MEMORANDUM – Final Review

To: Administrative Files; STN 125363/0 - Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine, MenHibrix®

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Consumer Safety Officer
CBER/OCBQ/DMPQ/MRB I, HFM-675

Through: Carolyn Renshaw
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Cc: Joseph Temenak, Chair – CBER/OVRR/DVRPA
Jason Humbert, RPM – CBER/OVRR/DVRPA
Jennifer Bridgewater, Regulatory Coordinator – CBER/OVRR/DBPAP
Sean Byrd, Reviewer – CBER/OCBQ/DMPQ/MRB I

Applicant: GlaxoSmithKline Biologicals **US License Number:** 1617

Subject: Review of GSK's BLA for the 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.

ADD: 12 June 2010

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1 Recommended Action:

Based on review of this BLA, I cannot recommend approval of this file at this time. There is currently no information regarding –b(4)---------- of this product other than the fact that it is performed on the final polysaccharide conjugate bulks. The following information should be included in a CR Letter to the firm:

- According to the information provided, the tetanus toxoid and polysaccharide conjugate bulks are –b(4)---------- formulation. Also, during final bulk formulation, the ---b(4)----------. Please provide validation summaries for each of the –b(4)---------- used in these processes.

In addition to the comment above the following should be included in the CR Letter:

- Please provide the registration number for your –b(4)---------- facility

2 Summary:

On 12 August 2009, GlaxoSmithKline Biologicals, S.A. (GSK) submitted an original submission in eCTD format seeking approval for MenHibrix 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.

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. The vaccine formulation is a lyophilized product supplied in a b(4) monodose glass container –b(4)-- stoppered with rubber closures for lyophilization and closed with flipoff caps. The vaccine is to be reconstituted prior to intramuscular injection, with a liquid saline diluent supplied in ---b(4)---------- containing b(4) mL of 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 following amendments have been submitted sine the original 12 August 2009 BLA:

1. 26 August 2009 – Response to clinical and statistical information request
2. 8 January 2010 – Response to clinical information request
3. 8 February 2010 – Minor changes to CMC, facilities and equipment, and validation documentation in Module 2, 3, and 5
4. 3 March 2010 – Notice of new reference standard qualification for "—b(4)----------
5. 12 March 2010 – Response to serology information request
6. 2 April 2010 – Form 483 responses from ----------b(4)----------
7. 21 April 2010 – Responses to Information Request made regarding analytical testing reagents and SOPs
8. 6 May 2010 – Response to Container Closure Integrity Testing information request

A Pre-License Inspection (PLI) was conducted at GSK's Tetanus Toxoid facility in –b(4)---------- in March 2010. This inspection was designated VAI and details can be found in the EIR and 483 response review memo. No issues were found impacting the approvability of the file. The inspection of GSK's Belgium facilities in –b(4)---------- and Rixensart were waived (see 20 April 2010 Inspection Waiver memorandum).

The summary review which follows focuses on Drug Substance manufacturing information only. Final formulation and Drug Product information has been reviewed by Sean Byrd, OCBQ/DMPQ. Please see his review memorandum for details. The following sections, including applicable amendments, of the eCTD are reviewed herein:

- 2.3.S and 3.2.S Drug Substance, hib-tt – gsk bio
- 2.3.S and 3.2.S Drug Substance, menc-tt – gsk bio
- 2.3.S and 3.2.S Drug Substance, meny-tt – gsk bio
- 2.3.A and 3.2.A.1 Appendices/Facilities and Equipment (sub-sections relevant to Drug Substance only)

2.1 Description of Drug Substance Manufacturing Process

2.1.1 Product Flow Overview

The following figure provides an overview of the entire Menhibrix manufacturing process. It includes the facility location of each ---b(4)----------.

[b(4)]

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

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Review of each facility and associated equipment involved in Menhibrix bulk manufacturing through final formulation follows. Review of the facilities and equipment associated with final Drug Product can be found in Sean Byrd's (DMPQ) memorandum.

2.1.3 Primary Manufacturing

The Belgium facilities (--b(4)-------- and Rixensart) were recently reviewed and inspected in conjunction with the Hiberix BLA which was approved 19 August 2009 (STN 125347/0). Since Hib polysaccharide component manufacturing has not changed post approval, I have not included review of this information in this memorandum. Please refer to the 03 August 2009 Drug Substance review memo prepared by Sean Byrd, DMPQ for additional details. Mr. Byrd recommended Hiberix approval based on the submitted information and the results of the inspection.

What follows is my review of all systems involved in production which are new to Menhibrix. Therefore most processes associated with *Haemophilus* manufacturing is excluded (unless novel to the Menhibrix process).

