



MEMORANDUM

Date: August 26, 2011

To: Joseph Temenak, HFM-481
Chair, BLA Review Team

From: Rajesh K. Gupta, Ph.D., HFM-680
Deputy Director, Division of Product Quality (DPQ) and
Lab Chief, Product Quality Laboratory

Through: William McCormick, Ph.D., HFM-407
Director, Division of Product Quality (DPQ)

Subject: STN 125363 — Amendment 0.12 – Meningococcal Groups C and Y and
Haemophilus b Tetanus Toxoid Conjugate Vaccine, Hib-MenCY-TT,
MenHiberix®, Review of GSK's Responses to CR Letter

Cc: William McCormick, Ph.D., HFM-680
Willie Vann, Ph.D., HFM-437

On 12 August 2009, GSK submitted a Biologics License Application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine. Division of Product Quality reviewed the analytical methods, associated validation protocols and reports and specifications on the Drug Substance and Drug Product in the original submission and subsequent amendments as listed below.

STN 125363/0, Sections 3.2.S.4.2, 3.2.S.4.3, 3.2.P.5.2, 3.2.P.5.3, Documents related to Methods in Section 3.2R

STN 125363/0.1 (amendment received 08/27/2009), List of SOPs, validation protocols and validation reports for the Drug Substance and Drug Product

STN 125363/0.3 (amendment received 02/08/2010) Additional method validation documents, Batch analysis data on clinical lots

STN 125363/0.4 (amendment received 03/03/2010) Additional method validation documents

STN 125363/0.7 (amendment received 04/21/2010) Additional methods related documents, responses to specific question related to methods and supply of reagents for in-support testing

METHODS REVIEWED

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

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

Drug Product

- ----- (b)(4) -----
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- ----- (b)(4) -----
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On May 7, 2010, DPQ review memo was submitted and all comments from that review memo were communicated to the sponsor in a complete response (CR) letter on June 11, 2010. GSK provided response to the comments in CR letter in an amendment (0.12 received on April 15, 2011. This memo describes review of GSK’s response to DPQ’s comments that were communicated in the CR letter.

RECOMMENDED ACTION

The responses and data submitted by the GSK in response to DPQ’s comments communicated as part of the CR letter on June 11, 2010 to support the analytical methods used for the testing of Drug Substance and Drug Product and related specifications for the Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine, MenHibrix® were reviewed. Most of DPQ’s questions and comments have been addressed to the satisfaction of DPQ’s reviewers. A number of comments are proposed to be addressed by additional studies to be performed by sponsor, which will be completed by 4Q2011. DPQ agrees with the experimental plans and rationale for completing these studies by 4Q2011. These are listed below.

1. In response to comments 42b, 42d, 42f, 42i and 42h, the sponsor proposed to perform additional studies on linearity, accuracy and precision for the following methods using drug substance and drug product samples and provide additional data by 4Q2011.
 - a. -----;
 - b. -----;
 - c. -----(b)(4)-----;
 - d. -----
 - e. -----
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2. In response to comments 43b, 43e, 43g, the sponsor proposed to perform additional studies on linearity using drug substance and drug product samples instead of assessing linearity from the standard curve for the following methods and provide the additional data by 4Q2011.
 - a. -----;
 - b. -----(b)(4)-----;
 - c. -----.

3. In response to comments 44a and 44b, the sponsor commits to complete the accuracy validation experiments for the following methods by 4Q2011.
 - a. -----(b)(4)-----;
 - b. -----.

4. In response to comments 45a, 45c, 45g and 45f, the sponsor commits to complete the precision validation experiments across the range of the method using samples from drug substance and drug product for the following methods by 4Q2011.
 - a. -----(b)(4)-----;
 - b. -----;

2 pages determined to be not releasable: b(4)

DETAILED REVIEW AND COMMENTS on GSK's Response to the CR Letter (Amendment 0.12)

DPQ's original comments from review memo of May 7, 2010 that was communicated to the sponsor in the CR letter dated June 11, 2011 are given in regular font with the comment number from the CR letter. GSK's response submitted in amendment 0.12 on April 15, 2011 is provided in *italics font* and DPQ review of the response is provided in **bold font**.

