



MEMORANDUM

Date: June 5, 2012

To: File for STN 125363/0

From: Karen Campbell, HFM-680
Regulatory Coordinator, Division of Biological Standards and Quality Control (DBSQC)

Through: William McCormick, Ph.D., HFM-680
Director, Division of Biological Standards and Quality Control (DBSQC)

Subject: STN 125363 – Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine, Hib-MenCY-TT, MenHiberix®, Review of the lot release protocol template submitted by Glaxo SmithKline Biologicals

CC: Rajesh K. Gupta, Ph.D.
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Willie Vann, Ph.D.

On 12 August 2009, GSK submitted a Biologics License Application (BLA) for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine. The Division of Biological Standards and Quality Control (DBSQC), then the Division of Product Quality (DPQ), reviewed the lot release protocol submitted in the original BLA and subsequent versions, reviewing versions 06, 07 and 08.

Submissions Reviewed in this Memo

STN 125363/0 (original submission) Lot Release Protocol Template
STN 125363/0.31 (amendment received 5/9/2012) Response to May 2, 2012 Information Request and draft LRP
STN 125363/0.32 (amendment received 5/16/2012) LRP Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine v07
STN 125363/0.34 (amendment received 5/25/2012) Lot Release Protocol (Draft 8)

Conclusion

Version 08 of the lot release protocol template submitted in STN 125363/0.34 (amendment received 5/25/2012) is acceptable for use.

Review and Comments on GSK's Lot Release Protocol Template:

DBSQC's comments on the Lot Release Protocol template submitted in the original BLA (8/12/2009) were combined with comments from the Division of Bacterial, Parasitic and Allergenic Products and communicated to the sponsor in a telecon with LRP comments dated 20-Mar-2012 and subsequent LRP comments on 02-May-2012. The LRP comments communicated by email in preparation for the March 20, 2012 telecon are given in regular font with the comment number from this communication. GSK's responses submitted in Amendments 0.31 and 0.32 are provided in *italics font* and DBSQC's final review of the responses and conclusion are provided in **bold font**.

1. In the header, drop the phrase: Licensed Name of the Product, and only list the product name. Also, remove the trade name from the header section.
2. In the header, cc: should be completed.
3. On page 1, a line may be added before the date of manufacture to list the trade name of the product, if desired.
4. On page 1, delete Virus strain.
5. On pages 2 and 3, remove the word antigen from tables.
6. On page 3, remove the word -(b)(4)- from in front of TRIS.
7. Please insert a Genealogical Tree similar to what was included on page 3 of STN125347 HIBERIX Lot Release Protocol. Include strain and/or batch numbers.
8. Pages 5-8 PURIFIED TETANUS TOXOID (TT) BULK:
 - a. ---(b)(4)--- tetanus toxoid by (b)(4) should be added. The specification proposed is not less than (b)(4), however, we are still discussing this.
 - b. On page 8, the sodium chloride is stated as between ---(b)(4)--- mg per ml. The BLA states the spec as -----(b)(4)-----.
 - c. On page 8, Absence of Tetanus Toxins in Guinea Pigs and Irreversibility of Tetanus Toxoid in Guinea Pigs, please use template provided. (Another format is acceptable, as long as the suggested data in the table are provided). See the templates at the end of the comments for the Irreversibility of Tetanus Toxoid in Guinea Pigs and the Absence of Tetanus Toxins in Guinea Pigs.
9. Pages 9-11 PURIFIED -----(b)(4)----- TETANUS TOXOID (TT) BULK
 - a. ----(b)(4)---- tetanus toxoid by (b)(4) should be added. Specification is not less than (b)(4) of the total surface as ----(b)(4)---- TT.
 - b. ---(b)(4)--- should be added. Specification is not more than ----(b)(4)---- Lf.
 - c. ---(b)(4)--- Content should be added. Specification is -----(b)(4)-----.
10. On pages 14, 25, 35 and 46, please spell out "μ" (-----)(b)(4)-----).

Comments 1 – 10 were adequately addressed

11. Page 16 HAEMOPHILUS INFLUENZAE TYPE B (PRR'P-TT) CONJUGATE BULK

- a. The BLA calls this Purified Activated Hib.

GSK response: "The release testing and specifications applied to the purified activated Hib are documented in the same monograph as those for the Hib-TT bulk conjugate. This is why the "activated Hib polysaccharide" step is included in the section related to the

“Haemophilus Influenzae Type B (Hib-TT) conjugate bulk”. This is consistent with the LRP for Hiberix™.”

- b. PRRP content by (b)(4) should be added. Specification is not less than -----(b)(4)---
- c. Free (b)(4) Content should be added. Specification -----(b)(4)-----.
- d. Activation Ratio should be added. Specification is -----(b)(4)-----.

Comments 11 a – d have been adequately addressed

12. Pages 17-20 HAEMOPHILUS INFLUENZAE TYPE B (PRR’P-TT) CONJUGATE BULK

- a. pH should be added. Specification = ---(b)(4)---
- b. On page 18, the specification for Free PRPP polysaccharide by -(b)(4)- is not more than (b)(4). The BLA states the specification is not more than (b)(4).

