



CBER REGULATORY REVIEW MEMORANDUM

Date 13 January, 2015

From Dr. James L. Kenney, Chief
Laboratory of Microbiology, ---(b)(4)-- Testing and Standards (LMIVTS)
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To Biologics License Application Submission Tracking Number # 125546/0

Subject BLA: Review of Bioburden, Sterility and Bacterial Endotoxin Test Method
Qualifications for Multicomponent Meningococcal Group B Vaccine (recombinant,
adsorbed) Bexsero[®]

Through Dr. William M. McCormick, Director, DBSQC/OCBQ/CBER/FDA

Applicant Novartis Vaccines and Diagnostics, Inc.

Product Multicomponent Meningococcal Group B Vaccine (recombinant, adsorbed) Bexsero[®]

Biologics License Application (BLA) Submission Tracking Number (STN) 125546/0**Submission Received by CBER** 03 July, 2014**Review Completed** 13 January, 2015**Material Reviewed**

Method qualifications for: 1) bioburden performed on the ----(b)(4)----- and 2) sterility and ----(b)(4)----- performed on the drug product (DP). In addition, the following were reviewed: ----(b)(4)----- release specification, to include the associated amendments: 1) 125546/0.9 – received on 03 September; 2) 125546/0.15 - received on 29 September; 3) 125546/0.27 – received on 21 November; 4) 125546/0.35 – received on 15 December; and 5) 125546/0.36 – received on 19 December, 2014.

Executive Summary

After a thorough review of this BLA, this reviewer finds Novartis Vaccines and Diagnostics, Inc. (Novartis)'s bioburden, sterility, and -(b)(4)- methods were qualified in accordance with --(b)(4)-----, respectively, by demonstrating the Meningococcal Group B vaccine (MenB vaccine) matrix is suitable for these intended test methods. In addition, CBER finds the ----(b)(4)----- Test provides the same level of purity assurance as the ---(b)(4)---- method and therefore, finds it acceptable for use as a pyrogen test in addition to the --(b)(4)--. Furthermore, CBER finds (b)(4) release specification acceptable for approval in this BLA.

Background

Novartis submitted this BLA on 16 June, 2014 requesting priority review based on the designation of breakthrough therapy, which was awarded to Novartis on 01 April, 2014. Even though Novartis (Cambridge, MA) submitted this BLA request, the MenB vaccine is manufactured by their affiliate Novartis Vaccines and Diagnostics S.r.l., in Sovicille, Italy. Novartis' MenB vaccine is indicated for the active immunization against invasive disease caused by *Neisseria meningitidis* serogroup B strains in subjects 10 through 25 years of age. Bexsero[®] is available as a white opalescent liquid suspension for intramuscular injections in pre-filled, single dose (0.5 mL) syringes and is to be administered as two doses with an interval of at least a month between doses. Each 0.5 mL dose contains sodium chloride (3.125 mg), histidine (0.776 mg), sucrose (10 mg) and water for injection up to 0.5 mL.

The multicomponent MenB vaccine is composed of three purified recombinant *Neisseria meningitidis* serogroup B protein antigens, that is: Neisserial adhesion A (a single protein), Neisseria Heparin Binding Antigen (a fusing protein) and factor H Binding Protein (a fusion protein); and also includes the main antigen of the outer membrane vesicles derived from *Neisseria meningitidis* serogroup B strain NX 98/254 (a.k.a., PorA P1.4). Bexsero[®] contains 50 µg of each of the three purified recombinant protein antigens, with 25 µg of the PorA P1.4 and 1.5 mg of aluminum hydroxide per 0.5 mL dose. Due to the presence of ---(b)(4)----- in the outer membrane vesicles from this non-recombinant component of Novartis' MenB vaccine, the bacterial endotoxin concentration of the DP is higher than most other injectable vaccines.

The Division of Biological Standards and Quality Control (DBSQC) reviews BLAs and their supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted

product samples and review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on: 1) bioburden method performed on their MenB (b)(4); 2) the sterility and --(b)(4)-- method qualifications performed on MenB DP; 3) the approval of the -----(b)(4)----- Test; and 4) the --(b)(4)-- release specification.

Review

Bioburden Test Qualification for MenB ----(b)(4)-----

-(b)(4)-

-(b)(4).

The bioburden results on their conformance -----(b)(4)----- showed 0 CFU/100 mL, which was within their proposed bioburden test specification -----(b)(4)-----.

The DBSQC usually only reviews the bioburden test method validation that is performed furthest downstream in the production process; for example: if it is a final product release test or performed before filtration of the final product. However, during the review of their lot-release protocol it was determined Novartis was not performing their bioburden test method in accordance with (b)(4)- for each of the three recombinant proteins. Novartis agreed to comply with the requirements of (b)(4)- and will qualify and implement this modified test method by the third quarter of 2015; this change will be reported by Novartis in their annual report in accordance with 21 CFR §610.12(d)(2)(i). Since the final product is tested for sterility, CBER is confident the releasing of final product before the implementation of this change is not a risk to public health.