Regarding Specifications and Analytical Methods Validation

Comment 40. In Modules 3.2.S.4 (Control of Drug Substance) for Hib-TT, MenC-TT and MenY-TT, you provide information on the proposed quality tests and specifications for --b(4)----- and drug substances. In order to ensure routine consistency of manufacturing, product quality, and safety and effectiveness of the product, we request that you add the following QC Release tests with appropriate specifications:

- d. For QC Release Test for Hib-TT:
 - i. --(b)(4)--- ;

GSK's Response

--(b)(4)--- content is assessed on purified TT after -----(b)(4)----- . As explained in response to Question 40.b.iii, the Company also commits to implement --(b)(4)--- content test on purified and --(b)(4)--- TT. In addition --(b)(4)--- is also performed as a QC release test on Hib PS and on final container vaccine. Specifications applied to the Hib-TT active ingredient are aligned to the latest revision of the --b(4)----- monograph for Haemophilus influenzae type b conjugate vaccines (----- (b)(4) and to WHO TRS N 897. --b(4)--- testing at the conjugate level is not referred to in either monograph. However, an --(b)(4)--- content test by the --(b)(4)----- method was performed for information only on the Hib-TT commercial consistency lots. Results are provided in Table 10 of the amendment 0.12 and show very low --(b)(4)--- levels.

In conclusion, control of --(b)(4)--- levels are monitored via QC release testing for earlier --b(4)----- and at the end for the final container vaccine. --(b)(4)--- content was measured for information only on commercial consistency Hib-TT lots and was found very low. Therefore, GSK proposes not to implement additional --(b)(4)--- testing on Hib-TT, since it provides little added assurance regarding the control of --(b)(4)--- levels during the manufacturing process and ultimately the final container vaccine.

DPQ's Review

We concur with the response. Due to control of --(b)(4)--- at a number of intermediate steps and final container, --(b)(4)--- at individual bulks of conjugates is not required.

- e. For QC Release Tests for MenC-TT and MenY-TT:
 - iii. --(b)(4)---

GSK's Response

--(b)(4)--- content is assessed on purified TT after -----(b)(4)----- . The Company commits to implement -(b)(4)--- content test on purified and----(b)(4)----- . In addition --(b)(4)--- is also performed as a QC release test on MenC and MenY PS and on final container vaccine. In view of these controls, the Company proposes not to implement --(b)(4)--- test on the conjugate bulks. Specifications applied to the Men-TT active ingredients are aligned to the latest revision of the -b(4)---- guideline for 'Meningococcal group C conjugate vaccine' (----- (b)(4) and the WHO guideline "Recommendations for the production and control of meningococcal C conjugate vaccines" (Adopted 2001, TRS 924). -b(4)----- test on conjugate bulks is not referenced in these guidelines, but is recommended at the level of PS bulks and final container. However, an --(b)(4)--- content test by the -----(b)(4)----- method was performed for information only on the MenC-TT and MenY-TT commercial consistency lots. Results have been provided in Table 15 of the submission in amendment 0.12 and show very low -b(4)---- levels.

In conclusion, control of --(b)(4)--- levels are monitored via QC release testing for earlier -b(4)----- and at the end for the final container vaccine. --(b)(4)--- content was measured for information only on commercial consistency MenC-TT and MenY-TT lots and was found very low. Thus GSK proposes that additional --(b)(4)--- testing on Men-TT provides little added assurance regarding the control of --(b)(4)--- levels during the manufacturing process and ultimately the final container vaccine. Therefore, GSK proposes not to include --(b)(4)--- test in QC release testing of Men-TT bulks.

