

DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA, Center for Biologics Evaluation and Research

MEMORANDUM

Date: July 30, 2009

From: Tina S. Roecklein, M.S., Consumer Safety Officer, DBPAP, OVR

Through Milan Blake, Ph.D., Director, DBPAP, OVR

Subject: Product Review Memo for BLA Supplement 125347/0 (Hiberix)

Sponsor: GlaxoSmithKline (GSK)

To: File for 125347/0

Summary/Background:

On 17 March 2009, GSK submitted a Biologics License Application (BLA) for Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate). The proprietary name is Hiberix. Hiberix is a non infectious vaccine that contains Haemophilus b capsular polysaccharide (polyribosyl-ribitol-phosphate, PRP). PRP is a high molecular weight polymer prepared from *Haemophilus influenzae* type b strain 20752, covalently bound to tetanus toxoid (referred to as PRP-TT or Hib-TT). After purification, the conjugate is lyophilized in the presence of lactose as a stabilizer.

Hiberix is a lyophilized vaccine supplied in a 3 mL monodose Type -b(4)- glass container stoppered with a rubber closure 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. Each 0.5 mL single dose is formulated to contain 10 µg Hib covalently bound to -b(4)-inactivated TT. The one excipient used in manufacturing the vaccine is lactose. The diluent used in reconstituting the lyophilized Hiberix vaccine is 0.9% sodium chloride.

GSK is requesting an expiration dating period of 36 months at 2-8°C. The date of manufacture of the Hiberix final container vaccine is defined as the start date of filling into final containers.

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 Hiberix is currently licensed in 98 countries worldwide and has not been withdrawn from any country due to regulatory action or safety concerns.

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 in the context of the current shortage of vaccine for this recommended immunization. Licensure of Hiberix will provide an additional source of the monovalent Haemophilus b Conjugate Vaccine to the US market for both routine and catch-up booster vaccination.

Hiberix is intended to be indicated for active immunization as a booster dose for the prevention of invasive disease caused by Haemophilus influenzae type b in children 15 months through 4 years of age (prior to fifth birthday).

BLA Review of Drug Substance:

Manufacture of Drug Substance:

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

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Reference Standards and Materials:

A listing of the current reference standards and reference materials used in the QC testing are provided. The stability of QC reference standard materials is monitored on an ongoing basis by the use of an internal control. The internal control is a lot representative of the standard tested as unknown in parallel to the analyzed samples. Each time an assay is conducted; the test result for the internal control is analyzed and compared to an established consistency range. A trend analysis of the internal control test results is conducted periodically every -b(4)-months. The analysis is documented and approved by the QC supervisor in charge of the test. Any trend toward an out of consistency for the internal control would trigger an investigation and corrective action may be taken. Future reference lots produced in house needs to pass all the QC release tests. The determination of the titer of a new reference standard batch should be based on a minimum of -b(4)- independent measurements, unless properly justified and approved by QA. During the inspection, I reviewed for several of the reference standards, the Qualification Reports, the SOP for future replacement of reference standards, and the internal control trend analysis performed every -b(4)- months. I found no deficiencies.

BLA Review of Drug Product:

Composition:

The Hiberix final container vaccine is presented as a lyophilized preparation in 3 mL Type b(4)glass vials sealed with a rubber closure and flip off caps. The target fill dose per vial is -b(4)-Hib. Each vial of Hiberix vaccine is reconstituted with 0.7 mL of 0.9% Sodium Chloride Injection. A-b(4)- overage is implemented during the manufacturing of Hiberix final bulk in order to guarantee an effective injectable dose of 0.5 mL containing 10 µg of polysaccharide.

The immediate packaging materials used for the container-closure system are equivalent to those used for other vaccines manufactured by GSK. Composition of the Hiberix lyophilized vaccine reconstituted with saline diluent is presented in the table below.

Table 1 Composition of the Hiberix™ vaccine

Ingredients	Quantity (per dose 0.5 ml)	Function	Reference to quality standards
<u>Active ingredient</u>			
<i>Haemophilus influenzae</i> type b capsular polysaccharide (Hib) conjugated to tetanus toxoid (TT)	10 µg Hib and ~25 µg of TT	Immunogen	Ph. Eur. 1219
<u>Excipients</u>			
Lactose	12.6 mg	Stabilizer	Ph. Eur. 1061
<u>Diluent</u>			
Sodium chloride			Ph. Eur. 0193
			Ph. Eur. 0169

- Pharmaceutical form: lyophilised product, to be reconstituted with saline diluent before injection
- Presentation: monodose in 3 ml type I glass vials
- Administration: intramuscular injection
- Storage: +2°C to +8°C
- Overfill: a formulation overage of approximately [redacted] is applied in order to guarantee an effective injectable dose of 0.5-ml containing 10 µg of Hib PS
- Abbreviations: Ph. Eur. = European Pharmacopoeia
Hib (or PRP) = capsular polysaccharide (Polyribosyl Ribitol Phosphate)
TT = Tetanus Toxoid

Manufacturing Process Development:

In order to meet the increasing demand the following manufacturing changes were implemented.

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A summary of the manufacturing changes is in the table below. Each modification has been validated by production of at least b(4) consistency batches. Data is included in the file. Information related to these changes have been reviewed and approved by the regulatory authorities of countries in which Hiberix is licensed.

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

Validation of Hiberix drug product production process is performed through the demonstration of process consistency. A retrospective validation is included in which consistency of Hiberix process was assessed through the analysis of data of -b(4)- lots manufactured at -b(4)- (formulation) and -b(4)- (filling/lyophilization). These lots were compared to b(4) lots formulated, filled, and lyophilized at -b(4)-. Batch analysis data are provided for all lots. All lots met release specifications.