2.1.3.1 ----b(4)---------- (polysaccharide manufacturing)

2.1.3.1.1 Cleaning Validation

Building –b(4)-- is a multi-product facility. Each piece of equipment is multi-product and the cleaning method is the same for all of the products. A worst case approach was developed for the choice of the challenge contamination and taken into consideration for all vaccines produced in Building –b(4)-- GSK states that if a new product is introduced in the facility after the initial validation, an evaluation will be made to verify if there is a need to validate the new contamination agent. For *Neisseria meningitidis* manufacturing the following parameters are used for all cleaning validations:

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Environmental monitoring PQ was performed under protocols 20080117 and 20080116 for viable and non-viable monitoring respectively. The qualification demonstrated operating status of each room as well as the effectiveness of cleaning and disinfection. Sampling was conducted with consideration representative coverage of total room square footage, material and personnel flow, and coverage of critical operations. Routine alert levels were used as acceptance criteria for these qualification challenging routine procedures. Each qualification was performed –b(4)- consecutive times and all met the acceptance criteria. I had no issues.

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

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

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The system was validated through IQ, OQ and PQ studies. Both IQ and OQ were successful verifying similar aspects and performance of the system similar to the other water systems already described. Performance Qualification consisted –b(4)--- ---------- All acceptance criteria used were equivalent to that of b(4) as detailed above. The qualification was carried out according to the following protocols:

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

Both summary reports were included in the BLA for review. All acceptance criteria were met. All microorganisms recovered were well below the acceptance criteria and identified as per protocol requirements. I found this acceptable.

Routing monitoring is performed with each use point tested for ----------–b(4)-in every –b(4)--. The samplings are evenly distributed within the –b(4)--. At least one designated use point is tested for ----b(4)---------- ---, on a rotating basis. All designated use points are tested (evenly distributed) within –b(4)----. The same acceptance criteria used for b(4) are used for –b(4)----------

Routine monitoring data from January to March 2009 was included in the BLA. This was not raw data but rather a table indicating the total number of each test performed and number of deviations of which there were none during this period of monitoring.

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

Clean compressed air is used for following purposes: --b(4)--- ----------. Clean compressed air is produced by ----------b(4)---------- of use. Each point is equipped with a point of use ---b(4)------

Validation of this system includes IQ, OQ and PQ. IQ included review of documentation; review of welding documentation; welds inspection; certificates and data sheets inspection; roughness verification; and system inspection versus P&ID. OQ included alarm tests; critical instrument calibration; moisture tests; and peak use verification.

Performance Qualification consisted of monitoring over the course of ----b(4)----------. Samples were taken and tested according to the following criteria:

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This qualification was carried out according to the following protocols:

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All summary reports included in the BLA were reviewed. All results met the acceptance criteria with no deviations noted.

Clean compressed air quality is monitored on a –b(4)-- basis and tested for –b(4)---------- content. One predefined use point is sampled that is the –b(4)--from the –b(4)----------. Routine monitoring results from January to March 2009 were included.

2.1.3.1.4 Cleaning Validation

All cleaning validations performed for –b(4)- including CIP, cleaning by machine, and manual cleaning, used a defined approach which includes specific challenge solutions and sampling plans. According to the equipment use, the cleaning is validated using the following solutions representing the worst case challenge for any equipment:

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I reviewed each of the validation summaries listed above. Each was completed successfully. All validations employed worst-case parameters including reduced rinse steps, maximum dirty hold times, and soiling solutions appropriate for the equipment being cleaned. All deviations encountered seemed to be thoroughly investigated and the root cause was identified. Where necessary, if a run was found non-conforming, and b(4) consecutive runs were repeated. I found no issues with any of these validations.

2.1.3.1.4.1 –b(4)----------

The same general approach for cleaning validation applies to materials cleaned in the ---------- ----------–b(4)-consecutive runs were used for each load to demonstrate the cleaning process was effective. The following acceptance criteria were used for final ----b(4)----------

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The following summary validation reports were reviewed:

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- All validations employed worst-case parameters including reduced rinse steps, maximum dirty hold times, and soiling solutions appropriate for the equipment being cleaned. It should be noted

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All validations were successful. I noted that all calculated F_0 values (minimums from –b(4)------ as well as all accumulated from all –b(4)-) far exceeded the required minimum –b(4)-------. No growth was seen for any BI. All deviations encountered seemed to be thoroughly investigated and the root cause was identified. Where necessary, if a run was found non-conforming, and b(4) consecutive runs were repeated. I found no issues with any of these validations.

2.1.3.1.5 Process Simulation

To demonstrate sterility by aseptic processing, the firm ran process simulations using b(4) instead of product material in multiple steps of manufacturing. The following validations were carried out and reviewed:

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All of the validations above incorporated worst case challenge conditions including maximum hold times in between process steps and maximum number of operators. All deviations were investigated and a root cause was found and addressed appropriately. I reviewed both the initial and latest process simulation validations performed for the –b(4)---------- during our inspection of the –b(4)-------- facility. I found these acceptable.

2.1.3.1.6 Autoclaves

There are –b(4)- autoclaves used in –b(4)---which I reviewed. The –b(4)----------, is used for ----------b(4)----------, is used for media --b(4)---------- --- Validation of each unit included IQ, OQ, and PQ studies. Both IQ and OQ for each unit were similar. They included:

- Verification of all required documentation
- Calibration of all critical instruments

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successful with only one minor deviation noted which did not affect the qualification. I found no review issues.

