



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: 125363/0

From: Sean Byrd, Sr. Reg. Rev. Ofc., CBER/OCBQ/DMPQ/BI, HFM-675

Through: Carolyn Renshaw, Chief, CBER/OCBQ/DMPQ/BI, HFM-675

Applicant: GlaxoSmithKline Biologicals, License #1617

Product: Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine [MenHibrix®]

Subject: Review Memo – Original Application for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine.

ACTION DUE 12 June 2010

RECOMMENDATIONS

After reviewing the submitted information I have the following comments that should be included in a Complete Response letter:

1. We acknowledge you have submitted the method validation study for container/closure integrity testing for vials and syringes used for *MenHibrix* and its diluent –b(4)-----
Please provide the results of container/closure integrity testing for the lyophilized product and diluent manufactured at your Belgium facility. Note that for the proposed ---b(4)-----

2. Regarding visual inspection of your diluent –b(4)----- (filled at GSK), we acknowledge you have provided validation for syringe tip-cap orientation, fill volume, and particulates. We also acknowledge you have provided summary data for the –b(4)---most recent aseptic simulation runs for the –b(4)----- with reject data. Please provide the validation of the 100% visual inspection with regards to container and closure defects. You should provide definitions of Critical, Major, and Minor defects with a rationale for how each type of defect was defined and the AQL/acceptance criteria for each type of defect. The validation should also cover inspector qualification and training. Finally, please provide the results of the 100% visual inspection for the diluent for the –b(4)--- commercial lots of *MenHibrix*.

3. Regarding shared equipment of the diluent –b(4)-----; please provide a description of how product-contact equipment is cleaned. In addition, please provide a summary of the validation data to support cleaning procedures.

BACKGROUND

GlaxoSmithKline Biologicals d/b/a GlaxoSmithKline (GSK), submitted their original Biologics License Application for MenHibrix[®] (or *Hib-MenCY-TT*, the name used under Investigational New Drug application –b(4)-) on 12 August 2009. The vaccine is indicated for active immunization of infants and toddlers 6 weeks through 15 months of age for the prevention of invasive diseases caused by *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y. The development program for *Hib-MenCY-TT* was granted Fast Track designation on 24 January 2005 due to unmet medical needs.

MenHibrix is a non infectious vaccine containing *N. meningitidis* serogroup C capsular polysaccharide (PSC), *N. meningitidis* serogroup Y capsular polysaccharide (PSY), and *H. influenzae* type b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP), each covalently bound to tetanus toxoid. The final product is lyophilized in b(4) monodose b(4) glass vials with rubber stoppers and flip-off caps. It is reconstituted at the time of use with –b(4)-- (0.5 mL dose) of supplied liquid saline diluent in ---b(4)------. The reconstituted product contains 2.5 µg of PRP-TT, 5 µg PSC-TT and 5 µg PSY-TT per 0.5 mL.

The diluent (0.9% NaCl) is manufactured by either ----b(4)-----or GSK. A letter of authorization to cross reference –b(4)-- Drug Master File –b(4)--- was submitted with the application. This DMF was reviewed under STN 125347 as part of the Hiberix BLA and was not repeated for this file. Testing of the diluent is performed by whichever firm manufactured the solution used. The rubber stoppers are manufactured by ----b(4)-----, and letters of authorization to cross reference Drug Master File –b(4)----- were submitted with the application. Diluent used during clinical trials was manufactured by GSK.

The submission is in eCTD format.

REVIEW

This review covers drug product manufacturing from final bulk formulation to final packaging and labeling. Review of the drug substance manufacture is covered in a separate document.

The vaccine is composed of three active ingredients as described above. The conjugates are coded Hib-TT, MenC-TT, and MenY-TT. Excipients per dose are 12.6 mg sucrose (cryo/lyo-protectant), 96.8 µg Tris-HCL buffer (--b(4)----) and 4.5 mg NaCl for isotonicity. The immediate packaging materials are equivalent to other GSK vaccines licensed for use in the United States. The product has an overfill of approximately b(4) to guarantee an effective injectable dose. The lyophilized product is stored at 2-8 °C.

