over time, or are not under sufficient control, then the supportive data from the earlier studies cannot be used in conjunction with the data from the later studies to support consistent estimates of efficacy. If assays are trending or are not under control within a study, then the possibility of bias is introduced.

We have multiple endpoints used in the clinical studies, both GMTs and percent responders. The performance of the assay needs to be considered in the context of the clinical data to determine if concerns about assay performance translate into questions regarding clinical study outcomes.

The data submitted to date are not sufficiently clear to provide reassurance that the data from the clinical studies can be clearly interpreted. We are asking for additional information regarding what has been submitted, which we will review with the information still to be submitted and the results of the clinical serology to assess whether the clinical data adequately support efficacy of the meningococcal components.

Acceptance of the serologic data as evidence of efficacy for this BLA does not mean that the assays as currently run are acceptable for future studies.

1. Submitted data **do not** indicate a consistent trend over time but we don't have sufficient information to make a formal determination of this yet.
2. Overall precision of the assay is potentially poorer than desirable.
- The Deming regressions and the CCC assess the agreement between original and repeat tests on the same sample and are indicative of precision.
- The values presented are all under 0.85 which are lower than expected.
- The trending charts of the repeats (which really aren't that helpful to show stability over time) show upper and lower boundaries of +/- four fold or an eight fold range. Even for SBA this is a wider range than is normally expected for this type of assay. Many of the retest ratios are out of that range, with a greater than 8 fold difference between repeated testing.
3. A significant amount of new data is presented in the preliminary response. It is unclear how the data were generated. GSK will need to provide the details and possibly the data for CBER to analyze.

Specific Serology Comments:

4. For all comparisons between original and repeat analysis, please provide the dates of the original and retest assays.

5. For all figures, please provide fully legible legends and explanatory text of each component of the figure.
6. Regarding Section 3, Table 1; Section 4, Table 4 and Figure 2, and Supplement 1, the r and CCC values are in some cases low, for example $r = 0.82$ and $CCC = 0.80$ respectively for study -013. In none of the comparisons was the r or CCC greater than 0.95 as would be expected for good correlation.
 - a. Please explain the differences in the data between the same studies presented in both Table 1 and Table 4.
 - b. Please comment on the contribution of assay imprecision versus agreement on the correlations.
 - c. Please provide Bland Altman plots for each study.
7. Regarding Figure 1; Supplement 2, the relevance of these figures to assay stability over time is unclear. Additionally the presentation is difficult to see in some cases, with the relevant data from a single study obscured by the aggregate data.
 - a. Are the data plotted according to the original test date or the retest date?
 - b. What is the span of time between an original and a retest date?
 - c. Did the original and retest dates span any changes of the assay modifications listed in Supplement 4?
 - d. Two figures entitled HibMenCYTT-013 are presented on pages 23 and 24. What is the distinction between the two figures? What is the meaning of the x axis legend in the figure at the bottom of page 24?
8. Regarding Supplement 5, we have the following comments.
 - a. The text states that the control value might be reassigned when C' lots are changed. Please indicate how changing the control values, and thereby shifting the limits on the system suitability criteria, prevents drift in the assay due to changes in C'.
 - b. In Supplement table 1, please provide the variance for each of the control values to demonstrate consistent assay precision over time.
 - c. Controls are tracked by the adjusted values rather than the raw values. Tracking by adjusted values may hide trends in the data. Please provide control data using the raw results rather than the adjusted values.
 - d. The text states that the system suitability criteria for the control values were set at $-b(4)$ from the mean. This implies an expected failure rate of approximately one assay in 100 $b(4)$. However some control charts indicate a much higher failure rate than $b(4)$. The failure rate also appears to be asymmetrical in some cases (for example, in figures 5 and 6). What investigations are performed when controls are out of limits? How is the unexpectedly high failure rate reconciled with the statistical expectation?
 - e. Noted are changes in the apparent precision of the assay as well as shifts in the control values when lots of C' are changed (for example, see change in the spread of the data in figure 5). What are the acceptance criteria for new lots of C'? Again, the effects of lot changes on assay performance are difficult to assess without raw control values.

Serology Discussion: GSK understood CBER's concerns and agreed that the MenY hSBA was variable. They agreed to submit all the new data indicated in their preliminary response and also indicated that they also have additional data from the

control groups that they can submit. CBER indicated that GSK should submit the hSBA data from the control group.

PART 3: GENERAL ISSUES

General Discussion: CBER acknowledged that GSK did not address every issue in the September 21, 2011 CR Letter and that GSK should call CBER with any questions or concerns before submitting their Complete Response. CBER asked if GSK was still planning on submitting their Complete Response on November 30, 2011. GSK said they were still planning to submit a Complete Response on November 30, 2011.

Call Ended.