

DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA/CBER/OVRR/DBPAP

Food & Drug Administration
1401 Rockville Pike
Rockville, MD 20852

MEMORANDUM

Date: May 2, 2012

To: File for 125363/0 (MenHibrix)

From: Daron Freedberg, Ph.D.,
OVRR/DBPAP/LBP

Through: Willie F. Vann, Ph.D., Chief,
OVRR/DBPAP/LBP

Subject: Product Review and Approval Memo for BLA 125363/0 (MenHibrix)

Sponsor: GlaxoSmithKline (GSK)

SUBMISSIONS REVIEWED

Amendment 19, dated 26 October 2011 (response to a second CR letter issued 21 September 2011)

Recommendation:

All of GlaxoSmithKline's (GSK) responses that I reviewed from a CMC standpoint were complete and acceptable. Details of my findings are listed in this memo under each CR letter comment. Based on GSK's responses, I recommend approval of the MenHibrix BLA.

Summary/Background:

On 12 August 2009, GSK submitted a Biologics License Application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine. Clinical development of this vaccine, which was originally designated Hib-PSCY-TT, was conducted under US IND -(b)(4)-. The proprietary name is MenHibrix.

MenHibrix is a non infectious vaccine that contains *Neisseria meningitidis* serogroup C capsular polysaccharide (PSC), *Neisseria meningitidis* serogroup Y capsular polysaccharide (PSY), and *Haemophilus influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP), each covalently bound to tetanus toxoid.

MenHibrix is a lyophilized vaccine supplied in a -(b)(4)- monodose glass container -(b)(4)-, stoppered with rubber closures for lyophilization and closed with flip-off caps. The vaccine is to be reconstituted prior to intramuscular injection, with 0.9% Sodium Chloride diluent. The reconstituted product contains 2.5 µg of PRP-TT, 5 µg PSC-TT and 5 µg PSY-TT per 0.5 mL dose volume.

Review of responses to CR letter of 11 June 2011, GSK- MenHibrix

On 11 June 2010, CBER issued an 88 item CR letter to GlaxoSmithKline (GSK). In my review, dated 5 May, 2010, I noted 15 deficiencies that were included in the CR. In the 11 June 2010 CR letter, CMC issues from my review were included, such as: expiry dating and date of manufacture; the establishment of a -----(b)(4)----- for the polysaccharides in the conjugate vaccine; inadequate -(b)(4)- and -(b)(4)- characterization of the drug substance; unsupported hold time for the -----(b)(4)-----; stability of the tetanus toxoid (TT) used in the conjugation step; and adventitious -(b)(4)-. GSK responded to all of the issues raised by CBER in their response dated 15 April 2011. However, they did not satisfactorily address issues concerning TT stability; adventitious -(b)(4)- in TT; residual -----(b)(4)----- and other byproducts from conjugation; -(b)(4)- characterization of the drug substance; and the stability of purified TT. Due to the inadequate responses by GSK on several issues, CBER issued a second CR letter on 21 September 2011.

On 21 September 2011, CBER issued a second CR letter containing 26 items to GSK. GSK responded to all of the issues raised by CBER in their response dated 01-Dec-2011. In my review, dated 13 September 2011, eight deficiencies of the original 15 deficiencies included in the original CR letter had not been properly addressed in the firm's response to the CR. I reviewed GSK's responses to this second CR letter and address these responses in the subsequent pages of this memo on a point-by-point basis in the following pages.

6. You provide the in-process quality decision and monitoring tests for each step of the TT purification and ----(b)(4)----- process performed at Rixensart (Table 1 in your response to Item 25). We do not concur with the -----(b)(4)----- testing performed at the ----(b)(4)----- as a ---(b)(4)----- . While we acknowledge that TT monitoring testing performed during downstream manufacturing steps is essential to maintain process consistency, CBER also believes that establishing a predefined specification in the --(b)(4)-- content of the purified TT --(b)(4)- immediately prior to -----(b)(4)----- is equally important in maintaining process consistency. We note that stability studies with the TT bulks clearly indicate that ---(b)(4)--- TT significantly ---(b)(4)--- over time. Please establish specifications for the TT ---(b)(4)--- content at the step --(b)(4)-- just prior to the ----(b)(4)----- of TT that occurs at Rixensart. Also, please revise this test to a quality decision test rather than a monitoring test.

