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Review Memo - August 5, 2009 - Hiberix

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: 125347/0

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: *Haemophilus b* Conjugate Vaccine (Tetanus Toxoid Conjugate) [Hiberix®]

Subject: **Review Memo** –, Original Application for *Haemophilus b* Conjugate Vaccine (Tetanus Toxoid Conjugate). Indication: active immunization as a booster dose in toddlers for the prevention of invasive disease caused by *Haemophilus influenzae* type b.

ACTION DUE: 5 August 2009

RECOMMENDATIONS: I recommend approval based on the submitted information and the results of the inspection, and with the following Post Marketing Commitment:

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

BACKGROUND

GlaxoSmithKline Biologicals (GSK), submitted their original Biologics License Application for Hiberix® on 17 March 2009. The vaccine is indicated for booster immunization against invasive disease caused by *Haemophilus influenzae* type b (Hib). The Agency confirmed with GSK on 12 December 2008 that the application would receive priority review status due to current vaccine shortages.

Hiberix® is a lyophilized vaccine containing 10µg of purified polyribosyl-ribitol-phosphate capsular polysaccharide (PRP) of Hib, covalently bound to approximately 25µg of inactivated tetanus toxoid (manufactured by -----b(4)-----) with 12.6mg lactose (stabilizer). It is reconstituted at time of use with supplied diluent (0.9% NaCl) in a prefilled syringe. Diluent is manufactured by -----b(4)-----.

The following review covers the drug substance manufacture up to the final formulation of the bulk drug substance. Review of the manufacture of the drug product is covered in a separate document.

The table below shows the specifications for the Hib-TT bulk Conjugate which are aligned to the latest revision of the -----b(4)----- monograph for *Haemophilus influenzae* type b conjugate vaccines -----b(4)-----.

[b(4)]

Changes since Initial License in Other Countries

GSK states that since the original licensing of Hiberix® in Europe (1996) and other countries, several changes to its manufacture have been implemented. Below is a table describing the changes and their rationale.

[b(4)]

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

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

Control of Materials

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[b(4)]

Control of Critical Steps

GSK states they classify in process controls as Quality Decision (QD) tests used to demonstrate the process is controlled and in Process Monitoring for process consistency evaluation and data accumulation for use during investigations. Consistency ranges have been established for both

GSK states the current bulks are stored in ----b(4)----- . Bulks may also be stored in ---b(4)-----
-----, though as discussed above, there is no data for bulks manufactured with the proposed
-b(4)- in the -b(4)- building that are stored in -----b(4)----- . GSK does provide extensive
supporting stability data for Hib-TT bulk stored in the -----b(4)----- that has been used for
Hiberix® sold in other countries. The data appear to indicate no difference in the final product after
storage in either type of container. The -b(4)- containers are closed with -----b(4)-----
---- caps, whereas the -----b(4)----- will be closed with ---b(4)----- caps.

GSK has not performed an extractable/leachable study on either the -b(4)- or ----b(4)-----
----- . See EIR for additional details. However, they have committed to perform the study and
submit the results to Agency before the --b(4)----- .

Stability

GSK states the critical stability attributes are -----b(4)----- and -b(4)- content as
monitored over -b(4)- months while stored at -b(4)- . All available stability data were discussed
above.

Facilities

Water Systems

Building -b(4)- is used for the production and purification of the -b(4)- bulk. ---b(4)-----water
comes from the municipal source ----b(4)----- located in buildings --b(4)---- (for
-----b(4)-----). --b(4)-- water is used for heat exchangers, condensers and the
production of chilled water. It is also used in the production of Purified Water and WFI.

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The WFI systems for the other Rixensart buildings are of similar design and operation as described above. Their qualifications and routine monitoring were reviewed during the inspection and are covered in the EIR. There were no objectionable issues noted.

Pure Steam

GSK states that the Pure Steam systems for buildings ----b(4)----- were previously reviewed and approved under the eight other U.S. licensed products manufactured at the -b(4)-- and Rixensart sites. At the Rixensart site the pure steam is generated in -b(4)- and is fed by

--b(4)--. For --b(4)-- Pure Steam is produced from ----b(4)----- by a pure steam generator located in ---b(4)---

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In -b(4)- the --b(4)-- system is comprised of a -----b(4)----- use points. The system was qualified through IOQ and certified by reference to the -b(4)- monograph for WFI. The IQ included review of documentation, protocols, instruments, and visual and mechanical inspection. Pressure testing and inspections were performed for the piping system. OQ included alarm testing, computer acceptance testing, document review, operational procedure, safety testing and inspection, functional evaluation under normal conditions, utilities supply, performance testing and point of use tests. Performance qualification and routine monitoring for all manufacturing areas involved in the production of Hiberix® were reviewed during the inspection and are found in the EIR. There were no objectionable issues noted.