In addition, aseptic operations are validated according to regulatory guidelines. This includes media formulation studies and media fill studies.

Control of Excipient:

The only ingredient other than the active substance is lactose. Lactose included in the formulation of Hiberix is tested according to the current ----b(4)----- . Lactose used in Hiberix is manufactured from milk sources in the USA. Lactose is purchased from ---b(4)----- . Upon receipt, each lot of lactose is tested according to the GSK Monograph for lactose, which contains -b(4)- confirmatory tests.

Control of Drug Product:

The QC release specifications are outlined in the following tables as presented in the original BLA. Several specifications were added as QC Release tests to these products. Commitments were made by the firm to either develop/validate a new test or change the classification of existing tests from monitoring or Quality Decision to Quality Release. Specifications have been established using information from the testing of development and commercial batches. The limits proposed in the Ph. Eur. 1219 and WHO TRS N°897 was also taken into consideration. Trending of the specifications for release of Hiberix final bulk and final container was evaluated. The specifications appear to be justified by the trending data. A description of the tests and a summary of the validation data are included in the file. Validation data have been generated for methods developed by GSK. The tests performed in accordance with official pharmacopoeia monographs are considered to be validated. GSK requests to assess moisture content by --b(4)----- in replacement of ----b(4)----- (currently used for the release of non-US commercial batches) for the release of commercial batches. The change does not affect the acceptance criteria. A comparison study of ---b(4)----- versus ----b(4)----- was performed on both final container release and stability testing. I reviewed the study and found the methods to be similar.

1 Page determined to be not releasable: b(4)

In addition, the specification for Hib PS content by -b(4)- has changed from not less than -b(4)- of the target to between ---b(4)--- per dose.

Batch analysis results are presented in the file. Batches ----b(4)----- are fully representative of the manufacturing process for US commercial product. Many other batches analysis results are included. These batches are representative of the manufacturing process proposed for US commercial product, except for some specific aspect (such as a -----b(4)-----). All results meet specifications for all batches. Batches ----b(4)- ----- are manufactured from a -b(4)-----

QC release data on the first two lots of Hiberix manufactured for the US market (----b(4)-----) are provided in Amendment 17. All data meet specifications.

A list of current reference standards used in the testing Hiberix final container is contained in the file. The control of reference standards and materials for drug product is similar to drug substance. A more detailed explanation can be seen above.

Stability:

Hiberix vaccine stability has been assessed by long term, real-time stability studies, accelerated stability studies and after reconstitution of the vaccine with the saline diluent. Stability data have been generated after 36 months of storage at 2-8°C. The main characteristics studied in stability are -----b(4)- ----- content. These parameters remain stable overtime. Based on the data, GSK is requesting an expiration dating period of 36 months at 2-8°C.

The vaccine lots included in the stability studies are summarized in the table below. Batches for the US market will be manufactured at -b(4)- and stoppered with the -b(4)- stoppers (Batches ----b(4)-----). The other batches are representative of the manufacturing process proposed for US commercial product, except for some specific aspect (such as a -----b(4)-----).

[b(4)]

The tests performed during stability studies are: -----b(4)-----

----- Analytical methods for these tests are those proposed for routine QC release testing. The proposed test method for water content is ---b(4)- ---- to replace ---b(4)----- . A comparison study of these two methods was performed and the results obtained showed the methods to be similar. It should also be noted that GSK harmonized the specification for the free --b(4)- ----- for all EU registered Hib-containing vaccines in final container. Some of the older stability data has a specification of -b(4)-

All lots meet specifications, except for moisture content on -b(4)- lot (----b(4)-----) at time-point -b(4)- months. A summary of the OOS investigation was reviewed. A slight --b(4)- --- in moisture content is observed overtime. Moisture content values are, on average, slightly --b(4)---- for lots -----b(4)- ----- compared to lots ---b(4)----- . The OOS result was with product using the --b(4)- ----- stoppers will be used for US marketed product.

-b(4)- lots of lyophilized Hiberix representative of Hiberix intended for the US market, i.e., manufactured at -b(4)- and stoppered with ----b(4)---- stoppers (Lots -----b(4)-----) were stored at 2-8°C for up to -b(4)- months and were tested for critical parameters. Study is ongoing and all lots meet specifications up to that point in time. GSK commits to complete the long-term, real-time stability study testing at ---b(4)----- . The --b(4)-- lots of Hiberix placed on stability were manufactured from the same formulation batch. There are no other data using the current manufacturing process for US product. GSK has committed to place -b(4)- lots on stability during the first year of approval.

-b(4)- lots of lyophilized Hiberix final container vaccine manufactured at -b(4)- and stoppered with -b(4)- stoppers (lots -----b(4)-----) were stored at 2-8°C for 36 months and were tested for critical parameters. Study is completed and all lots meet specification, except for moisture content on one lot at time-point -b(4)- months.

-b(4)- lots of lyophilized Hiberix final container vaccine manufactured at -b(4)- and stoppered with -b(4)- stoppers (lots ----b(4)-----) were stored at 2-8°C for 36 months and were tested for critical parameters. Study is completed and all lots meet specification.

-b(4)- lots of lyophilized Hiberix final container vaccine manufactured at -b(4)- (small scale facilities, around -b(4)- vials per batch) and stoppered with -b(4)- stoppers (lots ----b(4)-----) were stored at 2-8°C for 36 months and were tested for critical parameters. Study is completed and all lots meet specification.

Because there is only -b(4)- months of data on product using the current manufacturing process for US product and the lots placed in this study (Lots ----b(4)-----) were manufactured from the same formulation batch, GSK has committed to place-b(4)-lots on stability during the first year of approval. These-b(4)-lots will be tested according to the more stringent ICH Guidelines. After the first year, --b(4)- -- per year is intended to be followed for real-time stability according to the stability plan outlined in the below table. Stability data have been obtained on Hiberix final container vaccine reconstituted with saline diluent.