Comments 12 a and b have been adequately addressed

13. Pages 21-22 and 31-32 PURIFIED -----(b)(4)----- TETANUS (T) TOXOID BULK

- a. ---(b)(4)--- tetanus toxoid by -(b)(4)- should be added. Specification is not less than (b)(4) of the total surface as ----(b)(4)--- TT.
- b. ----(b)(4)---- Content should be added. Specification -----(b)(4)-----.
- c. ----(b)(4)---- should be added. Specification is not more than -----(b)(4)-----.
- d. On pages 21-22 and 31-32 The test for Absence of Tetanus Toxins in Guinea Pigs and Irreversibility of Tetanus Toxoid in Guinea Pigs should be added, refer to comment 8.c. above, see template.

GSK response: Instead of the “Absence of Tetanus Toxins in Guinea Pigs” and “Irreversibility of Tetanus Toxoid in Guinea Pigs” on the purified -----(b)(4)----- Tetanus toxoid bulk, the company has proposed to implement a “Specific toxicity on guinea pigs” on the final bulk. The test has been added in page 72. For further details on the proposal described above, please refer to the response to Item 13d of the lot Release Comments from 20 March 2012 sent in an email dated April 26, 2012.

Comments 13 a – d have been adequately addressed

14. Pages 23-27 MENINGOCOCCAL POLYSACCHARIDE TYPE C PURIFIED BULK

- a. ----(b)(4)---- specification is proposed as not more than ----(b)(4)----. We are still reviewing this specification.

GSK response: ---(b)(4)--- specification has been revised to “not more than -----(b)(4)---” (page 45) as proposed in the Response to Item 4 of the Information Request from March 20, 2012 (submitted on April 20, 2012. Sequence 0029)

- b. (b)(4) content by -----(b)(4)-----. Please spell out μ .

Comments 14 a and b have been adequately addressed

15. Pages 28-30 NEISSERIA MENINGITIS POLYSACCHARIDE TYPE C - TETANUS TOXOID (Men C-TT) CONJUGATED BULK

- a. ---(b)(4)--- by --(b)(4)-- should be added. Specification not less than ----(b)(4)---- mole PS.
- b. Identity by (b)(4) should be added. Specification is positive.

Comments 15 a and b have been adequately addressed

16. Pages 33-36 MENINGOCOCCAL POLYSACCHARIDE TYPE Y PURIFIED BULK

- a. ---(b)(4)--- specification is proposed as not more than ---(b)(4)--- PS. We are still reviewing this specification.

GSK response: ---(b)(4)--- specification has been revised to “not more than ---(b)(4)--- PS” (page 65) as proposed in the Response to Item 4 of the Information Request from March 20, 2012 (submitted on April 20, 2012. Sequence 0029)

- b. (b)(4) content by -----(b)(4)----- . Please spell out μ .

Comments 16 a and b have been adequately addressed

17. Page 37 MENINGOCOCCAL POLYSACCHARIDE TYPE Y -----(b)(4)-----
– BULK

- a. -----(b)(4)----- should be added. Specification is not more than (b)(4) before cutoff (b)(4).
- b. ---(b)(4)--- by (b)(4) should be added. Specification -----(b)(4)-----.
- c. ---(b)(4)--- should be added.

Comment 17a, the specification of Not less than (b)(4) before -----(b)(4)----- is correct.

Comments 17 a – c have been adequately addressed

18. Pages 38-40 NEISSERIA MENINGITIS POLYSACCHARIDE TYPE Y - TETANUS TOXOID (Men Y-TT) CONJUGATED BULK

- a. (b)(4) by -----(b)(4)---- should be added. Specification not less than -----(b)(4)----- PS.
- b. Identity by (b)(4) should be added. Specification is -(b)(4)-.
- c. On page 38, the specification for -----(b)(4)---- by (b)(4) is not less than -(b)(4)- per mL. The BLA states that the specification is not less than -----(b)(4)-----.
- d. On page 38, the specification for polysaccharide Y content by ---(b)(4)--- is not less than -----(b)(4)----. The BLA states that the specification is not less than -----(b)(4)-----.

Comments 18 a – d have been adequately addressed

19. Pages 42-49 FINAL CONTAINER

- a. Sucrose by (b)(4) should be added. Specification = -----(b)(4)-----.
- b. Osmolarity should be added. Specification = -----(b)(4)-----.
- c. ---(b)(4)--- by (b)(4) should be added. Specification = -----(b)(4)-----.
- d. On page 43, the test is written as polysaccharide C content by ----(b)(4)---- with a specification of not less than (b)(4) of the target value. The BLA states that polysaccharide C content is determined by calculation with a specification of not less than (b)(4).

GSK response: The specification for the test “PSC content by (b)(4) (calculation) has been revised to “Between -----(b)(4)----- per vial” as previously submitted in the Complete Response submission (CMC Question 70). Sequence 0012 on April 15, 2011.

- e. On page 44, please add the word “Total” in front of polysaccharides PSC-PSY content by (b)(4).
- f. On page 46, the ----(b)(4)---- is stated to be determined by -----(b)(4)-----.
- g. On page 48, the ---(b)(4)--- specification is not more than -----(b)(4)-----.
- h. On page 49, please include the information in the format suggested for Abnormal Toxicity-General Safety. (Another format is acceptable, as long as the suggested data in the table are provided.)

