



MEMORANDUM

Date: May 3, 2010

To: Joseph Temenak, HFM-481
Chair, BLA Review Team

APPROVED

By Rajesh K. Gupta, Ph.D. at 6:20 pm, May 06, 2010

From: Rajesh K. Gupta, Ph.D., HFM-407
Deputy Director, Division of Product Quality (DPQ) and
Lab Chief, Product Quality Laboratory Staff

APPROVED

By William M. McCormick at 10:31 am, May 07, 2010

Through: William McCormick, Ph.D., HFM-407
Director, Division of Product Quality (DPQ)

Subject: STN 125363 — Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine, Hib-MenCY-TT, MenHiberix®, Review of Drug Substance and Drug Product Analytical Procedures

Cc: William McCormick, Ph.D., HFM-407
Milan Blake, Ph.D., HFM-425
Willie Vann, Ph.D., HFM-437

Review of the analytical procedures, associated validation protocols and reports and specifications on the Drug Substance and Drug Product of the Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine, MenHiberix®, was performed by the staff of Division of Product quality (Reviewers from DPQ: Rajesh K. Gupta, Alfred Del-Grosso, James Kenney, Manju Joshi, Karen Campbell, Hsiaoling Wang, Nora Etz, Joe Progar, and Brandon Duong).

SUBMISSIONS REVIEWED

STN 125363/0, Sections 3.2.S.4.2, 3.2.S.4.3, 3.2.P.5.2, 3.2.P.5.3, Documents related to Methods in Section 3.2R

STN 125363/0.1 (amendment received 08/27/2009), List of SOPs, validation protocols and validation reports for the Drug Substance and Drug Product

STN 125363/0.3 (amendment received 02/08/2010) Additional method validation documents, Batch analysis data on clinical lots

STN 125363/0.4 (amendment received 03/03/2010) Additional method validation documents

STN 125363/0.7 (amendment received 04/21/2010) Additional methods related documents, responses to specific question related to methods and supply of reagents for in-support testing

METHODS REVIEWED

Drug Substance, -----b(4)-----

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Drug Product

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RECOMMENDED ACTION

The data submitted to support the analytical methods used for the testing of Drug Substance and Drug Product and related specifications for the Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine, MenHibrix® were reviewed. A number of issues with regard to the adequacy of method validations have been identified. Specifications for certain methods are wider than the data from lots used in the clinical trials. Additional information and documentation are required to further evaluate the Biologic License Application of this vaccine

DETAILED REVIEW AND COMMENTS

Analytical procedures, the associated validation protocols and reports and specifications for the drug substance and drug product were reviewed. A number of concerns and questions about the methods have been identified in the original submission and subsequent amendments submitted up to April 30, 2010. These deficiencies are described below.

A. Adequacy of Analytical Methods and Specifications

1. Test for –b(4)----- at Drug Substance. –b(4)-----
----- This test is performed on the
-b(4)----- and the Drug Product. Typically, --b(4)----- for
polysaccharide-protein vaccines –b(4)----- to monitor and control
purity of monovalent conjugates. Please provide a rationale for –b(4)-----

2. Specifications for –b(4)----- (tetanus toxoid) at Drug Substance. Specifications
for –b(4)-----, tetanus toxoid, for MenC-TT and MenY-TT conjugates at
not more than –b(4)- are wider than the data provided on clinical and commercial
consistency lots. Please revise these specifications to be consistent with the data
or justify the proposed specifications.
3. Specifications for Free Saccharide for MenY-TT Conjugate. Specification for
Free Saccharide for MenY-TT conjugate at not more than b(4) is wider than the
data provided on clinical and commercial consistency lots. Please revise this
specification to be consistent with the data or justify the proposed specification.
4. Clinical consistency lots for Drug Product have been tested for free saccharide for
Hib, MenC and MenY. This test was not performed for the commercial
consistency lots and has not been proposed for the commercial product. Since
Free Faccharide is a good stability indicator for the product, please provide the
rationale for discontinuing this test on the drug product.
5. Drug Product contains sucrose and is not tested for sucrose. Please include a test
for sucrose at the Drug Product.

B. General Comments on Analytical Method Validation

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

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

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

C. Tests on Drug Substance

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

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

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

Documents Reviewed

10 pages determined to be not releasable: b(4)

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

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

13. Sterility Test

The test is performed according to the -(b)(4)-. (Method of analysis.-b(4)- test for sterility of the product to be examined, --b(4)-----), to 21 CFR (Method of analysis 610.12 Sterility) and to ----- -b(4)-----
----- . The method has been evaluated for ---b(4)----- activities of monovalent bulk conjugates, Hib-TT, MenC-TT and MenY-TT.