There is no ongoing stability of final bulk as part of the original BLA. The firm provided justification on why bulk stability was not necessary. During a teleconference on 30 July 2009, the firm committed to provide a plan/protocol to perform on-going --b(4)-- stability studies on -b(4)- of Purified Hib-TT bulk conjugate per year.

The package insert states that reconstituted vaccine can be stored for up to 24 hours between --b(4)-----. The current ongoing stability protocol only addresses reconstitution with the description test. The 24 hour hold time after reconstitution is not addresses as part of the ongoing stability program in the original BLA. During a teleconference on 30 July 2009, the firm committed to revise the labeling in that the reconstituted vaccine can be stored for up to 24 hours between 2 and 8 oC. In addition, the firm committed to evaluate reconstitution as a part of their ---b(4)- stability plan. The firm plans to store the reconstituted stability sample for a minimum of 24 hours before testing.

1 Page determined to be not releasable: b(4)

Hiberix final container vaccine lots have been included in accelerated stability studies at ----b(4)- days and-b(4)-days. All lots meet the specifications. A slight --b(4)- ----- in moisture content can be observed. This has already been observed and discusses in the section above. An evaluation of -b(4) was not performed in all the accelerated stabilities. In the accelerated stability study in which-b(4)-was evaluated (Lots ----b(4)-----), no change in -b(4)-was observed. An evaluation of -b(4)- is being performed during routine stability.

Stability data have been obtained on Hiberix final container vaccine reconstituted with saline diluent. Stability was assessed after reconstitution with saline diluent and storage ---b(4)----- for 24 hours at --b(4)----- . Specifications were met for all parameters tested.

Drug Product – Diluent:

The 0.9% sodium chloride diluent is manufactured by -----b(4)-----
----- . The composition of the diluent is -----b(4)- -----
----- The diluent is ----b(4)- -----

The diluent for vaccine reconstitution is filled in Type-b(4) glass syringes fitted with rubber tip caps. Plunger stoppers are of ---b(4)----- . Plunger stoppers and tip cap are latex-free. A -b(4)- -month shelf life is currently proposed for the 0.9% sodium chloride diluent to be used for Hiberix vaccine reconstitution. The diluent may be stored at 2-8°C or 20-25°C. The test method procedures and acceptance criteria for the -b(4)--- diluent are included in the file. A test for description and an identity test (identity sodium and chloride) are performed at GSK before use in manufacture. The diluent is labeled and packaged at GSK -b(4)-.

BLA Review of Adventitious Agents:

Hiberix vaccine components are biotechnology products derived from bacterial seeds. Culture media that could support bacterial or fungi growth are used. Therefore, starting materials are tested for microbiological purity according to the relevant requirements or Notes for Guidance when available and possible microbial contamination during production is monitored. The raw materials used during production are ---b(4)- ---- by -----b(4)- ----- before use. Environmental monitoring is in place at all stages of manufacture.

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

Lactose is used as an excipient for the vaccine. Lactose is obtained from -b(4)- milk. Milk is sourced from the US and is collected from healthy animals in the same conditions as milk collected for human consumption. No other animal materials are used.

Some materials of animal origin were used in the preparation of the active ingredients. Upon FDA request, a new *Haemophilus influenzae* type b seed system was developed to maximize the dilution of materials of animal origin used in the production of the previous seeds. The only material of animal origin used in the preparation of the new -b(4)- and -b(4)- seeds is ---b(4)- ----- is obtained from hygienically collected and veterinary approved --b(4)----. The -b(4)- are exclusively sourced from ---b(4)-----. The meat and corresponding ---b(4)- ----- have been approved “fit for human consumption”.

The only materials of animal origin used in the preparation of Hib bulk antigen are --b(4)----- (see above). The culture medium contains ----b(4)-, an ---b(4)----- derived from -b(4)- sourced from USA, -b(4)----- or --b(4)----. -b(4)- is derived from milk sourced from healthy animals fit for human consumption.

Product information, as well as certificate of origin of the animals and veterinarian certificate are included in the file. It is concluded that all raw materials of animal origin used in the manufacturing process of Hiberix are in compliance with current US requirements.

BLA Review of Lot Release Protocol:

The proposed lot release protocol is included in the file. I reviewed the lot release protocol for the following:

- Is all the required information needed for approval of CBER lot release provided in the protocol?
- Is the lot release protocol consistent with other licensed US products?

BLA Review of Exemption from General Safety Test:

The General Safety Test (GST) was performed for each lot of Hiberix final container vaccine, as part of the release specifications, until 2002. The test was performed on guinea-pigs and mice according to the ----b(4)- ----- 21CFR610.11, and ---b(4)- ----- All lots of Hiberix final container vaccine tested prior to the discontinuation of the GST in 2002 (-b(4)- lots) met the acceptance criteria.

In ---b(4)-----, Vaccine, 1997, arguments were presented as to the usefulness of the ---b(4)- ----- for vaccines. The arguments include that the number ---b(4)- ----- of animals tested and the use of a single dose makes it unlikely that any toxic contamination could be detected. Based on this information, the -----b(4)- ----- session to delete the -b(4)- for certain human vaccines and for other vaccines to allow the omission

of the -b(4)- if a sufficient number of vaccine lots have passed the test. ----b(4)- -----
----- in which the GST is no longer required for routine
release of final container vaccines. Based on extensive experience with Hiberix and in
agreement with the ---b(4)- ----- and other international regulatory authorities, the
test was discontinued in 2002.

The manufacturing process and quality control tests performed on Hiberix adequately
characterize the product and validate its safety. Specific examples of the process and
quality control tests are listed. Justifications that the GST is unnecessary include the
following.