Heating, Ventilation, and Air Conditioning

HVAC units servicing rooms where Hiberix® manufacturing operations are performed receive fresh air through the -----b(4)-----b(4)----- efficiency) before distribution to rooms. -----b(4)-----

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

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Installation, Operational and Performance qualification, and re-qualification for the HVAC systems for Hiberix® manufacturing areas were reviewed during the inspection and are found in the EIR. There were no objectionable issues noted.

Environmental Monitoring

Environmental monitoring was reviewed during the inspection and the discussion is found in the EIR. There were no objectionable issues noted. An operating procedure describes the routine EM program for each facility to monitor air (viable and non viable particle counts), surfaces and personnel with defined acceptance limits for all classified areas. The air monitoring includes airborne particle counts and active air monitoring at designated sites throughout the controlled rooms. All personnel working in Grade -b(4)-areas are monitored by --b(4)----- day after a critical operation and for ----b(4)-----location on the -----b(4)-----.

Computer Systems

The computer systems associated with Hiberix® manufacturing were reviewed during the inspection and the discussion is found in the EIR. There were no objectionable issues noted.

Computer systems used in --b(4)-- include the --b(4)----- Process Control and Supervision System (-----b(4)----- monitoring system; Chromatography Columns Process Control; --b(4)--- Unit Process Control and Supervision; and Alarm Management System (AMS). --b(4)-- provides an integrated automated system for --b(4)-- and --b(4)----- . Access is password controlled and permits the system administrator to assign privileges to individuals and helps prevent unauthorized operation. The program provides process control and monitoring of the ---b(4)-----; alarm handling; real-time view and trending; historical trending; ----b(4)-----; and control of the WFI -----b(4)-----.

Containment and Cross-Contamination Control

Change over procedures, validation of equipment cleaning and disinfectant qualifications were covered during the inspection. Refer to the EIR for discussions on these topics. There were no objectionable issues noted.

For --b(4)--- disinfectant validation covered bactericidal, fungicidal, sporicidal and/or viricidal effects of agents in use. Validations demonstrated the agent in solution or on surface has a bactericidal, fungicidal, sporicidal or viricidal effect when in contact with predefined organisms (USP microorganisms and In House Isolates or process microorganisms). Depending on the intended use of the agent, the validation was conducted with interfering substances to show the presence of

organic matter does not reduce the efficacy of the disinfectants. Agents were individually tested on -----b(4)----- (if applicable). --b(4)---- were contaminated with predefined microorganisms and tested before and after exposure. All agents were validated by

--b(4)-- successive runs. Agents used include -----b(4)-----

Room cleaning procedures and frequency in -b(4)-are discussed in the EIR and shown here in tabular format. Sampling to demonstrate cleaning include -----b(4)---- for the floor, walls, doors, air in-takes, product contact equipment, mobile and fixed equipment, and airlocks. Organisms used in -b(4)- include -----b(4)-----.

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[b(4)]

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[b(4)]

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[b(4)]

Segregation of contaminated equipment and control of contamination are managed by material and personnel flows, equipment and facilities design; use of air locks; closed systems; HVAC; sanitizing agents; fumigation; cleaning and decontamination procedures; personnel gowning; and changeover procedures.

Critical operations are performed in Class -b(4)- dynamic -b(4)- in Class --b(4)-- surroundings. Production surfaces are smooth and hard with -b(4)- coated floors. Walls and ceilings are---b(4)--- -- coated with -----b(4)---- paint. Light fixtures, windows, doors and control panels are flush, minimizing potential for dust build-up.

Shared facilities are designed for temporal, physical and operational segregation with separate access for personnel and materials; separate exit for product; dedicated personnel with access key cards; dedicated HVAC; dedicated WFI; dedicated decontamination stations; validated cleaning methods for shared equipment; dedicated wash rooms, storage rooms, and cold rooms.

Fumigation

The validation of fumigation by -----b(4)----- for the -----b(4)---- areas, material and personnel airlocks, and aseptic rooms, was reviewed during the inspection and is covered in the EIR. Additional information is provided below.

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Material Flow

Prior to entering process rooms, all product-contact materials are cleaned or cleaned and sterilized by --b(4)----. The outer wraps of sterile-wrapped materials used under -b(4)- are discarded prior to entering under -b(4)-.

All contaminated materials, accessories and clothes coming from the ----b(4)---- area are decontaminated by --b(4)-- prior to removal from the ---b(4)---area. All contaminated effluents from the manufacturing process are collected in --b(4)-- and decontaminated by --b(4)-- before discharge to the --b(4)-- system. ---b(4)--- rooms are not used for Hiberix®bulk process in --b(4) --.

Equipment Cleaning

Building -b(4)- is a multi-product facility and most equipment is shared. Non-shared equipment is single use and is tested to show that a --b(4)- ----- in endotoxin can be achieved. Equipment cleaning is --b(4)-- for all products. -----b(4)-----

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----- Results of the validation demonstrated successful cleaning and deviations appear to be satisfactorily addressed.

