



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

Food & Drug Administration  
1401 Rockville Pike  
Rockville, MD 20852

**MEMORANDUM**

Date: May 04, 2010

To: File for 125363/0

From: James E. Keller, Ph.D.  
OVRR/DBPAP/LRSP

Through: Drusilla Burns, Chief  
OVRR/DBPAP/LRSP

Subject: Product Review Memo, Tetanus Toxoid Manufacturing and Testing

Sponsor: GlaxoSmithKline (GSK)

**SUBMISSIONS REVIEWED**

STN 125363/0 Original BLA, Sections 3.2.S, Section 3.2 P and Section 3.2 R  
STN 125363/0.1 (amendment received 8/27/2009)  
STN 125363/0.3 (amendment received 2/12/2010)  
STN 125363/0.4 (amendment received 2/12/2010)  
Batch Record for TT and Executed Batch Record for TT Lot -----(b)(4)-----

**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. 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 a liquid saline diluent supplied in --(b)(4)--  
 ----b(4)- containing (b)(4) of 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.

The proposed indication is 6 weeks to 15 months for the prevention of invasive diseases caused  
 by Haemophilus influenzae type b and Neisseria meningitidis group C and group Y. This review  
 pertains to drug substance and drug product data related to TT manufacture. Specifically, I  
 reviewed all CMC issues pertaining to TT and reviewed batch records for TT fermentation lot  
 ----(b)(4)---- and TT purified ----(b)(4)---- Lot ----(b)(4)-----.

**REVIEWER’S CONCLUSIONS**

The manufacturing process and process-controls for the manufacture of purified----(b)(4)---- TT  
 have multiple deficiencies that require resolution prior to approval. These issues have been  
 included on the final page of this memo for inclusion within a CR Letter to the sponsor. The  
 main issue pertains to commercial consistency TT Lots having multiple incidences of falling  
 outside of alert and action limits during various stages of manufacture. This is particularly  
 important in light of the fact that the firm -----(b)(4)----- operations for commercial  
 product to a (b)(4) manufacturing building -----(b)(4)----- Clinical consistency lots  
 were manufactured in building (b)(4). Other major issues pertain to inadequate or incomplete  
 assay validation data and inadequate stability data to support TT hold times, in particular, the  
 proposed ---(b)(4)---- of storage for TT manufactured in (b)(4) for which the firm submitted only  
 ---(b)(4)--- real-time stability data.

Section 3.2.S.2.1, Manufacturing Sites

Manufacturing sites for the TT portion of Menhibrix are provided below.

Manufacturing sites	Responsibilities
-----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	<div style="border: 1px solid black; padding: 5px;">             -----(b)(4)-----              -----           </div>
-----(b)(4)----- -----(b)(4)----- -----(b)(4)----- -----(b)(4)-----	<div style="border: 1px solid black; padding: 5px;">             -----(b)(4)-----              -----(b)(4)-----           </div>
GlaxoSmithKline Biologicals S.A. 89, rue de l'Institut 1330 Rixensart Belgium	<div style="border: 1px solid black; padding: 5px;">             Purified TT testing              Purified and ---(b)(4)---- TT manufacture              Purified and ---(b)(4)---- TT testing           </div>

Section 3.2.S.2.2, Preparation of Purified Tetanus Toxoid

The firm classifies TT by two distinct terms: “Purified TT” and “Purified----(b)(4)---- TT”.

Purified TT is made in -----  
---(b)(4)-----  
precipitation. Purified TT complies with WHO -(b)(4)-, the European Pharmacopoeia  
(Monograph (b)(4)). The firm has established specifications for TT purified from building (b)(4)  
at the ----(b)(4)---- site but the firm states that all future commercial TT manufacture, including  
validation lots, will occur in building -----(b)(4)----- . TT Lots that were  
used to synthesize clinical lots of MenHibrix were manufactured in building -----(b)(4)---- TT  
consistency lots for commercial manufacture were made in (b)(4). Data for these (b)(4) lots have  
been provided in this BLA. Data from (b)(4) lots have been provided in support of the  
manufacturing process.

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

A flow chart of the manufacturing process is provided below.

(b)(4)



5 pages redacted (b)(4)

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

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

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

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

**(b)(4)**

Section 3.2.S.2.4.2.2, Critical Manufacturing Steps and Intermediates

This section describes the methods and validation results for each of the in-process tests and specifications used during each stage of TT manufacture up to the final purified, concentrated form. Test methods and acceptance criteria are summarized in the Table on the top of the next page.

**In-Process Quality Decision Tests “Purified TT”**

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

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

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

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

23 pages redacted (b)(4)

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

12. In Section 3.2.S.2.5 Process Validation and/or Evaluation Hib-TT) We note that during Tetanus Toxoid manufacturing in building (b)(4) many of the monitoring test results failed to meet your predefined Alert limit or Action limits. Although we understand that these limits were initially determined for manufacturing in building (b)(4), we recommend that you establish updated Alert and Action limits for monitoring tests throughout the manufacturing process for the purified TT produced in (b)(4). Please provide updated Alert and Action limits for the TT manufacturing process or provide a proposal on how you will revise these specifications in the future. Please specify the number of lots you will use in establishing updated specifications.