- Due to the nature of the test, it is unlikely to detect any toxic contamination.
Consequently, the test was no longer required for routine release of final
container vaccines by ----b(4)-----.
- Prior to discontinuing the test, all-b(4)-lots passed the requirement of -b(4)- and
GST.
- The GST was originally used to detect extraneous toxic contaminants in
biological products intended for humans. Following the implementation of
various technological advances in the manufacture and aseptic processing of
products as well as incorporation of stringent in-process and final product
quality control requirements, the relevance of the -b(4)- can be questioned.
- Release testing for Hiberix, which includes sterility, ----b(4)- content, and
identity, continues to provide assurance of safety, purity, and potency.
- GST requires intraperitoneal injection. The route of administration is not
relevant to the route of administration used to deliver Hiberix to humans.
- GSK strives for harmonization of specifications and testing for all markets,
wherever possible and appropriate.

GSK proposes that the General Safety Test requirement be waived and that the QC
release tests for Hib seeds through Hiberix final container be considered alternatives to
assure the quality attributes of the vaccine. A listing of all-b(4)-lots tested from 17 March
1994 to 23 December 2002 is included with polysaccharide content results. All GST
results passed.

I concur that the General Safety Test requirement can be waived for Hiberix with the
caveat that ---b(4)- ----- is added as a release test for either Final Bulk or Final
Container. GSK committed to add ----b(4)- ----- as a release test for final formulated
bulk.

Information Requested from Original Submission dated 17 March 2009:

I performed a thorough review of all the summarized information above. Based on the
review I discovered the following deficiencies that were communicated to GSK.

Lot Release Protocol:

I noted that there was no flow diagram or table providing information on the strains used in the manufacture of tetanus toxoid and Hib polysaccharide, master and working seed lot numbers, and bulk lot number (Hib and Purified Tetanus Toxoid from --b(4)---). In addition, dates of manufacture for PS, TT, -b(4)--- PS, conjugate, etc. are not included. This information was already requested by DPQ in a 2 June 2009 Information Request (#1).

Specification for Hib Polysaccharide Content:

I noted that for the Batch Analysis Data in Section 3.2.P.5.4, some of the results for Hib Polysaccharide Content are greater than -b(4)-. The specification is not less than-b(4)- of the target. There is no upper limit to this specification even though you could not have more than -b(4)-. An upper limit should be added. This information was already requested by another product reviewer in the 21 May 2009 Information Request (#IIC1).

Information Request Communicated During Inspection on 8 June 2009:

1. Manufacture of Purified Hib

The manufacture of Purified Hib is described in Section 3.2.S.2.2. During the --b(4)----- (Section 2.4.2), it is stated that the polysaccharide is ---b(4)- -----
----- (Section 2.4.3), ----b(4)- -----

----- For both these steps, there is no maximum volume mentioned. I deferred this question to the other product reviewer who was on the inspection since he was going over batch records in detail.

2. Justification of Specifications

The justification for the release specifications for Hib-TT Conjugate (Drug Substance) is outlined in Section 3.2.S.2. Specifications applied to Hib-TT are aligned to the latest revision of -----b(4)----- . In addition, the justification states that the limit is based on historical data. The justification for the release specifications for Hiberix (Drug Product) is outlined in Section 3.2.P.5.6. The release limits, where proposed, have been established using information from the testing of development and commercial batches. The limits proposed in ---b(4)- ----- was also taken into consideration. I requested to see the trending of historical data for the release tests for both drug substance and drug product. I was given the trending and the limits appear to be justified.

I also requested if the release specification for Free Hib Polysaccharide for Hiberix had been changed from ---b(4)- -----The current specification is -b(4)- - ---but some of the older data had the specification as -b(4)--. The specification has indeed been changed in 1998 to align all Hib products. The limit was also changed for the stability specification. This change was approved by the

appropriate regulatory authorities. Information on the stability specification was requested in the 29 May 2009 Information Request #6.

3. Reference Standards (Sections 3.2.S.5 and 3.2.P.6)

The reference standard for Free Polysaccharide Content for Hib-TT is Hib lot --b(4)----. The reference standard for Free Carrier Protein for Hib-TT is TT lot --b(4)----. The reference standard for Identity Testing for Hiberix is Hiberix vaccine lot ---b(4)----- . The reference standard for Hib Polysaccharide content by -b(4)- for Hiberix is Hib-TT conjugate lot ----b(4)----- . The reference standard for Free Polysaccharide by --b(4)- --- for Hiberix is Hib lot -b(4)----- .

I asked to see the following related to the above reference standards.

- Qualification reports for the reference standards
- SOP for future replacements of reference standards
- The internal control trend analysis that is done every -b(4)- months

I reviewed the above information and found all of it to be acceptable.

4. Control of Excipients in Hiberix (Lactose) – Section 3.2.P.4

The -----b(4)-----, incorporated in Hiberix lyophilized vaccine is lactose. I asked the firm what confirmatory tests are performed on lactose by GSK before use in production. I also asked to see the method qualification for each test.

Upon receipt, each lot of lactose is tested according to ---b(4)----. A list of -b(4)- confirmatory tests was provided. I reviewed the Certificate of Analysis from both --b(4)----- . I reviewed the GSK monograph for lactose and the corresponding GSK Certificate of Analysis. Compendial methods are considered validated. A verification of suitability under conditions of actual use is performed during the first use of a method. Verification is based on the assessment of the complexity of the procedure testing to which the verification is applied. Verification is not required for common compendial tests that are routinely performed in the laboratory. The lack of method qualification for --b(4)- of the confirmatory testing for lactose was cited as a 483 item during the pre-approval inspection.

