

Review of Drug Product Information - September 16, 2009 - Hiberix

Department of Health & Human Services
US Food & Drug Administration
Center for Biologics Evaluation & Research
Office of Compliance & Biologics Quality
Division of Manufacturing & Product Quality
MEMORANDUM - Final Review

To: Administrative File
STN 125347/0 – Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate), Hiberix

From: Joseph George
Consumer Safety Officer
CBER/OCBQ/DMPQ/MRB I, HFM-675

Through: Carolyn Renshaw
Branch Chief
CBER/OCBQ/DMPQ/MRB I, HFM-675

Cc: Jay Slater, Chair – CBER/OVRR/DBPAP, HFM-422
Jason Humbert, RPM – CBER/OVRR/DVRPA/CMC3, HFM-481
Sean Byrd, Reviewer – CBER/OCBQ/DMPQ/MRB I, HFM-675

Applicant: GlaxoSmithKline Biologicals, S.A. **US License Number:** 1617

Subject: Review of Drug Product related sections of the original BLA for Hiberix active immunization as a booster dose for the prevention of invasive disease caused by Haemophilus influenzae type b.

ADD: 16 September 2009

Recommended Action:

Based on my review of Drug Product information found within the original submission, its amendments, inspection findings, and review of DMF --b(4)-- I recommend approval. Per agreement with GSK (Amendment 19 received on 31 July 2009), the following Post Marketing Commitment language should be included in the approval letter:

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

-----.

Summary:

On 17 March 2009 GlaxoSmithKline Biologicals, S.A. ("GSK") submitted an original submission in eCTD format seeking approval for Hiberix active immunization as a booster dose for the prevention of invasive disease caused by Haemophilus influenzae type b. The proposed indication is for active immunization as a booster dose for the prevention of invasive disease caused by Haemophilus influenzae type b (Hib) in children 15 months through 4 years of age (prior to 5th birthday). Licensure of Hiberix will provide an additional source of monovalent Haemophilus b Conjugate Vaccine to the US market for both routine and catch-up booster vaccination.

Hiberix was first licensed in Germany in 1996. Since the 1996 launch until 30 November 2008, ---b(4)-- doses of Hiberix have been distributed worldwide as a monovalent vaccine or in combination with other antigens. Hiberix is currently licensed in 98 countries worldwide and has not been withdrawn from any country due to regulatory action or safety concern.

On 22 December 2008 CBER provided written confirmation that it would consider a BLA 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. As such, GSK has been granted priority review for this submission.

Hiberix is a non infectious vaccine that contains the active ingredient 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 (within this application, PRP-TT and Hib-TT are used interchangeably to refer to the conjugated antigen). After purification, the conjugate is lyophilized in the presence of lactose as a stabilizer. Hiberix lyophilized preparation is supplied in 3 mL monodose glass container (Type -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 pre-filled syringes containing 0.7 mL of diluent (0.9% sodium chloride diluent is -----b(4)-----
-----).

The following amendments have been submitted since the original 17 March 2009 BLA: 31 March 2009 – clinical trial databases for the 7 booster studies; proprietary name research results; revised concept protocol for Study Hib-097.

1. 15 April 2009 – request assignment of Unique Ingredient Identifier (UNII).
2. 21 April 2009 – statistical programs for the 7 booster studies.
3. 30 April 2009 – responses to IR related to testing procedures; correction of ---b(4)-----
-----b(4)----- acceptance criteria.
4. 1 May 2009 – corrections to facilities section of BLA.
5. 8 May 2009 – general correspondence describing GSK's plan to supply b(4) million doses to the US market (this includes the use of the ----b(4)----- facility for final container packaging and labeling).
6. 21 May 2009 – response to CBER review of Study Hib-097 concept protocol submitted in Amendment 1.
7. 11 June 2009 – general correspondence: advertising/promotion.
8. 15 June 2009 – response to CBER 11 May 2009 IR (CMC).

Process Validation (3.2.P.3.5)

The consistency of Hiberix was assessed through analysis of -b(4)- qualification batches,

-----b(4)-----, which were formulated in -b(4)- and filled and lyophilized in -b(4)-. Results for these -b(4)- batches were compared to those obtained from batches -----b(4)----- which were formulated, filled, and lyophilized in -b(4)- (the EU registered facility). Results were included in Table 2 of this section. All results were passing with no deviations noted. The table included the mean and standard deviation for results obtained from -b(4)-batches manufactured in -b(4)-. All results fell within the specified ranges indicating manufacturing consistency.