Manufacturing Process *MenHibrix*

Formulation of the Hib-MenCY-TT component is performed at GSK in Rixensart, Belgium in

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

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

Vials are labeled automatically on a labeling machine. Labels are previously overprinted with lot number and expiry date and affixed to vials. The labeled vial is placed in a cardboard box simultaneously with a product information insert. Lot number and expiry date are printed on each individual box. Cardboard boxes are visually checked and manually placed in grouping boxes. Boxes are identified, palletized and stored at –b(4)---- until released.

Process Validation

GSK states the process validation for *MenHibrix* was demonstrated through the following:

- Process consistency on at least –b(4)- consecutive batches with compliance to pre-established quality specifications. Batches must show consistency of –b(4)- performances, and yields;
- Identification and validation of manufacturing critical parameters for specific operations.

Process control variables are categorized as critical or non-critical parameters based on their process validation policy. A parameter is considered critical if operating beyond its range has an impact on the safety or efficacy of the vaccine. Critical parameters are either validated or, alternatively, the performance of the process –b(4)- or module in which these critical parameters operate, will be controlled on each produced batch in order to guarantee the –b(4)- robustness.

Consistency of the vaccine production is demonstrated by analysis of the data collected during manufacture of formulated bulks and finished product and by analysis of QC release data for formulated bulks and finished product. Vaccine specifications are shown in the table below.

| Test | Specifications |
|---|----------------|
| Description | -----b(4)----- |
| Identity Meningococcal C conjugate by –b(4)- | ----b(4)----- |
| Identity Meningococcal Y conjugate by –b(4)- | ----b(4)----- |
| Identity Hib conjugate by –b(4)- | ----b(4)----- |
| Sterility test ----b(4)----- | ----b(4)----- |
| Sterility test -----b(4)----- | ----b(4)----- |
| Endotoxin content by -----b(4)----- | ----b(4)----- |
| -----b(4)----- | ----b(4)----- |
| -b(4)--- | ----b(4)----- |
| Hib content by –b(4)- | ----b(4)----- |
| Total PSC-PSY content by –b(4)- | -----b(4)----- |
| PSY content by –b(4)- | -----b(4)----- |
| PSC content by calculation | -----b(4)----- |
| -b(4)- Hib-TT by –b(4)- | -----b(4)----- |
| -b(4)- MenC-TT by –b(4)- | -----b(4)----- |
| -b(4)- MenY-TT by –b(4)- | -----b(4)----- |
| General safety – Abnormal toxicity on guinea pigs | -----b(4)----- |
| General safety – Abnormal toxicity on mice | -----b(4)----- |

Compatibility of the vaccine with diluent is validated by clinical evaluation and results of stability testing (see Stability Studies section below).

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GSK states that between 21 Oct 2005 and 16 Feb 2006, an additional aseptic process simulation study was conducted to validate the filling and lyophilization on –b(4)- during a one week filling campaign. The study showed the sterility of the filling, transfer, and –b(4)----- is maintained. This validation, with the previously submitted hold time validations, supports filling up to –b(4)- *Menhixrix* ----b(4)----- . The data provided appear to show all results conformed to the requirements of the validation. GSK also provides data from the three most recent aseptic process simulations dated 17, 18 and 19 Feb 2009. All data from simulated bulk formulation through –b(4)----- appear to comply with the acceptance criteria.

Manufacturing Process 0.9% NaCl Diluent (GSK)

---b(4)---

b(4)

Process Validation 0.9% NaCl Diluent (GSK)

Validation of the production process is by demonstration of process consistency. Each batch of product is tested according to GSK specifications as summarized below.

$$b(4)$$

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[
b(4)
]

All facilities listed are currently licensed and approved except for –b(4)–. This facility was the only one inspected for this BLA; all others having been recently covered under the *Hiberix* PAI of 2009 (STN: 125347/0 Approved 19 August 2009).