Sterility Test

Novartis qualified their MenB DP using their -----(b)(4)-----method by performing -----(b)(4)----- qualification studies on (b)(4) lots (i.e., numbers: -----(b)(4)----- to demonstrate their matrices are suitable for the intended test method. In addition, Novartis performed additional(b)(4) studies on three different DP lots (i.e., numbers: -----(b)(4)----- to demonstrate their matrices did not exhibit anti-microbial activity against the most frequently observed environmental contaminants isolated at the Novartis Rosia

facility. Note: MenB --(b)(4)-- were used in these (b)(4) tests and CBER finds this acceptable as the -----(b)(4)----- the final container DP. Novartis reported these results in their validation report (CST 07.001 VR 59), entitled ‘Validation of Analytical Procedures, Sterility (4CMenB – Suspension for Injection in Pre-filled Syringe)’. Note: Novartis abbreviates their MenB as 4CMenB (i.e., Multi-Component Meningococcal B Vaccine).

Qualification – -----(b)(4) Sterility Test Method

Novartis qualified their MenB DP matrix using (b)(4) of Bexsero[®] in -----

-(b)(4)-

-(b)(4).

Endotoxin

Novartis performs their BET using the -----(b)(4)----- method (SOP: 201708 – formerly CQS 07.149) on their MenB DP matrix in accordance with ---(b)(4)--.

----- (b)(4) ----- Test (b)(4) Method Qualification

Novartis qualified their (b)(4) for the MenB DP by testing ----- (b)(4) -----
----- to verify the product matrix is suitable for the intended test method; while assessing sample
matrix suitability they also assessed the intermediate precision and robustness of the method.

-(b)(4).

-(b)(4).

----- (b)(4) -----
 ----- In addition, CBER performed licensing support bacterial endotoxin testing using a (b)(4) method on these same DP lots (i.e., 131601, 131701 and 131801) using a 1:10,000 sample testing dilution and our results (i.e., 3,450, 3,190 and 2,830 IU/mL, respectively; Note: this licensing support test result memo is included in the STN file) were on average (b)(4) lower than Novartis' results; this could partially be explained by the use of (b)(4) kits from different manufactures. However, the BET results obtained from Novartis and CBER on these three lots are roughly --- (b)(4) --- percent of their release specification, respectively. The bacterial endotoxin specification of ----- (b)(4) ----- for MenB DP was calculated based on data from (b)(4) clinical lots of MenB (i.e X38D27N1, X38D28N1, X38D29N1, 090101 and 101601, which were manufactured on ----- (b)(4) -----; respectively), with bacterial endotoxin concentrations results roughly --- (b)(4) --- IU/mL (respectively); CBER finds it interesting that the average value of these lots is roughly two fold less than the proposed release specification, so the following to information request was submitted to Novartis on 03 September, 214:

CBER finds your bacterial endotoxin specification of --- (b)(4) --- does not reflect your production process capability, as the lots submitted in support of this application have a bacterial endotoxin concentration that is over 2 fold lower than the specification. Please lower this specification so it is more in-line with your process capability.

Novartis replied stating they understood why CBER was challenging their specification, but stated they justified this specification based on calculations from their available clinical lots. Then they further justified this specification using a capability analysis from (b)(4) production batches. However, the only supporting data provided from these calculations was a graph depicting the results of their process capability analysis; therefore on 15 September, 2014 CBER submitted the following IR:

CBER requests the details of the data of (b)(4) clinical lots and the analyses performed to justify the bacterial endotoxin specification of --- (b)(4) ---; to include the production dates, BET results and lot numbers of clinical lots, analyst who performed each endotoxin result, estimates of variance components, and calculation of degree of freedom by Satterthwaite's approximation used in computing the one-sided 99% prediction interval. Please also provide justification for calculating the upper bound of 99% prediction interval on the data in the natural log scale, while the data of (b)(4) batches show no significant deviation from normality.

CBER requests the supporting documentation and calculations for the process capability analysis performed on the (b)(4) batches used to justify the bacterial endotoxin specification of --- (b)(4) ---; to include their production dates, BET results, matrix phase(s) (i.e., DP or DS) and batch/lot numbers.

In addition, CBER requests the details of all production process changes impacting bacterial endotoxin concentrations during the production time frame for both the clinical lots and (b)(4) batches used to justify the bacterial endotoxin specification, as mentioned above, to include the implementation dates and the subsequent lots impacted by the change.