Documents Reviewed (SOP 9000002125 not provided)

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CBER's Comments

The method is suitable for intended purpose.

D. Tests on Drug Product

Documents Reviewed

3.2.P.5.2 Analytical Procedures (Hib-MenCY-TT GSK Biologicals) and

3.2.P.5.3 Validation of Analytical Procedures (Hib-MenCY-TT GSK Biologicals)

1. Sterility Test (section 1.1 and 2.6 of m3.2.P.5.2, SOP 9000002125 not provided) for both Final Bulk and Final Container

Test is performed according to the current –b(4)---- (Method of analysis –b(4)-
Test for sterility of the product to be examined, -b(4)-----), and to 21
CFR (Method of analysis 610.12 *Sterility*) and to current ----b(4)- Sterility Tests
by the –b(4)----- method using –b(4)-----
-----The method has been evaluated for –b(4)-----
activities of formulated bulk and Drug Product.

Documents Reviewed

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

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

CBER's Comments

The method is suitable for intended purpose

2. Identity of MenC and MenY conjugates by –b(4)----

The identity of Neisseria meningitidis polysaccharide - Tetanus Toxoid conjugate
is determined by ---b(4)----- PS-
TT conjugates in test samples are captured by anti-TT ---b(4)-----

----- Absorbances are read by –b(4)-----
----- The identity is positive when the absorbances are higher than that of
the background. The method has been evaluated for linear dose response curve
and has been validated for range, precision, reproducibility, accuracy and
specificity.

Documents Reviewed

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CBER's Comments

Identity by –b(4)- for the MenC-TT and Men-Y TT conjugates in Drug Product is established by a qualitative method. This method has been validated as a quantitative test for certain parameters such as precision and accuracy. Based on data from the validation reports, criterion for a positive test (absorbance of a test sample higher than the background or higher than the lower asymptote of the standard curve) is not stringent enough. Please establish criteria for a positive identity as absorbance of the test sample to be equal to or higher than the absorbance at –b(4)-- of the standard curve.

3. Identity of Hib-TT by –b(4)--

- SOP 9000007241: Determination of the conjugate (-b(4)-) of *Haemophilus influenzae* type b by -b(4)---
- Validation Protocol QCB153VALM001/1: Validation of the PRP-TT Identity test by ELISA.
- Validation Report QCB153VALM001/1: Validation of the PRP-TT Identity test by ELISA.

The method is suitable for intended purpose.

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CBER's Comments

The method is suitable for intended purpose.

5. Determination of PSC and PSY Content in the Final Containers by –b(4)---

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

Documents Reviewed

- SOP 900010691 (Translation of Procedure 90000010677 ver 01)
Determination of PSC and PSY Content in the Final Containers by –b(4)---

- Validation Protocol 9000006058 PVM001/01/V2.0, *Neisseria meningitides*.
Validation of the Assay “PS Content by ---b(4)-----” for Final
Containers HiB-MenCY
- Validation Report 9000006058 RVM001/01/02/V1.0, *Neisseria meningitides*.
Validation of the Assay “PSY Content by –b(4)-----” for Final
Containers HiB-MenCY
- Validation Report 9000006058 RVM001/01/01, *Neisseria meningitides*.
Validation of the Assay “PSC+PSY Content by –b(4)-----” for
Final Containers HIB-MenCY

CBER's Comments

- i. Section 5.5.1 SOP 9000010691, Please specify the procedures used to quantify the titre of the PSC-TT and PSY-TT bulks used as reference standards.
- ii. Section 5.7.3 SOP 9000010691, Please describe a rationale for the algorithm used to calculate PSC content from the total (PSC+PSYcontent) and PSYcontents. In particular please explain the basis for the factors 5.25 and 9.5 in this equation.

- iii. Section 5.8 SOP 9000010691, Validity Criteria. As a ---b(4)----- method, assay validity should include an evaluation of system suitability to verify the adequacy of resolution and reproducibility. This should include evaluation of injection precision, --b(4)----- resolution and peak symmetry. ----b(4)----- may be consulted for recommendations. Please submit a procedural revision to include system suitability evaluation.
- iv. Range is defined from a proportional relationship between the theoretical and the calculated values from the standard curve. Please re-evaluate range to include the measurement of precision across the intended range of the procedure.
- v. Precision (Repeatability) has been evaluated on the basis of ---b(4)-----

specific analyst. As defined in ICH Q2(R1), repeatability expresses the precision under the same operating conditions over a short interval of time. ICH Q2(R1) recommendations are that repeatability should be assessed using either a minimum of 9 determinations covering the specified range of the procedure or a minimum of 6 determinations at 100% of the test concentration. Please submit an evaluation of repeatability consistent with these recommendations.