2.1.3.1.7 Disinfectant Effectiveness

For the validation of disinfectant chemical agents each was individually tested on different surfaces: --b(4)----------. These –b(4)----- were contaminated with predefined micro organisms and tested before (to determine initial challenge organism concentration) and after exposure to the chemical agents. Each combination (micro organism – disinfectant) is validated by b(4) successive runs.

The validation conforms if for b(4) successive validation runs:

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All of the validations noted above met the acceptance criteria specific for each disinfectant's contact time. Standard USP microorganisms as well as in-house isolates were used as challenges. It is notable to mention that the majority of disinfectant effectiveness testing was performed previously in support of methods and materials used in GSK's Belgium facility. These validations are used globally. GSK did however include new validations to include --b(4)--- isolates into the studies.

2.1.3.2 Rixensart, ---b(4)---- ----------

The original validation protocols performed for support systems and equipment in Building – b(4)---------- were submitted previously:

- HiberixTM, STN BL 125347, approved 09 August 2009

The reviews which follow only cover equipment which are unique or new to the Menhibrix process in –b(4)----------

2.1.3.2.1 Process Simulation

The initial aseptic process simulation validations ---b(4)---------- conducted in the context of the Hib---b(4)---- process represent a worst case compared to the aseptic steps of the MenC and MenY process.

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They are used for following purposes:

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The firm performed IQ and OQ on these systems which included the verification and functional testing:

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The sanitization methods of the ---b(4)----------, used for the purification of TT and PS-TT respectively, are identical in both facilities ---b(4)----------. These validations have been reviewed and the details can be found below in section 2.2.1.4.3.

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2.1.3.2.3 –b(4)----------

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Cleaning validation for -b(4)----------, was not found in the original submission. I requested this information in my 04 June 2010 telecon with Norris Pyle of GSK.

2.1.3.3 Rixensart, -b(4)---------- (TT purification, --b(4)----------)

The logistic areas, support systems and equipment used in common for both coupling –b(4)---------- activities in Building –b(4)------, were submitted previously. The original validation protocols, performed for these logistic areas, support systems and equipment, were submitted and approved for these files or in their BLA supplements:

- 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
- HiberixTM, STN BL 125347, approved 09 August 2009

The reviews which follow only cover equipment which are unique or new to the Menhibrix process in –b(4)----------

2.1.3.3.1 Process Simulation

For the validation of the assurance of sterility during the –b(4)------ operations, the sequence of operation performed in production is followed but a growth medium of broad spectrum (--b(4)---

----------) is used instead of each product used in the process. Samples of growth medium taken before and after the Process Simulation must be able to support the growth of a possible contaminant (growth promotion test). Samples for sterility test, taken during and at the end of the Process Simulation must be negative. Environment tests are performed. For any environment test or contaminated sample, identification is performed by QC.
5 pages determined to be not releasable: b(4)

- Havrix®, ELA 96-1352, approved 31 March 1998 -b(4)------- and STN BL 103475, approved 30 July 2003 ---b(4)--------------
- Infanrix®, sBLA 103647 approved 30 July 2003 (---b(4)---- and STN BL 103647 - ELA 95-1926 approved 29 January 1997 & ELA 97-0359 approved 17 August 1998 -b(4)---
- Twinrix®, sBLA 103850 approved 30 July 2003 (-b(4)----) and STN 103850 - ELA 99-0152, approved 11 May 2001 ---b(4)---------
- Pediarix®, sBLA 103907 approved 30 July 2003 (--b(4)---) and STN 103907 - BLA 99-0800 approved 13 December 2002 -b(4)--------
- Boostrix®, BLA STN BL 125106 approved 03 May 2005 (--b(4)----) and sBLA 125106 approved 14 April 2006 -b(4)------------------
- Cervarix®, STN BL 125259/0, submitted 29 March 2007 (under review for approval)
- Rotarix®, BLA STN BL 125265, approved 03 April 2008 (--b(4)----------),
- Kinrix®, BLA STN BL 125260, approved 24 June 2008 (--b(4)----------),
- HiberixTM, STN BL 125347, approved 19 August 2009

Cleaning and sterilization of the equipment used for final bulk formulation (e.g. –b(4)--------) were initially validated and reported in conjunction with the products listed above. GSK provided reference to all relevant validation reports however, they were not included in this file. This seems acceptable given the fact that there were no new pieces of equipment used in Menhibrix formulation.

Additionally, the aseptic formulation process was initially validated through Process Simulation previously. As described in the Hiberix file and my review of that file, Process Simulations in --b(4)---------- cover the procedures found for multiple products which are manufactured in these areas. GSK provided reference to the relevant initial validations for Process Simulations in each formulation room. They also provided summary tables for their most recent Process Validation lots run from 2007 to 2009. All were passing. The deviations were not noted. I found this acceptable but ----b(5)----------