Novartis' replies were reviewed with the statistician assigned to this file and it was determined there is a lot of variability between the lots and also between the analyst/method/(b)(4) detection kits variability (which is confounded). The individual analyst replicate results - in general - have less precision than should be used to generate this data (i.e., the average %CV results for the data set was 11.7%, with a N of (b)(4); but since Novartis averaged this data into a reportable result - it could be considered acceptable. It was determined Novartis' production process could have more control to decrease the variability seen between lots. So CBER submitted the following information requests to Novartis on 03 December:

- 1) *Please provide additional method development and validation data to address the following:*
 - a. *That variability is controlled such that DP release specification is supported and justified;*
 - b. *That variability is controlled such that DP stability testing results in useful trending data that do not have recurring out-of-trend and OOS results;*
 - c. *That assay robustness, sample handling procedures, and testing sample dilution are included in the re-evaluation and optimization of this assay; and*
 - d. *That variability is controlled such that DP release specification is supported and justified.*
- 2) *The relationship between --(b)(4)- endotoxin levels and endotoxin content levels reported in final DP does not appear to be consistent. Please comment.*
- 3) *The product release specification for Endotoxin Content of DP is upper bounded only and should be both upper and lower bounded. This becomes apparent upon review of product composition and release test data provided in amendment number 9 received September 2014.*
- 4) *The (b)(4)-- release specification for endotoxin content per microgram protein is upper bounded only and should be both upper and lower bounded*
- 5) *Please clarify the history of changes to BET used for DP release and stability testing explaining the following:*
 - a. *The changes that were made and the date and purpose of each change; and*
 - b. *The version of the test used in each lot of product released.*
- 6) *Based on the data from the stability testing, the assay does not appear to be performing as validated. Please provide an analysis that compares the testing performed in support of the product stability with that performed during routine release testing. Please describe any differences with regard to testing dates, operators, equipment or system suitability results that might explain the increase in variability seen for the stability tests. Please include any changes to the assay made since validation.*

Novartis' detailed responses can be found in amendment 125546/0.35, which summarizes data from three technical reports (i.e., TR 292507, TR 294387 and TR 292581) that address results from specific developmental work aimed to identify and minimize sources of variability within their assay. As a result of this developmental work, Novartis re-evaluated the assay's robustness, sample handling procedure and testing sample dilution and updated their assay in 2012, which reduced its variability and brought it into alignment with assay performance exhibited when testing this product at (b)(4). Novartis believes their current assay's overall performance and consistency has improved since it was up-dated in 2012. The residual variability measured during their stability testing after assay improvement studies were implemented was approximately 16%, compared to approximately 18% variability measured during the original assay validation. Therefore, Novartis believes their proposed BET assay is suitable for monitoring endotoxin content over time as part of their stability program. In addition, Novartis stated there is no relationship between --(b)(4)-- endotoxin levels and endotoxin content levels reported in the final DP, as more than ---(b)(4)-- batch is normally used during DP batch formulation and that the formulation process takes into account --(b)(4)-- endotoxin concentrations when assigning a theoretical '(b)(4) related endotoxin content'.

CBER suggested in the latest IR that Novartis develop a lower bound for the DP endotoxin specification and for the (b)(4). This was inspired upon review of release test data for a number of recently manufactured lots (data submitted in Amendment 15) where a 3 standard deviation range either side of a mean of ---(b)(4)--- established a range of ----(b)(4)----- (99.7% of manufacture lots should fall within this range). This was interpreted as an opportunity to measure endotoxin content as an indication of manufacturing consistency and therefore prompted the request to consider a lower bound

in the DP (b)(4) specifications. However, further discussion with product reviewers has clarified that even lower endotoxin levels may be desirable to be attained and may not be detrimental to the immunogenicity and efficacy of the vaccine antigen. Novartis declined the request and described quality assurance procedures that require an investigation of any release test value exceeding a 3 standard deviation range from a sequential trending mean regardless of whether the result is in spec or not. With this response, CBER is assured that unusually low DP endotoxin levels are investigated to assure product attributes remain appropriate.

After complete review of Novartis' reply to CBER's information requests and considering that supporting data used to justify the DP release specification was generated using an improved version of the assay, this reviewer agrees with the Statistical reviewer and finds the upper bounded specification to be justified and acceptable. The determining factor for setting the licensed specification for bacterial endotoxin was based on the risk to public health and safety, as the lots at the upper limit of the proposed specification has been shown to be clinically safe and there is enough historical data to support this. Therefore after review of the test qualification results, CBER's licensing in-support test results and the information contained in this license application and its many amendments, this reviewer concludes their (b)(4) was performed and qualified in accordance with ---(b)(4)-- and the MenB DP matrix is suitable for this test method and that DP endotoxin specification is appropriate.

In addition, CBER finds the -----(b)(4)----- Test provides the same level of purity assurance as the ----(b)(4)-- method and therefore, finds it acceptable for use as a pyrogen test in addition to the (b)(4). Novartis performs their pyrogen [4CMenB – Suspension for Injection in Pre-filled Syringe] test method in accordance with ---(b)(4)---- using a product sample diluted (b)(4) in (b)(4), injected intravenously at ---(b)(4)----- the marginal ear vein of each rabbit.

Conclusions

After a thorough review of the information submitted in this BLA, this reviewer finds Novartis' bioburden, sterility, and --(b)(4)-- methods were qualified in accordance with -----(b)(4)-----, respectively, by demonstrating the MenB vaccine matrix is suitable for these intended test methods. In addition, CBER finds the -----(b)(4)-----Test provides the same level of purity assurance as the -(b)(4)-- method and therefore, finds it acceptable for use as a --(b)(4)- test in addition to the -(b)(4)--. Furthermore, CBER finds -(b)(4)-- release specification acceptable for approval in this BLA.