The maximum storage time for the final formulated bulk is -----b(4)----- . This was established using -b(4)- batches of formulated bulk (-----b(4)-----) each used to fill multiple final container lots. Each formulated bulk was held between -b(4)- days before filling. Batch testing results were included in Tables 4 through 6. All testing results passed and met acceptance criteria. Sterility testing was conducted on the final bulk and final container. Endotoxin testing was performed on the final container only. No deviations were noted and no trends were apparent with one exception. Testing for -----b(4)- ----- seemed to -b(4)- slightly as hold time duration -b(4)-. However, results were well below the acceptance criteria of -b(4)---for all lots. I found this acceptable but defer to the product office for full assessment.

The lyophilization cycle was challenged to demonstrate its robustness. This was done through evaluation of lots lyophilized under b(4) unique worst case conditions and compared to a reference lot (Lot -b(4)-). The worst case conditions included:

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

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

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

Container Closure (3.2.P.7)

- **Hiberix**

An information request sent to GSK on 30 April 2009: Container closure integrity PQ/validation data for the Container Closure System was not included in section 3.2.P.7 of your BLA submission. Please provide this information and include summary data of any extractables/leachables studies.

At the time of the initial approval in the EU, the stoppers used for the 3 ml vials of lyophilized vaccines were provided by -----b(4)----- . An additional supplier, -

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

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

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

Container closure integrity testing and extractable and leachable information contained in DMF -b(4)- was found to be acceptable. In addition GSK indicates that sterility and identity testing will be performed on each lot of diluent received.

Sodium Chloride Diluent (----b(4)-----)

NOTE: The following is a summary of the sodium chloride diluent manufacturing and controls. I conducted an independent review of the information contained in ---b(4)- ---- and found it adequate in support of this file. Additional details can be found within that review but have not been included here in an effort to protect --b(4)- --- proprietary information.

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

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

-.

The following release specifications are used for this diluent:

[

b(4)

]

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

A b(4)-month shelf-life is currently proposed for the 0.9% sodium chloride diluent to be used for Hiberix vaccine reconstitution. The 0.9% sodium chloride diluent may be stored refrigerated between 2° and 8°C or at a controlled room temperature between 20° and 25°C. Stability information provided in ---b(4)- ---- in support these of these claims. I reviewed Sterility, Endotoxin and Container Closure Integrity testing which were all passing. I defer to the product office to determine the ultimate acceptability of the stability claim.

Hiberix Stability (3.2.P.8)

The following stability studies have been performed:

- Real time 36 month storage at 2 to 8°C
- Accelerated b(4) storage at b(4)
- --b(4)--- for 24 hours at ----b(4)----- after reconstitution



b(4)



I reviewed the Sterility, Endotoxin, and Container Closure Integrity Test results. All were passing with no deviations noted. Please note that GSK will be using the -b(4)- stoppers for US distributed product. GSK is indicating a 36 month dating period for this product. GSK indicates that routine stability testing will continue for lots -----b(4)-----, and -----. Routine real-time stability panel testing (-b(4) per -b(4)-) will include Sterility testing at -b(4)-, and 36 months and Container Closure Integrity testing at 36 months.

Facilities and Equipment (3.2.A.1)

The following facilities are involved in Hiberix manufacturing:

Building	Site	Activities
Building b(4)	-b(4)-	-----b(4)-----
N/A	-b(4)-	-----b(4)-----
Building -b(4)-	Rixensart	-----b(4)----- ----- -----
Building -b(4)-	Rixensart	-----b(4)----- ----- -----
Building -b(4)-	Rixensart	-----b(4)-----
Building -b(4)-	-b(4)-	-----b(4)----- -----
N/A	-b(4)-	-----b(4)-----
Building -b(4)-	-b(4)-	-----b(4)----- -----

Building -----b(4)-----: Hiberix ---b(4)-----

Building -b(4)- is a multi-product facility approved for use in the ---b(4)----- of the following products:

- Engerix-B®, STN BL 103239/5054, approved 30 July 2003
- Havrix®, STN BL 103475/5048, approved 30 July 2003
- Infanrix®, STN BL 103647/5048, approved 30 July 2003
- Twinrix®, STN BL 103850/5035, approved 30 July 2003
- Pediarix®, STN BL 103907/5012, approved 30 July 2003
- Boostrix®, STN BL 125106/63, approved 14 April 2006
- Rotarix®, STN BL 125265, approved 03 April 2008
- Kinrix®, STN BL 125260, approved 24 June 2008

The media simulation covered the procedures found for multiple products which are manufactured in these areas. The following table illustrates how this general procedure applies specifically to the Hiberix final formulation process. The simulation appears to incorporate all worst case parameters.