Comments 19 a – h have been adequately addressed

20. Throughout the Lot Release Protocol, inconsistent names are used for the manufacture steps. In bold is what is at the top of each section, after the hyphen is at the top of the subsequent pages, this is not enough information to know clearly what is being reviewed. In red is what we could find that corresponds in the BLA submission, those highlighted definitely need to change (see the original Tcon for the list). As much as possible please be consistent with the terminology of the intermediates used in the BLA to avoid confusion.

GSK response: In order to address comment 20, the names of the manufacturing steps were further aligned with the names used in the BLA. In particular, the name of the section related to the “Purified Tetanus toxoid” step was corrected as requested: the following title “Purified Tetanus Toxoid” appears in the updated LRP.

Regarding the names that appear at the top of each page, such as “Purified Bulk” or “Bulk Conjugate”, these names refer to manufacturing steps that are generic among antigens and vaccines that are produced in Belgium. Consequently, these names cannot be corrected to reflect any product specificity. For the specific case of Tetanus Toxoid bulk which is produced in the ---(b)(4)--- manufacturing site of ---(b)(4)---, the name that appears on each page has been changed to “Purified Tetanus Toxoid”. The company would like to emphasize that for each intermediate, the batch number appears at the top of each page: as described in the BLA, the nomenclature used for the PS bulks and for the conjugate bulks allows to differentiate unambiguously the bulks related to each serotype. In addition, the batch number listed on each page is also referred to in the lot history table of the demonstration LRP with reference to the concerned production step.

Examples of batch numbers are provided below to illustrate that the identification of the process intermediates that relate to a specific drug substance will be unambiguous:

- “—b(4)-----” manufacturing step for Meningococcal Polysaccharide Type Y: ----(b)(4)----
- “—b(4)-----” manufacturing step for Meningococcal Polysaccharide Type C: ----(b)(4)----
- “—b(4)-----” manufacturing step for Hemophilus Influenzae Type B: ----(b)(4)----
- “—b(4)-----” manufacturing step for MenY-TT: ----(b)(4)----
- “—b(4)-----” manufacturing step for MenC-TT: ----(b)(4)----
- “—b(4)-----” manufacturing step for Hib-TT: ----(b)(4)----

For the “--(b)(4)-- Hib polysaccharide” step, it should be highlighted that the release testing and specification applied to the --(b)(4)-- Hib PS are documented in the same monograph as those for the Hib-TT bulk conjugate. This is why the “--(b)(4)-- Hib polysaccharide” step is included in the section related to the “Haemophilus Influenzae Type B (Hib-TT) conjugate bulk”. This is consistent with the LRP for Hiberix™.

Comment 20 has been adequately addressed

21. For Sterility and LAL tests, use the full template presentations for the drug substance (conjugates) and final container. We recognize that LAL testing is not done on the (b)(4) conjugates. In this case the template presentation is only needed for final container. For Sterility and LAL tests on intermediates the results may be presented in table format similar to that shown in comment 22.

See Tcon record (20-Mar-2012) for the template Examples:

GSK response: The templates for Sterility and --(b)(4)-- tests were reviewed to provide the information requested with the exception for the elements detailed below:

Template for sterility:

The following information was not included as it is not considered relevant/informative:

*“(b)(4) Test Date”: is redundant with the “On Test Dates” provided in the Table
“------(b)(4)----- Test Date”: the -----(b)(4)----- properties of all media and their sterility are verified before testing. Moreover the expiration date has been validated for all media. The information related to media is adequately documented and available during inspection.*

Template for --(b)(4)--:

The following information was not included as it is not considered relevant/informative:

- *The “Mean Onset Time” for the Standard Curve and for the Product: are determined automatically by the software being used and do not provide valuable information for the interpretation of the final results.*
- *The CV (%) observed on replicates for the standard curve and Product: As described in the SOP, validity criteria are defined on the CVs between replicates.*

Consequently, the procedure ensures that results are only considered valid providing that acceptable CVs are observed between replicates.

- The “--(b)(4)-- recovery”: As described in the SOP, validity criteria are defined on the ---(b)(4)--- recovery. Consequently, the procedure ensures that results are only considered valid providing that acceptable ---(b)(4)--- recovery are observed.*
- Results for “Beginning – Middle – End“ are not relevant on purified –b(4)--. On final containers, the result which is encoded corresponds to the highest value observed among the “Beginning”, “Middle“ and “End” results. The 2 lower results that are not encoded do not bring further information on the product.*

Comment 21 has been adequately addressed

22. Except for tests where more information has been requested, the following format may be used to present the data throughout Lot Release Protocol. (Another format is acceptable, as long as the suggested data in the table are provided):

GSK response: The company proposes to keep the presentation of results as originally planned. Although the format used in the proposed LRP is different from the one proposed by CBER, all requested information are provided. Moreover, the current format to report results are common to other vaccines including Hiberix™.

Comment 22 has been adequately addressed