Review of Novartis' responses to the CR Letter Memo - Menveo

MEMORANDUM – Final Review

To:	Administrative File; STN 125300/0 – Meningococcal ACWY Conjugate Vaccine, Menveo®
From:	Joseph George Consumer Safety Officer CBER/OCBQ/DMPQ/MRB I, HFM-675
Through:	Carolyn Renshaw Branch Chief CBER/OCBQ/DMPQ/MRB I, HFM-675 Willie Vann – Chair, CBER/OVRR/DBPAP/LBP, HFM-437
Cc:	Nicole Trudel – Reviewer, CBER/OCBQ/DMPQ/ MRB I, HFM-675 Cara Fiore – RPM, CBER/OVRR/DVRPA, HFM-481 Elizabeth Valenti – RMP, CBER/OVRR/DVRPA, HFM-481
Applicant:	Novartis Vaccines and Diagnostics, Inc. **US License Number:** 1751
Subject:	Review of Novartis' responses to the CR Letter related to the Comparability Protocol for Filling Line -b(4)- to be used for filling of Menveo® final product.
ADD:	20 February 2010

I. Recommended Action:

Based on my review of Novartis' responses, I recommend approval of this CP for the addition of -b(4)- for use in Menveo filling. The implementation supplement should be categorized as a CBE-30 when submitted.

II. Summary Review:

A Comparability Protocol (CP) for filling MenCWY Liquid on Novartis -b(4)- filling line in Rosia, Italy was included in the original BLA for Menveo. My review of the original CP, as found in the BLA, can be found in my 24 June 2009 memo --b(4)---------- An Information Request was sent to Novartis on 21 May 2009. The firm provided a response on 22 June and 21 August 2009. My review of these responses follows. Please note that review of the Novartis responses follows each item as it was included in the CR Letter which is in bold italics. It is also important to note that since the submission of the original BLA for Menveo, the b(4) filling line has been approved for use for filling Influenza Virus Vaccine (approved 17 September 2009).

1. ***Regarding Comparability Protocol (CP), Post-Submission Introduction of a --b(4)---------- at the Rosia, Italy Facility (Building b(4)) (sections 2.3.R.2.2 and 3.2.R.2.2 of the BLA), CBER acknowledges your proposed CBE-30 reporting category. Please note that CBER reserves the right to upgrade the submission to a PAS due to either your compliance status at the time of the submission, or if validation fails during its execution. Also note that should significant changes be made to any of the procedures affecting the content of this CP, you must submit a revision to the CP for review and approval prior to execution or you will need to submit the change as a stand-alone PAS. In addition, please provide the following information:***

   a. ***The CP lacks a description of the proposed -b(4)---- components and systems IOQ and PQ studies and information on how the results of these studies will be reported in the implementation supplement. Please provide this information.***

Novartis' response included Validation Master Plan, Module 2, 42/058/VMP/04. This document describes all validation activities which will be performed for -b(4)- and include formulation, filling, and visual inspection. The document includes all equipment associated with -b(4)- production and details what level of validation is required for each (i.e. DQ, IQ, OQ, PQ). Validation report numbers and schedules are also included for each piece of equipment. Novartis proposes to provide these validation reports within the implementation supplement.

I found this acceptable and have no comment.

   b. ***Regarding the -b(4)---------- Cleaning Validation, please provide the rationale for not including b(4) testing. Also, -b(4)----- testing has been omitted from cleaning validation; please indicate how product contact equipment clean hold times will be established.***

Novartis has found that b(4) testing is not suitable for use with the Menveo product contact equipment cleaning evaluation. They state that during the preparation of the sample, the -b(4)---------- ----------. Given that the b(4) filling machine (-b(4)-------) product contact parts (----------b(4)----------) are either dedicated to MenCWY or are disposable (--b(4)----------) and that --b(4)---------- I found this acceptable. As stated, the firm will use --b(4)---------- In general, this method of testing is less sensitive than b(4) however, the nature of the MenCWY Liquid filling process is low risk in terms of lot to lot product carryover having deleterious effects on product quality.

With regards to -b(4)----- testing, Novartis states that this testing will be implemented for cleaning validation according to the current revision of cleaning validation master plan 42-22/064/CVMP, as applicable. However, the firm states that the --b(4)----------. Thus, -b(4)------- testing in support of a equipment clean hold time is unnecessary and will not be established. I found this acceptable.

   c. ***Please provide information regarding how -b(4)-- product contact equipment will be sterilized and how these processes will be validated.***

The -b(4)-line is equipped with --b(4)---------- for cleaning and sterilization of most product-contact parts. Product-contact parts not sterilizable with -b(4)------- are sterilized off-line through the ----b(4)----------.