The sponsor agreed to “revise the -----(b)(4)----- TT (tetanus toxoid) by ---(b)(4)--- performed at the -----(b)(4)----- processes to a quality decision test rather than a monitoring test”. To support this, they provide two tables of data (Table 3 and Table 4). Table 3 shows the -----(b)(4)----- and Table 4 displays the ----(b)(4)----- ----(b)(4)----- . The batches displayed in Table 3 are different from those displayed in Table 4. I note that the average -----(b)(4)----- in table 3 and (b)(4) in table 4.

Table 3. -----(b)(4)-----

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

(b)(4)

[(b)(4)]

The average ----(b)(4)----- is listed near the bottom of each table and the standard deviation is directly below it. The proposed lower limit specification is the last entry in each table. This limit is calculated by multiplying the standard deviation by three, then multiplying the result by a constant called the Performance Quality Factor (**PPQ**). This constant is a scaling factor that represents the quality of the manufacturing process and is intended to reflect the reproducibility of the process. Multiplication of the three standard deviations by this factor and subsequent subtraction from the difference between the mean and three standard deviations (**Mean – 3SD*PPQ**), results in lower specifications that are close to the lower end of ----(b)(4)-----.

The details of setting specification limits by subtracting 3 standard deviations followed by applying a scaling factor were reviewed by the statistician on our team, Dr. Tsai-Lien Lin. I defer the evaluation of scaling the specifications to her. GSKs proposal to revise the monomer specification is acceptable, from my point of view as a CMC reviewer.

7. ----(b)(4)----- **can have varying amounts of --(b)(4)--- that interfere with quantitation of antigens in glycoconjugate vaccines. Please quantify the amount of --(b)(4)--- present in TT -----(b)(4)------. Alternatively, please present data that demonstrate that the -(b)(4)-content of tetanus toxoid used in conjugate manufacture is consistently below a level that would interfere with the quantitation of antigen in drug substance and drug product.**

GSK responded to question 7 by stating that the -----
------(b)(4)-----

The final formulated product contains sucrose, which yields --(b)(4)--- and --(b)(4)--- when --(b)(4)---. Therefore, the --(b)(4)--- resulting from sucrose --(b)(4)--- would interfere with the smaller amount of -----(b)(4)------. The sponsor demonstrates instead that, in an assay validated to detect as little as ---(b)(4)----, TT (tetanus toxoid) contains small measureable amounts of --(b)(4)---.

GSK provides data for -(b)(4)- TT commercial consistency lots. These lots are -----
------(b)(4)------. These are the -(b)(4)- commercial TT lots produced in -(b)(4)-. CBER's concern was that --(b)(4)--- can interfere with the quantification of total polysaccharide in some bulk conjugates. As the question above states, GSK should either institute a release test to quantify -----(b)(4)----- or show that the --(b)(4)--- level is consistently low. GSK demonstrated that historically, -(b)(4)- levels are low in the -(b)(4)- commercial lots from --(b)(4)- and therefore they will not have to test for --(b)(4)- in TT. This is acceptable since the drug substance will be produced from TT manufactured in --(b)(4)---.

2 Pages Determined to be Not Releasable: (b)(4)

9. Please explain why the percentage of conjugate that elutes before the ----(b)(4)----- is as low as -(b)(4)- in the formulated drug product, but is consistently above -(b)(4)-in the -(b)(4)- conjugates prior to formulation.

GSK responded that the measurements are made using different pieces of equipment. Each piece of equipment has an-(b)(4)- as part of it, but one -(b)(4)- has an -----(b)(4)-----; the other has an -----(b)(4)-----. The differences in instrumental setup dictate the measured differences in retention time.