DPQ's Review

We concur with the response. Due to control of --(b)(4)--- at a number of intermediate steps and final container, --(b)(4)--- at individual bulks of conjugates is not required.

Comment 41. Your specifications for --(b)(4)----- in the MenC-TT and MenY-TT Bulk Conjugates (Modules 3.2.S.4.5, Justification of Specifications) are not more than (b)(4). These specifications are wider than those in the actual data you provided for clinical and commercial consistency lots for MenC-TT and MenY-TT (Modules 3.2.S.4.4, Batch Analysis). Please revise your proposed specifications for ----(b)(4)-- to be consistent with actual data or provide a justification for your proposed specifications.

GSK's Response

The Company has revised the specification limits for the ---(b)(4)-- content in MenCTT and MenY-TT conjugates based on the actual data for clinical and commercial consistency conjugate lots. The revised specification for the free TT content in MenC-TT and MenY-TT conjugate bulks is “Not more than (b)(4).

DPQ’s Review

The response is adequate. We agree with the revised specifications.

Comment 42. Linearity, accuracy and precision for most of the quantitative methods have not been evaluated across the range of the method using drug substance and drug product samples [(Modules 3.2.S.4.3, Validation of Analytical Procedures, Hib-TT, MenC-TT and MenY-TT) and 3.2.P.5.3, Validation of analytical Procedures, Drug Product)]. Generally, the specified range of an assay is established by confirming that the analytical procedure provides an acceptable degree of linearity, accuracy and precision when applied to samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure. Please define a range for all your quantitative methods and evaluate linearity, accuracy and precision across the range of the method using actual drug substance and drug product samples, as appropriate, for the following test methods:

- a. -----
-----;
- b. -----
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- c. -----
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- d. -----

- e. -----

- f. -----

-----;
- g. -----
-----;
- h. -----

- i. -----

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GSK’s Response (Comment 42a)

2 pages determined to be not releasable: b(4)

- a. -----(b)(4)-----
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- b. -----(b)(4)-----
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- c. -----(b)(4)-----
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- d. -----(b)(4)-----
-----;
- e. -----(b)(4)-----
-----;
- f. -----(b)(4)-----

- g. -----(b)(4)-----
-----.

GSK’s Response (Comment 43a)

With regard to the ----(b)(4)----- content, the Company has provided additional validation data in the frame of Hiberix BLA, commitment 20, in February 2009 (see also response to Question 42). Briefly, during validation, it was shown that –b(4)-- recovery is only (b)(4) and therefore, validation of accuracy across the range is not possible. In addition, since –(b)(4)-- CN content is below the detection limit in the Hib-TT drug substance, evaluation of linearity across the range is not possible either.

DPQ’s Review

This has been addressed in response to comment 42a. An information request regarding use of this test as a limit test should be communicated, as discussed above.

GSK’s Response (Comments 43b. e. g)

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

DPQ’s Review

DPQ concurs with this proposal.

GSK’s Response (Comments 43c.d.f)

Revised validation reports (9000000693RVM010, 9000005946RVM001-01 and 9000010197RVM001/02) for Free-PS content tests (for Hib-TT, PSC-TT and PSY-TT

1 page determined to be not releasable: b(4)

DPQ's Review

Data presented in revised validation report is acceptable.

Comment 45. You have generally evaluated the precision of your analytical methods by using (b)(4) analysts on ---(b)(4)--- days. The process of using -(b)(4)- analysts on -(b)(4)- days does not assess repeatability of the method. Please provide validation data evaluating repeatability for the following methods:

- a. -----(b)(4)-----
-----;
- b. -----
------(b)(4)-----
-----;
- c. -----
-----;
- d. -----
-----;
- e. -----(b)(4)-----
-----;
- f. -----

- g. -----
------(b)(4)-----
-----.

GSK's Response (Comments 45a. c. g. f)

The Company commits to complete the validation using actual drug substance and drug product samples with amounts at the extremes of the range. The following experimental design is proposed for each method:

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

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

The Company proposes that the existing validation data are sufficient to guarantee the suitability of the tests and proposes to provide the additional validation data as a Post Marketing Commitment by 4Q2011.