6. ---b(4)----- of Hib-TT Conjugate by -b(4)-----

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

The method has been validated for Precision (Repeatability, Intermediate Precision); Robustness; Stability indicating assay, Accuracy and Specificity of
-b(4)-----

Documents Reviewed

- SOP 9000010110, (Translation SOP 9000006816-ver 02), Haemophilus influenzae type b: Determination of the -b(4)----- of HIB in the
----b(4)-----.

- Validation Protocol QCNP066PVM001/01 (9000004369): *Haemophilus influenza* type b: Determination of the ---b(4)-----
-----of *Haemophilus influenza* type B on the ---b(4)-----.
- Validation Report QCNP066RVM001/01 (9000004369): *Haemophilus influenzae* type b: Determination of the ---b(4)-----
----- of *Haemophilus influenza* type B on the ---b(4)-----.

CBER's Comments

The method is suitable for intended purposes. As a ---b(4)----- method, assay validity criteria should include an evaluation of peak symmetry or tailing factor. Please submit a revised procedure to include symmetry of the ---b(4)----- system suitability parameter.

7. ---b(4)----- of MenC-TT and MenY-TT Conjugates by ---b(4)-----

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

The method has been validated for Precision (Repeatability, Intermediate Precision); Robustness; Stability indicating assay, Accuracy and Specificity of ---b(4)-----

Documents Reviewed

- SOP 9000010603 (Translation SOP 9000006776-ver 02), b(4) Determination of individual polysaccharides in final container Hib Men CY by ---b(4)-----

- Validation Protocol 9000002109 PVM001/01: *Neisseria meningitidis* Validation of the method “---b(4)----- on FC HibMenCY
- Validation Report 9000002109 RVM001/01/01: *Neisseria meningitidis* Validation report of the method “---b(4)----- on FC HibMenCY

- Validation Report No. 9000002109 RVM001/01/02: *Neisseria meningitidis*
Validation report of the method “-----b(4)-----
on FC HibMenCY

CBER’s Comments

- i. Type and different lots of –b(4)----- have significant effect on the results of –b(4)----- test for the drug substance and drug product samples. This has been mentioned in several documents, including SOPs, validation documents, and batch analyses records. CBER is aware the sponsor qualifies the –b(4)----- for this test and the sponsor has supplied a screened and qualified –b(4)----- to CBER for the testing of HibMenCY vaccine. Please provide a comprehensive report on the effect of different types of –b(4)----- on determination of –b(4)----- and also the SOP used to qualify the ---b(4)-----
- ii. As a ---b(4)----- method, assay validity criteria should include an evaluation of peak symmetry or tailing factor. Please submit a revised procedure to include –b(4)----- peak symmetry as a –b(4)----- system suitability parameter.

8. -b(4)---- content by ---b(4)-----

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

Documents Reviewed

- SOP 9000006236 (Translation SOP 9000001055-ver 04), --b(4)----- in Polysaccharides and in the -----b(4)-- -----

- Validation Protocol QCB253VALM006/1, -b(4)-- Content Determination in HibMenCY Vaccine by -----b(4)-----
- Validation Report QCB253VALM006/1, -b(4)--- Content Determination in HibMenCY Vaccine by -----b(4)-----

CBER's Comments

Important sample -b(4)- parameters are not described in the -b(4)----- procedure. Please submit a revised SOP to include sample -b(4) beginning temperature, heating rate and ending temperature

9. Endotoxin content by ---b(4)----- (section 2.7 of m3.2.P.5.2).

Endotoxin is measured by the -b(4)----- method as described in the current -(b)(4)--. (Method of analysis ---b(4)----- and to the current ---b(4)- Bacterial Endotoxins Test. The method has been evaluated for maximum valid dilution and recovery of -b(4)----- into samples.

Documents Reviewed (SOP 9000002991 not provided)

- Validation Protocol VALQC-A-033-M, Endotoxin test following the -b(4)-----
- Validation Report VALQC-A-033-0149, Endotoxin Test on -b(4)-----

CBER's Comments

The test is suitable for intended purposes.

10. General Safety – Abnormal Toxicity (sections 2.14 and 2.15 of m3.2.P.5.2)

The test is performed according to the -----
-----b(4)- the CFR (Food and drugs. General biologicals products standards. *General safety. 21CFR610.11*) and the WHO (TRS 800). The test is performed in guinea pigs and mice.

Documents Reviewed (SOP 9000002699 Not provided)

- Validation Protocol, QCA035VALM001, Validation of method of General Safety test on mice and on guinea pigs.

CBER's Comments

The method is consistent with 21 CFR 610.11 and is suitable for intended purpose.