GSK cleans glassware, small materials and various ---b(4)--- containers by --b(4)-- washing. Methods of validation follow those as described. Materials cleaned by this method include columns, tubing, plastic funnels, and various caps. Results of the validation appear to demonstrate successful cleaning and deviations appear to be satisfactorily addressed.

Regarding routine testing for cleaning verification, the submission is very vague and merely states cleaning is performed according to the SOP which is readily available to the operator. However, during the inspection an investigator reviewing this topic collected two SOPs for the validation of --b(4)-- cleaning and for the mobile tanks. Both of these documents describe routine testing performed along side of the validation testing performed. For the ---b(4)--, testing includes --b(4)-- inspection and ---b(4)--- of the --b(4)--. For the mobile tanks, testing includes ---b(4)----- and

-b(4)-. Acceptance criteria are the same as described above.

Steam Sterilization

Validation of the autoclaves used in the manufacture of Hiberix® was reviewed during the inspection. There were no objectionable issues noted. Please refer to the EIR for detailed discussions. Additional discussions are provided here.

In addition to the autoclaves used for the sterilization of equipment and parts used in production, there is also an autoclave used for decontamination. The IOQ were performed followed by the PQ. -----b(4)-----

--- Results of the validation appear to demonstrate successful validation and the one deviation appears to have been satisfactorily addressed. All autoclaves are requalified ---b(4)--.

Additionally, there are -b(4)- stations dedicated to the -----b(4)- -----in facilities -----b(4)----- The IOQ was successfully completed. GSK states the PQ was based on the temperature measurement -----b(4)- ----- and on the associated --b(4)-- (4)-- with a microbiological challenge. Acceptance criteria include a minimum ---b(4)----- for b(4) minutes for all probes; no BI survives, sterile filters pass integrity testing; and all cycle phases are respected. The run time for validation was reduced from b(4) minutes to b(4) minutes under worst

case conditions (all tanks and associated piping were full). There were -b(4)- ruins completed. Results of the validation appear to demonstrate successful cleaning and deviations appear to be satisfactorily addressed.

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

b(4) is used to sterilize the -----b(4)----- and associated piping found in -b(4)-. Validation was reviewed during the inspection and no objectionable issues were noted. Please refer to the EIR for further discussions. Additional details are provided here.

Validations included a -b(4)- decrease in dwell time and reduction of -b(4)- in temperature and a biological challenge. All temperature probes were associated with a BI. Acceptance criteria include no BI survival, ---b(4)-----, all filters pass integrity testing, and pre- and post calibration of probes are compliant. Results of the validation demonstrated successful sterilization and deviations appear to be satisfactorily addressed.

Media Simulations: -b(4)-

Validation was reviewed during the inspection and no objectionable issues were noted. Please refer to the EIR for further discussions. Additional details are provided here.

Media used in validation must support growth as tested before and after the process. All samples collected must be negative for growth. The validation must simulate all controlled bioburden stages and aseptic stages of -b(4)- production using a growth medium of broad spectrum (generally, --b(4)-----). All the production sequences and operations must be respected. If using a closed system (--b(4)--), samples tested for sterility are first held for --b(4)-- before being sent for testing. The validation must cover -b(4)- successive successful runs.

For the ----b(4)----- run is performed using the maximum time allowed for aseptic manipulations and -b(4)- additional reduced time runs. In worst case conditions stages that require a -b(4)- hold are changed to -b(4)-, there is an increase in the time of manipulations, for -b(4)- steps there is a maximum of a ---b(4)--- followed by a ---b(4)----- temperature. Processes validated include the -----b(4)----- --; introduction of media to the ---b(4)-----; and the ----b(4)-----step.

Chromatographic Systems

There are b(4) columns used in the chromatography steps of Hiberix® manufacture. The IQ included functional tests for -----b(4)----- . The PQ required contamination with worst case process solution covering -----b(4)----- . The columns also require that they be ---b(4)--- free. Cleaning validation acceptance criteria are as described. Results of the validation data appear to be acceptable.

----b(4)---- *Systems*

Validation was performed to demonstrate the sanitization is effective and that the agent can be removed. Additionally, -----b(4)----- must be removed. Acceptance criteria include -----b(4)----- to the quantification limit of the dosage; ----b(4)----- are within specified limits. As before the worst case conditions for

cleaning were employed, in that the dirty hold was -----b(4)----- step to keep from -----b(4)----- . Cleaning validation acceptance criteria are as described. Results of the validation data appear to be acceptable.

Validations for Building ----b(4)---GSK states that the facilities validations have been approved previously for the eight other U.S. licensed products manufactured in this building. The requalification and re-validation of these followed the same methods as described. Successfully requalified systems include -----b(4)-----

----- . Review of the results for each of these systems appears to show successful requalification and deviations were satisfactorily addressed.

COMMENTS:

Though I recommend approval of this file, -----b(5)-----

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