Other products manufactured in buildings ---b(4)----- are shown in the list below.

Building –b(4)---

- 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

Building ---b(4)---

- Engerix-B[®], sELA #94-1206, approved 1 August 1995
- Infanrix[®], STN BL 103647, ELA ref. #95-1926, approved 29 January 1997 & ELA ref. #97-0359 approved 17 August 1998
- Havrix[®], sELA #96-1352, approved 31 March 1998
- Twinrix[®], STN 103647-sELA #99-0152, approved 11 May 2001
- Pediarix[®], STN 103647-BLA #99-0800, approved 13 December 2002
- Boostrix[®], STN 125106, approved 3 May 2005
- Rotarix[®], STN BL 125265, approved 03 April 2008
- Kinrix[®], STN BL 125260, approved 24 June 2008

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

[b(4)]

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

Stability data for reconstituted vaccine has been collected for product after ---b(4)-----
GSK states release specifications were met for all tested parameters.

The data presented in section 3.2.P.8.3 appear to indicate the product remains stable under the testing conditions. However, I defer final comment to the Product Office reviewer.

GSK provides data for the –b(4)-commercial and –b(4)- clinical batches in support of their process validation. The data presented appear to indicate a robust manufacturing process and all acceptance criteria were met. Where appropriate, I defer final comment to the Product Office reviewer.

Container Closure System (Lyophilized Vaccine)

GSK states the proposed glass vials with latex-free rubber stoppers and caps containing the lyophilized product are approved for use with the U.S. licensed product, Rotarix[®] (STN 125265). It was also recently approved for use with *Hiberix*. They claim compatibility of the system with *MenHibrix* is demonstrated through stability studies (see Stability Studies section).

Container Closure Integrity Testing (CCIT) Lyophilized Vaccine and Diluent

COMMENT: After review I am unable to locate information regarding validation of CCIT. Therefore, the following discussion is based on the recently approved Comparability Protocol for Pediarix[®] (STN: 103907/5287 trans BLA) in which a new GSK global CCIT method was approved which covered both vials and syringes. The method was applied to the *Hiberix* system as part of a Post Marketing Commitment submitted on 22 December 2009 (STN 125347/62). Because *Pediarix*, *Hiberix*, and *MenHibrix* have a common CC system the validation submitted to the *Hiberix* file is applicable to *MenHibrix*. However, since all submissions are “stand alone”, I recommend the validation be submitted to this file.

COMMENT: I contacted GSK on 3 May 2010 and requested the validation be submitted to the file. On 6 May 2010 I received E-mail confirmation this validation had been submitted to the electronic gateway. The information has not been reviewed and will be part of a Complete Response letter to GSK.

GSK uses a –b(4)----- test to demonstrate integrity of the –b(4)--- systems: lyophilized vials and diluent ---b(4)----- . To validate the method they performed a Limit of Detection (LoD) test for --b(4)----- and compared those results to an identical process substituting ---b(4)----- . The validation was performed using –b(4)----- runs over as many days. The LoD is outlined as follows:

- Prepare b(4) containers in the following way:
 - ----b(4)-----
 - -----b(4)-----
 - -----b(4)-----
 - -----b(4)-----
 - -----b(4)-----
 - -----b(4)-----

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

[b(4)]

A similar LoD was performed for –b(4)---used as the container closure for diluent. Final results found that for vials the LoD was a –b(4)- opening and for –b(4)----- it was a –b(4)- opening.

Next, vials and –b(4)----- were prepared as described but filled with ---b(4)----- were applied with containers in a culture of –b(4)----- Acceptance criteria were the same in that

for detection to be considered above the limit, -----b(4)----- of the same -b(4)----- diameter for each of the -b(4)---. Results are shown in the tables below.

[b(4)]

[b(4)]

GSK concludes the LoD is observed with a -b(4)--- with an internal diameter of -b(4)--

Technicians were tested on their capacity to detect varying concentrations of the -b(4)--- solution in vials and -b(4)---. Results found technicians could detect ---b(4)----- in vials and -b(4)- in -b(4)--. According to the -b(4)----- equation the theoretical volume of -b(4)- that could pass through a ----b(4)-----, which is above the LoD.

