

Review Memo - July 31, 2009 - Hiberix

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

Memorandum

Date: July 31, 2009
From: Scott E. Norris, BS. CBER/OVRR/DBPAP/LBP
Product Reviewer, HFM-419
Through: Willie Vann, PhD. OVRR, DBPAP, LBP
Laboratory Chief, HFM-437
Subject: Review Memo: [GlaxoSmithKline Biologicals, S. A.],
Hiberix® [Haemophilus b Conjugate Vaccine
(Tetanus Toxoid Conjugate)]
US License No. 1617
To: Administrative File STN 125347/0

Summary

BLA 125347/0 is submitted by GlaxoSmithKline Biologicals, S. A. (GSK) for approval of *Hiberix*® for booster immunization against invasive diseases caused by *Haemophilus influenzae* type b under accelerated approval regulations (21 CFR 601.41) in the context of the current shortage of vaccine for this recommended immunization.

Hiberix® is a non infectious vaccine that contains as active ingredients Haemophilus b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP), a high molecular weight polymer prepared from *Haemophilus influenzae* type b strain 20,752, covalently bound to Tetanus toxoid. After purification, the conjugate is lyophilized in the presence of lactose as a stabilizer. *Hiberix*® is supplied in 3 mL monodose glass container including 10µg Hib, ~25 µg TT, and 12.6mg Lactose, stoppered with --b(4)-- rubber closures and closed with flip-off caps. The vaccine is to be reconstituted prior to intramuscular injection, using pre-filled syringes containing 0.7 mL of 0.9% saline diluent.

The Hiberix vaccine is manufactured at the GSK Rixensart, and --b(4)--, Belgium facilities.

Review Narrative

I have reviewed the Manufacturing Process, Process Monitoring (PM), Quality Decision (QD) and Quality Control (QC), SOPs, validation lot release criteria and stability. My review includes submissions:

STN 125347/0 sections 3.2.S, 3.2.P and 3.2.R.

STN 125347/0.4 sections 3.2.S, 3.2.P

STN 125347/0.9 sections 3.2.R

STN 125347/0.11 sections 1.11.1

STN 125347/0.16

STN 125347/0.17

The manufacturing process includes Hib polysaccharide -----b(4)-----/purification, tetanus toxoid purification, and Hib polysaccharide ---b(4)---, Hib polysaccharide conjugation to the purified tetanus toxoid, formulation, filling, lyophilization and packaging. The Hiberix™ drug substance and intermediates will be commercially manufactured and tested as outlined below:

The Hib purified polysaccharide is prepared and QC testing is done at:

GlaxoSmithKline Biologicals S.A. in --b(4)--, Belgium

The tetanus toxoid is prepared for GlaxoSmithKline at:

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

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

The Hib-tetanus toxoid conjugate is prepared at:

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

QC testing is performed by:

GlaxoSmithKline Biologicals S.A.

These steps and the facilities where they take place are summarized in Figure 1.

[b(4)]

10 Pages determined to be not releasable: b(4)

Figure 4 Manufacturing flow diagram for Hiberix™ vaccine in Final Container

[b(4)]

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CBER analysis: Formulation of *Hiberix* vaccine m.3.2.P.3.2 and testing methods are adequate. The following items have been requested from the sponsor:

m3.2.P.4.1.- m3.2.P.4.4. Control of Excipient Lactose (Compendial) Hiberix™

1. INTRODUCTION

The -----b(4)-----, incorporated in Hiberix™ lyophilized vaccine is lactose.

SPECIFICATION

The lactose ingredient complies with the current -----b(4)-----, -----b(4)-----.

ANALYTICAL PROCEDURES

Lactose included in the formulation of Hiberix™ is tested according to the current -----b(4)-----b(4)-----.

VALIDATION OF ANALYTICAL PROCEDURES

Analytical procedures used for testing of lactose is performed according to the ----b(4)----- requirements referenced above and therefore, it is considered to be validated.

JUSTIFICATION OF SPECIFICATIONS

Specifications for control testing of lactose have been set based on the -----b(4)-----b(4)-----.

EXCIPIENTS OF HUMAN OR ANIMAL ORIGIN

Lactose used in Hiberix™ vaccine is manufactured from milk sourced in USA and is tested according to ---b(4)---

CBER analysis: There is no SOP, Validation or test results included for Lactose. On 5/21/09 this information was requested. The sponsor needs to provide this information.

Filling the *Hiberix* vaccine into single dose final containers

Final container QC release assays are:

- - Description – QC
 - Identity – --b(4)-- – QC
 - Sterility – --b(4)-- – QC
 - --b(4)-- – b(4) – QC
 - Moisture Content – --b(4)-- – QC
 - Endotoxin content – b(4) – QC
 - ----b(4)--- – --b(4)-- – QC
 - -----b(4)----- – QC
 - b(4) – QC

CBER analysis:

CBER notes that --b(4)-- is a raw material -----b(4)-----, and thus needs to be an included QC release test. It is acknowledged that the sponsor does not have a validated test method and will need to develop this as a post-marketing commitment. Also, -----b(4)----- needs to be changed from a --b(4)- to a QC test. ----b(4)----- of TT has also been requested by CBER as a QC for Final container.

CBER analysis: m.3.2.P.3.5.2.1; Validation of a holding time -----b(4)----- includes table 3. Final container lot numbers -----b(4)----- are not consistent with formulated bulk lot number ----b(4)----- (figure 5). The sponsor was requested to resubmit this information on 5/21/09. This has yet to be received.

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Stability data presented in m.3.2.P.8.2

Hiberix™ final container vaccine stability data for long-term, real-time stability studies, accelerated stability studies and data obtained after reconstitution of the vaccine with the saline diluent are provided.

All lots are presented in 3 ml monodose Type b(4)glass vials. Table 14 summarizes for each

Hiberix™ lot followed in stability, the data obtained and the main characteristics of the lot.

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CBER analysis: Data presented in m.3.2.P.8.2 are adequate.

Batch Records:

m.3.2.R Regional Information includes batch records for manufacture of representative batches/lots for Hib ---b(4)---, Purification, ---b(4)-----, Formulation, Filling, and Lyophilization. The files which include raw data have not been translated into English. The English translations are blank forms with no records from manufacture. This reviewer did however evaluate batch records for Hiberix manufactured for the US market during the PAI. These batch records were adequate.

Outstanding items:

1) Tetanus Toxoid (TT) Purification

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

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

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

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This is adequate.

Recommended action:

The firm has adequately addressed the outstanding issues. I recommend approval of this submission for the licensure of *Haemophilus influenzae* type b-tetanus toxoid vaccine.