In the -(b)(4)- system used to ----(b)(4)---- on conjugate-(b)(4)-, the ---(b)(4)--- is connected in series, following the ----(b)(4)----. This means that it takes the ----(b)(4)----- ----- . Since the retention time enters in the calculation of -(b)(4)-, a difference in retention time will necessarily impact the -(b)(4)-, from the conjugate -(b)(4)-, as compared to -(b)(4)-, in the final product.

This response is acceptable.

10. In your response to Item 38, you provide additional data and information in support of your proposal to replace current assays for -----
------(b)(4)-----
assays. However, you have not provided all necessary information in support of this proposal. Specifically:

- a. You state that the -----(b)(4)----- . Please provide a more reliable -(b)(4)-, data analysis method to assess the identity of the polysaccharides that is less susceptible to human error to ensure that the polysaccharides used in the vaccine are free from other contaminants.
- b. Please provide the following:
 - i. An explanation for the difference in values for -----(b)(4)----- as measured by the current method and the proposed ---(b)(4)---.
 - ii. An explanation why the measured values for ----(b)(4)-----, and ----(b)(4)----- do not correspond to the theoretical value calculated from the molecular structure.
 - iii. The details of the method used to calculate theoretical content from molecular structure.
- c. Please provide a method that would account for overlap of the -(b)(4)-- with other signals to determine -----(b)(4)-----.
- d. Please modify the -(b)(4)-, methods so that the -(b)(4)-, data are acquired in such a way that they can be processed without baseline corrections.
- e. Please provide validation data for the determination of formate by -(b)(4)-, to demonstrate accuracy, precision including repeatability and intermediate precision, specificity, detection limit, linearity, and range.

GSK responded that they will remove the (b)(4)-, based tests and keep the original tests for (b)(4)-. They plan to submit the (b)(4)- assays as a PAS sometime in the future.

This response is acceptable.

11. We do not concur with your implementation of the following tests as monitoring tests. Please add these tests as QC Release Tests:

- a. (b)(4)- on Purified Tetanus Toxoid manufactured and released at (b)(4)-.
- b. (b)(4)- PSY polysaccharide.

I defer this review to Ms. Tina Roecklein.

12. We do not concur with a (b)(4)- shelf life for Purified TT as proposed in the BLA. Please revise the expiration date to reflect the real time stability data (i.e., (b)(4)-). In addition, please provide a specification for the test (b)(4)- Profile (b)(4)- performed during the stability protocol.

I defer the review of this response to Ms. Tina Roecklein.

13. The (b)(4)- PSY can be held for (b)(4)-. A prior approval supplement will be required to (b)(4)- this hold time from 11 days to (b)(4)- should be added to your proposed stability plan to support the increase in hold time. Please acknowledge.

GSK acknowledged that the (b)(4)-PSY can only be held for (b)(4)-. GSK further acknowledges that a prior approval supplement will be required to (b)(4)- the hold time. GSK currently assesses the stability of (b)(4)- PSY by measuring (b)(4)-.

GSK plans to file a supplement to (b)(4)- the hold time and this supplement will include stability studies. They will include (b)(4)-.

This response is acceptable.

14. Please explain how the Free Polysaccharide (PS) results provided in Tables 2 - 5 of your response to Item 66 are represented since some of the results are reported as absolute numbers and some are reported as a limit (i.e., -(b)(4)-). In addition, you state that the -(b)(4)- in Free PS for PSC-TT between time -(b)(4)-and subsequent time points and the -(b)(4)- in Free PS for PSY-TT between time -(b)(4)- and subsequent time points is due to method variability. Please provide a detailed description of the investigation conducted to determine that the root cause is method variability. Also, the variability in your Free PS assays was not provided as requested. Please provide the assay variability for your -(b)(4)- assay in comparison to ----(b)(4)-----.

I defer the review of this response to Ms. Tina Roecklein.