Based upon the results GSK makes the following claims: the CCI tests using -b(4)- is at least as sensitive as the microbial challenge; the human detection limit corresponds to a -b(4)----- opening, and there is no deference between -b(4)---- and vials in regards to detection limits.

The results of the validation appear acceptable. The use of b(4) as opposed to actual lyophilized product for the vial validation appears to present a worst case condition in that a dry vial might be more difficult to detect -b(4)---. The -b(4)--- validation was conducted using media instead of b(4). This appears to present a worst case condition in that the -b(4)----- may make detection of the b(4) more difficult as compared to -b(4)- or 0.9% saline.

COMMENT: The validation appears acceptable; however, recent advancements in CCIT technology indicate it is better suited as a developmental study. Integrity failures are rarely, if ever, seen in elastomeric stoppers as they are, by design, self-sealing. Most integrity failures are due to defects in the glass where cracks present a torturous path for ingress or incomplete/poor setting of the closure device (stopper) allows ingress. Therefore, future CCIT validation should present artificial defects that are part of the packaging material; i.e., not an inserted tube, and mimic natural defects.

COMMENT: According to the stability protocol, CCIT is supposed to be performed at the end of the -b(4)-- expiry date. Since this filling line is proposed as a -b(4)---- we would expect to see CCIT

performed as a release test as well. After review I was unable to find any CCIT results and contacted GSK by telephone and E-mail (see teleconferences of 3 May and 6 May 2010) and requested the location of these data within the submission. I was directed to sections 3.2.P.8.2 and 3.2.P.2 section 2.5 and did not find CCIT results. I recommend this data be provided.

Visual Inspection (Lyophilized Vaccine)

GSK performs a 100% manual visual inspection of filled product. Procedures and operator training was reviewed and found acceptable during the *Hiberix* inspection and is the same for *MenHibrix*.

Container Closure System (Diluent)

The latex-free syringe plunger stopper and tip cap comply with -----b(4)-----
-----GSK references the --b(4)----- for leachable and extractable data that demonstrate conformance to ----- --b(4)- This information was not examined as a part of this review, but was covered under the *Hiberix* BLA.

Visual Inspection (Diluent)

GSK submitted validation reports for -----b(4)----- used to inspect filled diluent --b(4)--- from the --b(4)-. Reports discussed below apply to both inspection modules. Challenge kits are prepared for each type of validation (particulate, fibers, fill volume, stopper or tip-cap position). The kits are processed --b(4)-- on each module and must meet the acceptance criteria. GSK states data from the initial validations and from additional validations performed in 2005 following the implementation of the *Cervarix* vaccine were previously submitted, and all results conformed to the requirements. These data are not presented in this file. In 2007 and 2009, the b(4) inspection equipment was revalidated following upgrade of the electronic system and implementation of a plastic rigid tip-cap check. The validations conducted in the context of these modifications are discussed below. Additionally, GSK makes the remark that the --b(4)--- is being validated for a fixed particles check, stopper presence, broken flange, and cracked --b(4)--- detection.

COMMENT: After review I find no description of a 100% visual inspection with regards to cracks, stopper presence, breakage, etcetera, after filling. Though GSK states the --b(4)--- is currently being validated to detect such defects these should be a part of their current manual inspection process. I recommend GSK provide their validated 100% manual inspection process for detection of Critical, Major and Minor defects along with the Acceptable Quality Limit for each type. They should also provide a rationale for how each defect was classified. GSK does provide summary data for the b(4) most recent aseptic simulation runs for the --b(4)----- dating from 5 May 2008 to 15 May 2009 (documents 3.2.A.1 - media fills and formulation runs 2007 through 2009). These data provide the number of --b(4)--- rejected at each point of the process and why they were rejected. Defects listed as reasons for rejection include tip-cap, stopper, broken --b(4)--, empty, missing stopper, low volume, upside down stopper, dropped --b(4)-----, cracks and lack of integrity, and liquid trapped within stopper lips. However, without proper validation, and with no acceptance criteria provided, these data appear meaningless. A 100% visual inspection should be performed on each batch according to the -----b(4)----- standard.