5. --b(4)- ---- as Release Test for Hiberix Moisture Analysis – Section 3.2.P.5.1

GSK proposes to assess moisture content by ---b(4)- ---- in replacement of ---b(4)- ----- (currently used for the release of non-US commercial batches) for the release of commercial batches. The change does not affect the acceptance criteria for moisture, which remains as “---b(4)-----”. I asked the firm if they had any results for release using the --b(4)- ----- method.

All US commercial lots will be released using the ---b(4)- ---- method. The older stability data was obtained by either ---b(4)- ----- method only or both methods. All new stability data will be obtained using the ---b(4)- ---- method only. A comparison study was performed on both final container release and stability testing. I reviewed the study and found the methods are very similar. This question ties in with a question asked in the Information Request on 29 May 2009 (#4).

6. Moisture Content during Stability – Section 3.2.P.8.3

During stability studies, a slight --b(4)- ----- is observed overtime for moisture content. All moisture content values provided in the file are within specification except for lot Hib--b(4)----- . I asked for the study into the ---b(4)- --in moisture content overtime.

The root cause from the investigation into the --b(4)- in moisture content is the --b(4)---. Moisture content values are, on average, slightly -b(4)- for lots ---b(4)- ----- compared to lots -----b(4)- ----- For Hiberix for the US market, the -----b(4)- ----- has been replaced by --b(4)- ----- so this should hopefully not be an issue. For non-US marketed Hiberix, the ---b(4)- ----- is still used. For these products the end of shelf-life specification for moisture content was --b(4)- ---- from ----b(4)----- . This question ties in with a question asked in the Information Request on 29 May 2009 (#5).

7. Validation of Working Seed Viability Protocol #20060040

I reviewed Protocol #20060040, Validation of Working Seed Viability (Quality Appendices – Facilities & Equipment Section). The study showed that there is no loss of viability after-b(4)- years of storage. The study concludes that the storage is validated and routine monitoring will be performed upon production of commercial batches. I asked what routine monitoring is and is this documented.

Routine Monitoring is that viability will be continued to be tested -b(4)-. The working seed was manufactured in -b(4)-. The validation protocol was performed from ---b(4)----- . The protocol concluded that there is no loss of viability after -b(4)- of storage. Starting in 2009, the responsibility of the routine monitoring -b(4)- viability testing) will be transferred to the Stability Unit. A formal stability plan is being drafted to follow the viability of the working seed. This question ties in with a question asked in the Information Request on 21 May 2009 (#IIa1).

During the inspection, I was informed that this Protocol was submitted to the file in error. There is no narrative linked to this protocol and it was mistakenly submitted while still in draft format. The firm plans to withdraw this protocol from the file. Because this was important to have in the file, I requested the final

validation report be submitted to the file (Information Request on 19 June 2009 #5a).

8. Validation of Inactivation by ---b(4)----- (Protocol #20050116)

I reviewed Protocol #20050116, Validation of Inactivation by ---b(4)- ----- (Quality Appendices – Facilities & Equipment Section). The aim of the validation protocol was to determine the inactivation duration of Haemophilus influenzae type b -----b(4)----- . I asked for clarification on the following:

- Please provide the data for the additional runs in which the time and ---b(4)- ----- were varied to determine the worst case condition.
- Please justify the use of a small scale study instead of the performing the study on production scale.

The firm provided me with the data from one study performed in -b(4)- and two studies performed in -b(4)-. The -b(4)-study evaluates the ---b(4)- ----- at the -b(4)- scale. The first -b(4)- study at the -b(4)- scale compares inactivation ---b(4)----- . The study concluded that the worst case -b(4)----- was -b(4)- . The study also concluded that ---b(4)- ----- could not be determined at production scale (-b(4)-) since complete inactivation occurs too quickly (i.e., in some cases at time -b(4)- minutes). This is because the -b(4)-----does not start until all ---b(4)- ---- reach the required ----b(4)----- . Therefore, the -b(4)- study was performed at worst case -b(4)----- on small scale.

During the inspection, I was informed that this Protocol was submitted to the file in error. There is no narrative linked to this protocol and it was mistakenly submitted while still in draft format. The firm plans to withdraw this protocol from the file. Because this was important to have in the file and all studies were not included in the original application, I requested the final validation report be submitted to the file (Information Request on 19 June 2009 #5b).

9. Validation of Tetanus Toxoid Storage Duration (Protocol #20050214)

I reviewed Protocol #20050214, Validation of Tetanus Toxoid Storage Duration. It was unclear as to what hold times were being validated. The firm explained the validation to me. The lack of complete hold time validations resulted in a 483 item (#3) during the pre-approval inspection. This question ties in with a question asked in the Information Request on 21 May 2009 (#Ib5).

During the inspection, I was informed that some protocols were submitted to the file in error. There is no narrative linked to the protocols and the protocols were still in draft form. I thought that the firm was planning on withdrawing this protocol. Because this was important to have in the file, I requested the final validation report be submitted to the file (Information Request on 19 June 2009

#5). I later found out that this protocol was not one of the protocols that were asked to be withdrawn.

10. TT from -b(4)-

I asked if the TT coming from -b(4)- is the same material that can be used in -- -b(4)-. It was explained to me that the nonadsorbed TT purchased from -b(4)- can either be used in the manufacture of Hiberix or --b(4)----- . GSK also receives adsorbed DT from -b(4)-. This can be used in the manufacture of ----b(4)-----.