[b(4)]

[b(4)]

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

(2) For the -b(4)- systems, the volume used can be -b(4)- than the maximum production volume and --b(4)-- to minimum -b(4)- of production. It must be sufficient to cover the repetitive operations completely, and to ensure the qualification of the operators.

GSK provided a summary of results from recent validations performed in each room in -b(4)-- and --b(4)-- as listed above. GSK states that the original validation of the formulation process has been submitted previously. The results provided were obtained from routine re-validations of this process which are performed at least --b(4)-- per year. Results included environmental monitoring, sterility, growth promotion, gowning, and visual inspection of the first --b(4)-- final container units. All were passing and no deviations were noted.

- **Final Formulation Bulk Tank**

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

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

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

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

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

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

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

Again, since these ---b(4)----- are used for other, previously approved products (see list above), the initial validation was not included in this submission. The firm states that all results met the acceptance criteria. More recent validations were performed for the use of these tanks in --b(4)-- while construction was on-going in other formulation areas. Both tanks and --b(4)----- was validated under protocols 20060072 and 20060106 respectively. The firm states that both met all acceptance criteria. Since data from these two protocols were not included in the submission and not reviewed during the PAI, -----b(5)-----.

Building --b(4)--: Hiberix -----b(4)-- ----- operations

Building --b(4)-- is a multi-product filling manufacturing facility dedicated to ---b(4)-----

. Building b(4)-b(4) is currently approved for the -b(4)- of the following vaccines:

Summary validation data for these loads was reviewed and found acceptable during inspection.

- **Stopper -----b(4)----- equipment**

The stopper --b(4)----- in area -----b(4)-----) automatically --b(4)---
--,
----b(4)-----). This unit was validated previously however additional
validations were carried out between March 2008 and June 2008, in the context of a
future software modification. The purpose of the validation was to ensure that this
modification has no impact on the efficiency and reproducibility or the cleaning,
sterilization and drying of the -b(4)-- stoppers. Validation Protocol 20080232 was
followed for this process and was included in the submission. The following acceptance
criteria were used for validation:

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

All results met the specifications listed above. The data was summarized in Annex 5
and found acceptable. No deviations were noted.

- **Cleaning of Filling -----b(4)-----**

A manual process is employed for cleaning the filling --b(4)---, small materials and --
b(4)---. The following criteria are used to validate this process:

[

b(4)

]

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

Following decontamination, product contact equipment is cleaned. Cleaning validation was performed previously in support of the ----b(4)-----) according to validation protocol 20060471 entitled "Validation of the Cleaning of the -b(4)-- filling -- b(4)---- system after the filling of ----b(4)----, in Building --b(4)--, Filling Unit, room --- b(4)----." This validation successfully demonstrated that the manual cleaning process used was able to remove residual product and cleaning agents to the levels listed in the table above.

Routinely, after cleaning of the --b(4)----- in routine conditions, the -b(4)- and --b(4)-- ----- are determined to ensure cleanliness. For small material, a visual check is performed for dryness and cleanliness. -----b(5)-----

Filling --b(4)-- are ----b(4)----- autoclaves after cleaning. Autoclave validation has been described above.

• **--b(4)-- Sterilization**

The -b(4)- cycle is used to sterilize all surfaces ---b(4)----- prior to filling operations.

-b(4)-- consecutive -b(4)- cycles were used for validation with biological and chemical indicators distributed throughout the isolators to test effectiveness. A -b(4) cycle was used to challenge the process. The following has been included in PQ for the vial filling, transfer, and loading isolators:

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- -----b(4)-----
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- -----b(4)-----
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- -----b(4)-----
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The -b(4)-aspects of this validation were performed successfully meeting all acceptance criteria. The initial validation data was reported in a previous submission (-----b(4)-----). Requalification data was included in Annex 5 of this submission. I found the result acceptable and no deviations were noted. During the inspection these validations were reviewed. It was found that the ---b(4)--- for the -b(4)- vial filling had not been validated for the ---b(4)----- as indicated. Data generated over the last b(4) months only supported a b(4)day hold. The firm has committed to changing the --b(4)-- clean hold time to --b(4)--- for non-product contact surfaces. I find this acceptable and have no other comment.