DPQ's Review

DPQ concurs with this proposal.

GSK's Response (Comments 45b.d.e)

For the free PS content assay, additional validation was performed according to the following experimental design:

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

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

Revised validation reports (9000000693RVM010, 9000005946RVM001-01 and 9000010197RVM001/02) for Free-PS content tests (Hib-TT, MenC-TT and MenY-TT respectively) are annexed in Module 3.2.R.

DPQ's Review

Repeatability data have been submitted in revised validation reports and are satisfactory.

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

a. ---b(4)-- -----

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

GSK's response

46a. The Company has provided additional validation data in the MenHibrix BLA amendment dated February 8, 2010 (Sequence No. 0003). These reports (rpert-9000001149RVM003 and rpert-9000001149RVM004) are provided in Module 3.2.R. The LOQ is now defined at (b)(4) µg/mL as outlined in rpert-9000001149RVM004.

3 pages determined to be not releasable: b(4)

the test sample that is equal to or higher than the absorbance at (b)(4) of the standard curve.

GSK’s Response

The validation protocols and reports have been revised to take into account CBER’s comments.

The list of validation protocols and reports has been provided in Table 1 of submission (amendment 0.12).The validation protocols and reports are provided in module 3.2.R.

DPQ’s Review

GSK has reevaluated the criteria for positive identification of PSC-TT and PSY-TT conjugate in Drug Product by an (b)(4) method. In addition to harmonizing the calculations between the Hib, PSC-TT and PSY-TT components in the HibMenCY vaccine, GSK has also modified the criterion for positive Identity of Hib. The proposed criteria for all three conjugates have been established as, “identity will be positive if the absorbance of the sample is equal to or higher than the absorbance at (b)(4) of the standard curve”. The data presented in the validation reports for b(4) final container lots of vaccine show that the new criteria for positive identification of each of three vaccine components are sufficiently stringent for Identity testing by (b)(4). The response is adequate.

Comment 52. Please address the following with respect to SOP 9000010691, Determination of PSC and PSY Content in the Final Containers by –(b)(4)-- (After --(b)(4)-):

- a. --b(4)-- -----

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

GSK’s Response

52a. *The PSC-TT and the PSY-TT contents in the HibMenCY-TT final container are measured by (b)(4) using a PSC-TT and a PSY-TT ---(b)(4)----- respectively as a reference standard. The titer determination of a new biological standard (PSC-TT and PSY-TT) is measured as described in the procedure 9000006817 provided in Module 3.2.R. The determination of the titer is performed on a minimum of (b)(4) independent values except justified cases based on rational and approval by the QA, i.e. during the investigational phase of product development the determination of the titer is performed on a minimum of (b)(4) independent values.*

---b(4)---

-b(4)-

(b)(4)

(b)(4)

(b)(4)

(b)(4)

DPQ's Review

Explanation of calculation factors used for PSC-TT and PSY-TT is satisfactory.

Comment 53. Regarding the -----(b)(4)----- of MenC-TT and MenY-TT -----(b)(4)----- (SOP 9000006776), you have mentioned in the SOP, the validation documents, the BLA, and batch analysis records that a different type and/or different lots of -----(b)(4)----- have significant effects on the results of the (b)(4) test for the drug substance and drug product samples. We are aware that you qualify the -----(b)(4)----- for this test, and you have supplied a screened and qualified -----(b)(4)----- to CBER for testing of MenHibrix vaccine. Please provide a comprehensive report on the effect of different types of -----(b)(4)----- on

4 pages redacted due to (b)(4)

7 pages redacted due to (b)(4)

DPQ's Review

We do not agree with the GSK's response not to include the test for --(b)(4)----- content on the final container vaccine. ---(b)(4)----- content on the final container vaccine should be monitored as a parameter for consistency in manufacture of this product.