Information Request on 21 May 2009:

II. Process Validation

a. Working seeds

- 1. In section m.2.3.S.2.3.1 you state that -b(4)-----for working seed Lot ---b(4)- -- is measured at --b(4)- ---- per year. Your current data demonstrate that working seeds are stable for at ----b(4)-. What expiration date have you assigned to your working seeds? Will you continue to measure -----b(4)- ----- measurement on the working seeds?**

The firm responded to this request in Amendment 17. Expiration dates are not assigned to Hib working seed lots. GSK will measure ----b(4)- ----- to ensure -----b(4)- ----- of the initial --b(4)----. The Stability Master Plan describing GSK's process for --b(4)--- testing of the Hib working seed is provided in the amendment.

- 2. In section m.3.2.S.2.3 you propose that future working seed changes be reported in your annual report. Please be advised that working seed changes cannot be reported in an annual report in the absence of an approved comparability protocol containing detailed written procedures regarding the process and acceptance criteria to be used for replacement of a working seed. We do not agree the information you have provided is sufficient to allow for reporting of replacement of working seeds via an annual report. Please provide a detailed comparability protocol supporting this request. Alternatively, you may submit a Prior Approval Supplement (PAS) with a comparability protocol for -b(4)- replacement of working seeds post-approval.**

The firm responded to this request in Amendment 17. A written comparability protocol for controlling and qualifying changes in the working seed is provided. There is not sufficient detail in the comparability protocol. Detailed procedures for the production of -b(4)- working seed are not included. Details of testing procedures with specifications are not provided. The comparability protocol is not detailed enough to support reporting of replacement of working seeds via an annual report. This was communicated to the firm in a 30 July 2009 teleconference. The firm withdrew the comparability protocol in Amendment 19 and therefore will not submit working seed changes in the Annual Report. The firm plans on submitting a complete comparability protocol with the next change in working seed as a prior approval supplement after licensure.

b. Hold Time Validations

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

-----.

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

-----.

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

-----.

2. **Regarding the Purified TT manufactured at --b(4)- ---- - please specify the hold time and provide validation data supporting the hold time for this ---b(4)-----.**

1 Page determined to be not releasable: b(4)

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

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

6. Regarding the manufacture of Hib-TT (section m.3.2.S.2.5), no validation data are provided supporting the proposed b(4) hour hold time of the sterile Hib-TT.

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

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

IV. Stability

a. Please provide a plan/protocol to perform on-going -b(4)- stability studies on bulk products.

Please note that this overlaps with the June 19 Information Request #4. They will be handled in this section together.

The firm responded to this request in Amendment 17. The firm does not want to commit to perform -b(4)- stability studies on -b(4)- of purified Hib-TT bulk conjugate per year. The firm provided their justification on why bulk stability was not necessary. The firm provided their plans to obtain the consistency/trending of stability indicating parameters for the Hiberix batches produced during the year, evaluating the ---b(4)- -----
----- entering these drug products in lieu of performing ongoing

stability studies on bulk products. I do not concur with the plan provided by GSK. This was communicated during a 30 July 2009 teleconference. The firm commits to place -b(4)- lot of Hib-TT bulk on stability per year.

GSK commits to provide a plan/protocol to perform on-going -b(4)- stability studies on -b(4)- of Purified Hib-TT bulk conjugate per year by ---b(4)-----

Information Request on 29 May 2009:

Hold Time Validation

- 1. You state that Hiberix final formulated bulk can be stored for b(4) days at b(4) °C prior to filling (section m.2.3.P.3.2). Please provide validation data supporting this hold time.**

The firm responded to this request in Amendment 17. Validation data supporting this hold time was provided.

Batch Analysis of Hiberix

- 2. You provide in section m.2.3.P.5.3 batch analysis results on Hiberix final container. Batches ---b(4)----- are all manufactured from a single formulation batch. These were the only lots provided using the current manufacturing process. Please provide the batch analysis results for b(4) additional lots using the current manufacturing process.**

The firm responded to this request in Amendment 17. Batches ---b(4)----- were manufactured using the current manufacturing process for US licensed product. The other batches provided in the BLA are representative of the manufacturing process proposed for US commercial product. This means that these lots were manufactured at all steps in exactly the same conditions as lots intended for the US market, except for a specific aspect such as ----b(4)-----, etc. The changes in these specific aspects have shown to have no impact on product quality.

QC release data on the first b(4) lots of Hiberix manufactured for the US market are provided in the Amendment. Data for lot ----b(4)----- are provided. All data are within release specification.

Stability

Section m.2.3.P.8.4, Hiberix Stability Data

3. **You provide (up to b(4) months) data for Hiberix lots ----b(4)-----
----- manufactured under your current
manufacturing process. Please clarify whether these lots are manufactured
from the same formulation batch. Please confirm that the additional stability
lots provided are not manufactured using the current manufacturing
process, and specify the differences between the current and previous
manufacturing processes. Please provide the stability results for additional
lots using the current manufacturing process.**

The firm responded to this request in Amendment 17. GSK confirms that the final container lots were manufactured from the same formulation lot. The additional stability lots provided in the BLA are not manufactured using the current manufacturing process. The differences in these lots are in the --b(4)-----
-----, etc. These changes have been validated to show no impact on product quality. GSK plans to finish the study on the above Hiberix lots. I concur with the 36 month expiration date for Hiberix with the caveat of the below PMC.

GSK commits to follow -b(4)- US commercial lots in stability according to the stability plan provided in Amendment 17 (Table 17). The lots of Hiberix placed on stability will be manufactured from different formulation batches. The study will be submitted to the license application file for review upon completion. After the first year of approval, GSK commits to have ----b(4)----- per year followed in stability. The stability data will be available for review during inspection.

4. **All stability results provided for moisture are determined using the
--b(4)----- method. However, you propose to use the ---b(4)-----
method for moisture determination on stability. Please provide any results
you may have on stability using the ---b(4)----- method.**

The firm responded to this request in Amendment 17. Several Hiberix final container lots were tested by both the -----b(4)-----
methods at release. Results are provided in the Amendment. The values obtained by both methods are similar.

