Record of Telephone Conversation, March 20, 2012 - MenHibrix

Submission Type: BLA   Submission ID: 125363/0   Office: OVRR
Product:
Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine
Applicant:
GlaxoSmithKline Biologicals
Telecon Date/Time: 20-Mar-2012 12:50 PM   Initiated by FDA? Yes
Telephone Number:
Communication Categorie(s):
1. Information Request

Author: KIRK PRUTZMAN
Telecon Summary:
Lot Release Protocol IR and CMC review IR
FDA Participants: KIRK PRUTZMAN, JOSEPH TEMENAK, DAVID STATEN
Non-FDA Participants: JODY GOULD, NORRIS PYLE
Trans-BLA Group: No

Related STNs: None
Related PMCs: None
Telecon Body:
Dear Jody,
Please find attached an Information Request for the Lot Release Protocol and an
Information Request regarding issues identified by the product reviewers.
Regards,
Kirk Prutzman, PhD
Food and Drug Administration
Primary Reviewer/Regulatory Project Manager
CBER/OVRR/DVRPA/CMC3
1451 Rockville Pike (WOC2)
Room 2241
HFM-481
Rockville, MD 20857
Phone: (301) 796-2640
IR Comments (DBPAP)
1.   In your response to Question 11a, you provide the validation data for the -----
(b)(4)--- used at ---(b)(4)--- to quantify -------------(b)(4)---------------. Please address the
following concerns surrounding the validation.

a.   Identify each of the three major peaks shown in TT ------(b)(4)------ (Figures 1-3).
b.   Please provide a description of how ----------(b)(4)---------- is calculated from the
validation data in Figures 1-3.

2. You propose a ---(b)(4)---. You also propose a -------(b)(4)-------   release specification of not less than (b)(4) for Purified TT measured directly   -----------(b)(4)------------ in Belgium. In your response to Question 12, you propose a -------(b)(4)------- stability specification of not less than (b)(4) for Purified TT manufactured at ---(b)(4)---.

a. Please revise your stability specification to not less than (b)(4) so that it is in line with the specification needed to be used for further manufacture.

b. You propose a (b)(4) month expiration date on Purified TT based on a ------(b)(4)-- stability specification of not less than (b)(4). Using a stability specification for ------ (b)(4)------ of not less than (b)(4), you only have data to support an expiration date of (b)(4) months. Please revise your expiration date to ---(b)(4)---.

c.The -------(b)(4)------ results for Purified TT are known to decrease over time. To ensure that a -------(b)(4)------ result of not less than (b)(4) is obtained at the end of expiry, the -------(b)(4)------ content at release should be closer to not less than (b)(4). Please comment.

3. In your response to Question 14, you state that values for free polysaccharide are reported as a limit when the result is less than the first calibration point. For consistency, if the value for free polysaccharide is below the limit of quantitation it should be reported as < LOQ value (i.e., ---(b)(4)--- for Hib-TT).

4. In your response to Question 16, you provide the statistical method (process performance indices) used to calculate specification. Using this method for setting endotoxin specifications is not appropriate due to the high number of <LLOQ values. Assigning the <LLOQ values to be equal to the LLOQ values makes the estimated mean and thus the upper specification higher than it should be. Please set your ---(b)(4)-- specifications using a scientifically justified method to ensure process consistency.

5. You provided the validation data for the ---------(b)(4)--------- of Purified and   ---(b)(4)--- TT in this response. We note that you had originally committed to provide as a PMC in response to Question 40b of the CR letter sent on June 11, 2010. The validation submitted does not include an evaluation of intermediate precision. Please provide data that demonstrate that the assay intermediate precision is adequate for its intended use.

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 stabiliser 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 Irrevesibility 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)--------.
   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)----------).

11. Page 16 HAEMOPHILUS INFLUENZAE TYPE B (PRR'P-TT) CONJUGATE (b)(4)
    a. The BLA calls this Purified Activated Hib.
    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) of total surface.
    d. Activation Ratio should be added. Specification is ----(b)(4)----.

12. Pages 17-20 HAEMOPHILUS INFLUENZAE TYPE B (PRR'P-TT) CONJUGATE (b)(4)
    a. (b)(4) 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).

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)----.
    b. Residual (b)(4) Content should be added. Specification -(b)(4)- TT.
    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.

14. Pages 23-27 MENINGOCOCCAL POLYSACCHARIDE TYPE C PURIFIED BULK
    a. ---(b)(4)--- specification is proposed as not more than --(b)(4)-- PS. We are still reviewing this specification.
    b. ----(b)(4)---- by ----(b)(4)----. Please spell out µ.