Validation of the b(4) sterilization b(4) has been performed and the results are reported in the attached validation report 42/058/b(4)-FM-3375/PQR/02

Product-contact parts sterilized with the -b(4)----- are the following:

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

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

The reports referenced above were included in the response with summaries translated into English for review. Both seemed adequate having all acceptance criteria met. Both studies verified that --b(4)--- ---------- The results will be reviewed further when included in their subsequent CBE-30.

d. ***There are discrepancies throughout the Media Fill protocol, MediaFill/42/058/FM-3375/PVP/00, regarding the number of fills required for validation. Some sections of this procedure refer to b(4) media fills while others refer to b(4). Please clarify the number of fills required for validation and amend your protocol accordingly. Also, please provide the acceptance limits for these media fills.***

Novartis clarified that -b(4)---------- media fill runs will be used for validation of their aseptic process. They attribute the discrepancies to incorrect English translation. The acceptance limits for this validation are as follows:

- Media Fill performed with less than --b(4)--------: Alert limit: b(4), Action limit: b(4) -b(4)---------- --

  Reaching or exceeding the action limit leads ----b(4)--- ---------- ---------- ---------- ---------- ----b(4)---- ---------- ---------- ---------- ---------- ------

- Media Fill performed with more than --b(4)---------- containers or media fill performed with more than -b(4)--- containers: Alert limit: --b(4)----------, Action limit: --b(4)----------

  Reaching the alert limit leads to thorough investigations and, --b(4)--- - ----------

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Reaching/exceeding the alert limit ----b(4)--- ----------

Reaching or exceeding the action level leads to thorough investigation --b(4)--- ----------

I found this acceptable.

e. ***You state that filling process validation results for -b(4)- will be compared to process validation results obtained for clinical and -b(4) ---------- batches. Please provide the acceptance criteria for this comparison. How will this comparison be documented?***

Novartis states that a side-by-side comparison will be made between the b(4) process validation lots filled on b(4) and the b(4) process validation lots filled on b(4). The comparison will evaluate the current final release test results between the two sets of lots. They state that --b(4)----- and -b(4)---------- testing will not be included. These methods were used for process validation only. Novartis states that a change in filling machines should not impact these two characteristics. I agree, and find this acceptable. Although Novartis states that this comparison will be made, they have not set any statistical criteria for this comparison. For example, they have not set correlation coefficient acceptance criteria for each quantifiable test result. Even though a statistical evaluation of comparability may be useful, there is no requirement for this. In addition, the potential adverse affect to product quality due to filling on a new, similar, filling line is low. Furthermore, product lots (the b(4) 3) will be put on stability and evaluated extensively through the product dating period providing assurance of safety and quality.

f. ***Please clarify where visual inspection will be performed for Meningococcal ACWY Conjugate Vaccine final container –b(4)------- filled on -b(4)--***

Novartis states that MenCWY Liquid --b(4)------ filled on the -b(4)-- line will be inspected using the automated inspection machine -b(4)-, located in Room b(4) of Building b(4) at the Rosia site. This inspection machine is currently validated and used for --b(4)---------- ---------- inspection. Validation of this machine for Menveo final product inspection is included in the Validation Master Plan, 42/058/VMP/04.

The inspection of ---------- --b(4)------- will look for the following defects:

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

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

Novartis uses the --b(4)---------- Product in order to verify the percentage of findings of particles inside of the liquid which are determined by -b(4)--. Novartis has set an acceptance criterion of -b(4)---- I found this acceptable.

g. ***Please describe how you will evaluate stability of Meningococcal ACWY Conjugate Vaccine filled on -b(4)--. Your stability testing panel should include container closure integrity testing, sterility, and final product release tests.***

Novartis intends to put three lots of MenCWY Liquid filled on -b(4)-- on stability. Testing will be preformed at Time 0, 3, 6, 9, 12, 18, 24, 36, and --b(4)------- for the following:

- Appearance – conforms
- ---b(4)----------
- ----------b(4)----------
- ----------b(4)----------
- ----------b(4)----------
- ----------b(4)----------
- ----------b(4)----------
- ----------b(4)----------

Sterility testing will also be included in the stability program but only tested at Time --b(4)---------- Container Closure Integrity testing will also be included at Time --b(4)----------

I found this acceptable but defer to the product office for additional review.