5. **Lot ---b(4)----- had an out-of-specification result for moisture content at
b(4) months. Please provide the investigation into this result.**

The firm responded to this request in Amendment 17. A summary of the investigation is included in the Amendment. A ----b(4)----- in moisture is observed overtime for all lots. Moisture content values, on average, are slightly -b(4)--- for lots -----b(4)----- compared to lots --b(4)----- with the -b(4)--- stoppers. The OOS result was with product using the ----b(4)-----
The -b(4)-- stoppers will be used for US product.

6. Lots -----b(4)----- have a --b(4)----- of not more than -b(4)- The other stability data provided in this section have a specification for ----b(4)----- of not more than b(4). Please comment.

The firm responded to this request in Amendment 17. GSK harmonized the specification for the ----b(4)----- for all EU registered Hib-containing vaccines in final container.

Section m.2.3.P.8.5 Hiberix Stability Data

7. Accelerated stability data for Hiberix is provided in section .2.3.P.8.5. Stability results for b(4) are only provided for lots -----b(4)----- . Please provide b(4) results for the additional lots in this section.

The firm responded to this request in Amendment 17. Results for b(4) on additional lots followed in accelerated stability studies are not available. Stability results for b(4) are provided for lots -----b(4)----- . An evaluation of b(4) is also being performed during routine stability.

Diluent Manufacture

8. You provide in section m.2.3.P a summary for production of the diluent used for reconstitution of Hiberix. You state that -----b(4)----- manufactures and tests the diluent. Please provide a copy of a Certificate of Analysis for a recently received lot from --b(4)--. Please specify what confirmatory tests you perform on the --b(4)-- diluent. Please explain how the b(4) month shelf life was determined (i.e., by -b(4)- or GSK). Please provide any additional stability testing performed by GSK.

The firm responded to this request in Amendment 17. A Certificate of Analysis for a recently received lot from --b(4)-- was provided. A test for description and an identity tests (identity sodium and chloride) are performed at GSK on 0.9% saline diluent received from --b(4)-. The data to support the b(4) month shelf life of diluent comes from both --b(4)-- and GSK.

QC Methods and Validation

9. You provide in section m.3.2.S.2.4 a listing of the in process quality decision tests and the QC release tests for the manufacture of Hib, Purified --b(4)---- TT, and PSAH. You also provide a listing of in process quality decision tests for Hib-TT. For each of these tests, a summary is provided of the method and validation. For each test, please submit a detailed SOP and validation report.

The firm responded to this request in Amendment 17. A listing of in-process and QC release tests, including SOP and validation report numbers, are provided in the amendment.

- 10. **You provide in section m.3.2.S.2.4 a listing of specifications for QC release of Hib, Purified and --b(4)----- TT, and PSAH. You provide justification for the specifications as the limit is based on historical data. Please provide the historical data analysis performed to set these specifications.**

The firm responded to this request in Amendment 17. Historical data are provided for the QC release tests. Trending data is provided from 01 January 2006 to 31 December 2008.

- 11. **You state in section m.3.2.S.2.4.2 that Purified Tetanus Toxoid is received from ----b(4)----- . Please provide a copy of a Certificate of Analysis for a recently received lot from --b(4)----. Please specify what confirmatory tests you perform on the Purified Tetanus Toxoid.**

The firm responded to this request in Amendment 17. A copy of a Certificate of Analysis of a recently received lot from -b(4)- is provided. --b(4)----- TT is tested at GSK for sterility, -----b(4)-----
----- content and absence of ---b(4)-----

- 12. **You state in section m.3.2.S.2.4 that Effectiveness of -----b(4)----- is an in process quality decision test during Hib manufacture. Please provide trending data for this test for the last 2 years.**

The firm responded to this request in Amendment 17. Trending data was provided for the last 2 years. All results passed specification.

Information Request on 19 June 2009:

Note: The additional release specification should be added to the Lot Release Protocol. We were planning on calling the firm on 06 July 2009 to clarify this. This did not happen because the firm responded to these requests on 06 July 2009.

Specifications

- 1. **We feel that the following tests are important for confirmation of safety and efficacy of product. Please add the following QC Release tests with appropriate specifications.**

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

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

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

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

(4) -----b(4)----- with a specification for
b(4) of polysaccharide and % of PS eluted before -b(4)-

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

c) QC Release Tests for the Purified Hib-TT bulk conjugates (Section 3.2.S.4.1)

(1) b(4)

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

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

(2) Residual -b(4)-

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

d) QC Release Tests for the Hiberix final container (Section 3.2.P.5.1)

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

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

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

(2) ~~---b(4)-----~~
~~-----~~
~~-----~~

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

(3) ~~---b(4)-----~~

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

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

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

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

(5) **Tetanus Identification**

The firm responded to this request in Amendment 17. The -b(4)- QC release test for Hib identity performed on Hiberix final container is designed to recognize (identify) the Hib-TT conjugate. The -b(4)- test for Hib identity is specific for both Hib and TT. I concur that an additional test is not needed.

(6) ~~---b(4)-----~~

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

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

Hold Time Validation

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

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

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

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

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

Stability

4. **Please provide a plan/protocol to perform on-going -b(4)--- stability studies on -b(4)- of Purified Hib-TT bulk conjugate per year. Please provide details in your protocol to ensure that the same bulk conjugate lot is not represented in both bulk stability and final container stability.**

Please note that this overlaps with the May 21 Information Request #IV a. They will be handled in that section together.