15. Pages 28-30 NEISSERIA MENINGITIS POLYSACCHARIDE TYPE C - TETANUS TOXOID (Men C-TT) CONJUGATED BULK
    a. ---------(b)(4)----------- should be added. Specification not less than --------(b)(4)----- PS.
    b. Identity by (b)(4) should be added. Specification is positive.

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.

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

17. Page 37 MENINGOCOCCAL POLYSACCHARIDE TYPE Y ---------(b)(4)---------- – BULK
    a. ------------------(b)(4)------------------- should be added. Specification is not more than (b)(4) before ---(b)(4)---.
    b. Assymetry by (b)(4) should be added. Specification = ---(b)(4)---.
    c. Viscosity should be added.

18. Pages 38-40 NEISSERIA MENINGITIS POLYSACCHARIDE TYPE Y - TETANUS TOXOID (Men Y-TT) CONJUGATED (b)(4)
    a. -(b)(4)- by -(b)(4)- should be added. Specification not less than ------------- (b)(4)------------------.
    b. Identity by (b)(4) should be added. Specification is positive.
    c. On page 38, the specification for protein content 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 -----------(b)(4)-----------. The BLA states that the specification is not less than   -------(b)(4)------.

19. Pages 42-49 FINAL CONTAINER
    a. Sucrose by (b)(4) should be added. Specification = ---------(b)(4)---------.
    b. ---(b)(4)--- 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).
    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)-------. The BLA states -----(b)(4)------.
    g. On page 48, the ---(b)(4)--- specification is not more than ------(b)(4)--------. We are currently reviewing a specification of -------(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.)

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.

As much as possible please be consistent with the terminology of the ---b(4)--------used in the BLA to avoid confusion.

Pages 5-8 **PURIFIED -----(b)(4)------- TETANUS TOXOID (TT) BULK** - Concentrated

BLA – GSK Bio b(4). Purified Tetanus toxoid specifications

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

Example:

Test	Analytical Method	Test Date	Results	Specifications
pH				
Identity				
Protein				

Absence of toxin for tetanus toxoid on Guinea pigs
Method Reference: ---(b)(4)--.
Weight of Guinea Pig (G.P.)   xxx-xxx g:
Route of injection   Subcutaneously

Toxoid conc. Lot Number	Date injected	Number of G.P.	Dose (mL)	Lf/mL	Days Obs.	Number of G.P. survive

Observation (obs.) End Date:

Result:
Specification: No tetanus toxicity

Irreversibility of test for tetanus toxoid on Guinea Pigs
Method Reference: ---(b)(4)--.
Weight of Guinea Pig (G.P.)   xxx-xxx g
Route of injection   Subcutaneously
Date of end of observation (obs.):

Toxoid conc. Lot Number	Lf/mL	Incubation Temperature (°C)	------(b)(4)-------- (beginning and end)	Number of G.P.	Date Injected	Days Obs.	Number of G.P. survive
		-----(b)(4)-----					
		(b)(4)					
		-----(b)(4)----					
		(b)(4)					

Result:
Specification: No reversion to toxicity

 Sterility
Method used: _____
Type: for example, Viral Harvests, Bulk, Final Container
-b(4)- Test Date: _____
Media Growth Promotion Test Date: b(4)_____
b(4)_____

On Test Date	Medium/Temperature	Tested Quantity	Off Test Date

Result:
Specification:

General Safety Test
Method used: Specification:

On Test Date	Animal	Route of	Amount	Weight (gm)		Off Test Date
	Species	Inoculation	Inoculated	Initial	Final	

Result:

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

Method θ--b(4)------- θ -b(4)-----

Test date   _____
Name of Lysate Manufacturer _____

Lysate Lot number   _____

Standard Curve Information
Endotoxin lot number _____
Endotoxin Mfr/Supplier_____
Standard Curve *(performed for each analytical session)*

	Standard Endotoxin Concentration EU/mL	Mean Onset Time (seconds)	CV%
1			
2			
3			
4			
5			
6			

Correlation coefficient (r): _____   Intercept: _____   Slope: _____

Product Test Summary
MVD _____

	Results EU/mL	Test Dilution	Mean Onset Time	CV%	% Spike Recovery
Beginning					
Middle					
End					

Results (EU/mL): _____ Specifications: _____

Calculations or additional comments