- **Lyophilizers**

The ---b(4)----- vial filling line accesses to --b(4)--- lyophilizers (-----b(4) -----
-----) in room -b(4)-. These units are equivalent with -b(4)--- batch size capability. The firm states that IQ and OQ have been performed. Performance Qualification included the following:

- Validation of the sterilization cycle of the lyophilizers (PQ).
- Validation of the product homogeneity (PQ).
- Product validation (consistency lots) (as described above).

The Lyophilizers are cleaned via a b(4) system followed by --b(4)-- by an -b(4)- system. The validation --b(4)-- cycle parameters are maximum b(4) minutes at --b(4)---, the lower tolerance of the routine production target temperature (worst case situation). Routine production sterilization cycle: b(4) minutes at temperature of --b(4)--. Validation is successful if the following acceptance criteria are met:

- -----b(4)-----
- -----b(4)-----
-b(4)- runs are performed on a single lyophilizer to validate the process and demonstrate reproducibility of the ---b(4)--- process. -----b(4)----- was performed on -b(4)----- other lyophilizers to confirm the efficacy of the --b(4)--- process on the other lyophilizers. Revalidation summary results were provided in Annex 5. This summary was inadequate for determining acceptability of this validation (i.e. data did not include results of BI testing) however, lyophilizer cleaning and ---b(4)--- was reviewed during the inspection and found acceptable. Please see the EIR for details.

- **Visual Inspection**

GSK performs a 100% manual visual inspection of filled products. Visual inspection procedures and operator certification was reviewed and found acceptable during the inspection.

Building -b(4)-: Hiberix labeling and packaging operations

The labeling and packaging operations and warehousing of the finished product take place in the -b(4)- which was previously described in --b(4)----- (approved 30 January 1998).

Labeling, packaging and warehousing procedures for Hiberix vaccine are essentially the same as for the other U.S. licensed vaccines. Briefly, packaging materials, which include primary container labels, are approved and released by QA prior to use. The materials are prepared for production purposes according to the -----b(4)----- printed from the ---b(4)-----. The packaging

materials storage is followed up with a bar code reader (as vaccines). Upon request of the production lines, the packaging materials are transferred to the --b(4)----- storage areas close to the production lines. Before the entry of the components to the production area, a line clearance is performed according to specific check lists. Then the packaging materials together with the corresponding vaccines are entered into production area and loaded on the line. A bar code control is done on all the elements and vaccines before their use on the line.

At the start up of the production, the detection systems are tested. The first final pack elements are controlled on line by the line responsible and by QA, and samples are taken.

The online detection systems include:

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

In process controls are performed every --b(4)---: the detection systems are tested and final packs are controlled.

At the end of a production order, the operators perform a line clearance according to specific check list. Before an order is sent out, the line responsible and QA perform the following sequence of operations:

- The detection systems are tested and final packs are controlled.
- The vaccine and packaging element supplies are reconciled.
- The vaccine lot is stored at +2 to +8°C.
- All unused packaging elements are destroyed.

Finally, the batch record is reviewed by responsible line operators and reviewed and released by QA.

Amendment 0006 received on 6 May 2009 described GSK's strategy to meet their commitment for supplying b(4) million doses of Hiberix to the US market by 2009. This strategy includes what is described as "minor packaging and labeling changes...to package Hiberix in --b(4)----- following approval of this facility. These changes are planned to be provided to the BLA and review team appropriately or filed as an annual reportable change if the Hiberix BLA is approved prior to [7 August 2009]." The changes referred to have not been described in the amendment. Moreover, GSK has not, as of the date of this memorandum, transitioned the --b(4)-- facility for Hiberix packaging and labeling use. Therefore, this information will be included in GSK's next Annual Report after approval of the facility (---b(4)-----) and the Hiberix BLA. Review and Inspection related to the -----b(4)-----) has been completed. The inspection of this facility revealed no objectionable conditions and a 483 was not issued.