Validation Protocols (Section 3.2.A.1)

5. **Please provide complete validation reports for the following:**

a. **Validation of the Haemophilus Influenzae Working Seed (WS) Viability in Building #-b(4)-**

The firm responded to this request in Amendment 17. The validation report is not located in Annex 2 as stated in the Amendment. The firm committed to provide the requested validation in a 30 July 2009 teleconference. The firm provided the requested validation in Amendment 19.

b. Validation of the inactivation process by --b(4)----- treatment Haemophilus Influenzae Type B

The firm responded to this request in Amendment 17. The validation report is not located in ---b(4)----- as stated in the Amendment. The firm committed to provide the requested validation in a 30 July 2009 teleconference. The firm provided the requested validation in Amendment 19.

c. Validation of the Tetanus Toxoid Storage Duration

The firm responded to this request in Amendment 17. During the teleconference on 13 July 2009, this request was clarified. Protocol 20060040 was already submitted to the file.

Information Request on 29 June 2009:

The current ongoing stability protocol only addresses reconstitution with the description test - upon reconstitution the sample shall be a clear, colorless solution. The 24-hour hold time after reconstitution needs to be addressed as part of your ongoing stability program (see 21 CFR 211.166).

The package insert states that reconstituted vaccine can be stored for up to 24 hours between --b(4)----- . The current ongoing stability protocol only addresses reconstitution with the description test. The 24 hour hold time after reconstitution is not addresses as part of the ongoing stability program in the original BLA. During a teleconference on 30 July 2009, the firm committed to revise the labeling in that the reconstituted vaccine can be stored for up to 24 hours between 2 and 8 °C. In addition, the firm committed to evaluate reconstitution as a part of their --b(4)-- stability plan. The firm plans to store the reconstituted stability sample for a minimum of 24 hours before testing.

GSK commits to provide a plan/protocol to address the 24 hour hold time after reconstitution during on-going -b(4)- stability by -----b(4)-----

Amendments Received:

Amendment #1 received 31 March 2009:

- Clinical

Amendment #2 received 15 April 2009:

- UNII Codes

Amendment #3 received 21 April 2009

- Clinical

Amendment #4 received 30 April 2009

- The response to SOP and Validation Questions (DPQ)
- GSK is correcting an error in the acceptance criteria for the test “----b(4)-----
-----” which was inadvertently submitted as “--b(4)-----
-----”. The correct acceptance
criteria for the test “----b(4)-----” have been
corrected to read “-----b(4)-----
-----”. Five sections were updated to reflect this.
- -b(4)- currently performs the test for -b(4)- content by -----b(4)----- on
the Hib-TT bulk conjugate drug substance. -b(4)- was not identified as a
testing site in the initial BLA. This amendment updates the appropriate
sections.

Amendment #5 received 1 May 2009

- Facilities

Amendment #6 received 8 May 2009

- GSK outlines plan to supply -b(4)--- doses to public and private marketplace
in 2009.

Amendment #7 received 21 May 2009

- Clinical (Concept Protocol)

Amendment #8 received 11 June 2009

- Advertising and Promotional Material
- Logo

Amendment #9 received 15 June 2009

- Responses to 11 May 2009 Information Request (DPQ)
- Partial Response to 21 May 2009 Information Request (DPQ)

Amendment #10 received 17 June 2009

- Clinical (Concept Protocol)

Amendment #11 received 17 June 2009

- Facilities (Container Closure)
- Pharmacovigilance

Amendment #12 received 19 June 2009

- Facilities
- Removal of 5 validation protocols that were submitted in Annex 6. These
protocols have no reference to them in the narrative part of the text. These
protocols were in draft and should not have been submitted. This protocol
numbers are 20050116, 20060040, 20070679, 20050489, and 20040645. Two
of these protocols (20060040 and 20050116) were those that I requested in the

19 June 2009 Information Request. This error was discovered during the Pre-Approval Inspection.

Amendment #13 received 10 July 2009

- Labeling

Amendment #14 received 6 July 2009

- Responses to 483 issued during Preapproval Inspection

Amendment #15 received 24 July 2009

- Labeling including ----b(4)----- calculation

Amendment #16 received 24 July 2009

- Clinical (Concept Protocol)

Amendment #17 received 27 July 2009

- Responses to Information Requests of 21 May 2009, 29 May 2009, 19 June 2009, and 13 July 2009 (CMC and DPQ)

Amendment #18 received 27 July 2009

- Amended responses to 483 issued during Preapproval Inspection

Amendment #19 received 31 July 2009

- Post Marketing Commitments
- Lot Release Protocol
- Final Responses to CMC Issues
- Package Insert

Post Marketing Commitment Recommendation:

Based on the review of all the submitted information, I would recommend the following post marketing commitments be obtained from GSK before approval.

Regarding Stability

1. GSK commits to provide a plan/protocol to perform on-going -b(4)- stability studies on --b(4)-- of Purified Hib-TT bulk conjugate per year by ---b(4)----- ----. The bulk b(4) chosen for stability will not be the same b(4) which is used to manufacture the Hiberix final container placed on stability.
2. GSK commits to follow -b(4)- US commercial lots in stability according to the stability plan provided in Amendment 17 (Table 17). The lots of Hiberix placed on stability will be manufactured from different formulation batches. The study will be submitted to the license application file for review upon completion. After the first year of approval, GSK commits to have --b(4)----- batch per year

followed in stability. The stability data will be available for review during inspection.

3. GSK commits to provide a plan/protocol to address the 24 hour hold time after reconstitution during on-going annual stability by 31 December 2009.

Regarding Hold Time Validation

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

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

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

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

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

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

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

Regarding Addition of QC Release Testing

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

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

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

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

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

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

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

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

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

Approval Recommendation:

Based on the review of all the submitted information, I would recommend approval of Hiberix vaccine with the above CMC post marketing commitments. I would recommend a 36-month expiry period for this product when stored at 2-8 °C.