COMMENT: I contacted GSK on 3 May 2010 and requested this information be submitted to the file. The firm responded by Email on 6 May that this information would be submitted to the file through the electronic gateway.

The –b(4)--- tip-cap orientation validation report is dated 15 February 2008. The purpose of the validation was to demonstrate the method for tip-cap inspection is reliable, reproducible and efficient. The validation used a kit composed of b(4) -----;b(4) with artificial defects and b(4) conforming. The defects included b(4)----- with the tip-cap not satisfactorily inserted and b(4) ---- with tip-cap inappropriately oriented at a $\geq 9\%$ angle. The machine has ---b(4)----- of which are involved in ---b(4)----- were performed. Acceptance criteria are that 100% of defective –b(4)----- must be rejected. The validation was completed without deviation and results showed the machine rejected all defective –b(4)----- and accepted all conform –b(4)---. The information presented appears to be acceptable in that GSK is claiming the automated inspection machine has already been validated. The testing appears adequate.

The –b(4)--- volume inspection validation report is dated 22 August 2008. The purpose of the validation was to demonstrate the method for volume inspection is reliable, reproducible and efficient. One of the –b(4)--- is used to detect volume. The validation used a kit made with b(4) ---- where b(4) were under filled at b(4) (acceptance criterion is –b(4)----- were overfilled at –b(4)----- were correctly filled. Acceptance criteria are that 100% of defective –b(4)----- must be rejected over the course of –b(4)-runs. The validation was completed without deviation and results showed the machine rejected all defective –b(4)--- and accepted all conform –b(4)----. The information presented appears to be acceptable in that GSK is claiming the automated inspection machine has already been validated. The testing appears adequate.

The –b(4)--- particle inspection validation was performed from 28 January to 27 February 2008 and the report is dated 3 March 2008. The purpose of the validation is to demonstrate the method for particle inspection of –b(4)--- is reliable, reproducible and efficient. Of the b(4) cameras b(4) are involved in particle detection -----b(4)-----

For validation purposes a kit of—b(4)----- is prepared as described below. First, the kit is inspected manually b(4) times by b(4) qualified operators. The efficiency of the manual inspection is calculated, and the “Desired Rejects” are identified. “Desired Rejects” are units of the validation kit that are inspected b(4) times, and rejected b(4) times or more by qualified operators. Then, the kit is inspected b(4) times on each of both inspection modules. The global machine efficiency is calculated, and also the efficiency per type of particle. These efficiencies are then compared to the acceptance criteria.

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

The acceptance criteria are that the –b(4)---must –b(4)----- of defective –b(4)----- and –b(4)- of each type of particle. The data provided appear to indicate both –b(4)----- modules are equal to or better than manual visual inspection.

Regarding particulate matter determination, GSK provides SOP 08-02-008 which references -----
-----b(4)-----

-b(4)--- These methods are for the detection of sub-visible particulates by the ----b(4)-----

Cleaning

Final Formulation Bulk -b(4)-

Cleaning is done through a CIP system. Initial validation of this b(4) cleaning process was submitted previously for building -b(4)- and includes both the vaccine and diluent -b(4)-. Briefly, -b(4)-- consecutive runs were used to demonstrate the process was able to adequately clean -b(4)----- and reduce the -b(4)-----content to acceptable levels. Acceptance criteria included the following:

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

The initial validation was reviewed during the inspection for *Hiberix*. Briefly, the ---b(4)-----
-----, were validated using a matrix approach of -b(4)--consecutive runs on a -b(4)----- following by -b(4)----- . Validation incorporated a -b(4)--
----- time. In routine cleaning, -b(4)----- is used. This validation met acceptance criteria. Routine cleaning tests include TOC and conductivity.

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

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

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