



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
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To: DATS: 586296

STN BLA 125546/0
Meningococcal Group B Vaccine

From: LCDR Donald Ertel, Regulatory Officer, OCBQ / DMPQ / MRB1

Through: Carolyn Renshaw, Branch Chief, OCBQ / DMPQ / MRB1

Through: Jay Eltermann, Division Director, OCBQ / DMPQ

CC CDR Edward Wolfgang, RPM, CBER/OVRR/DVRPA/CMC32
Margaret Bash, Chair, OVRR/DBPAP/LBP

Subject: DMPQ Addendum Review #1 (Final) for Biologics License Application filed per 21 CFR 601.2 for Meningococcal Group B Vaccine Manufacturing Facility for active immunization to prevent invasive meningococcal disease caused by N. meningitidis serogroup B in individuals 10 through 25 years of age.

Applicant: Novartis Vaccines and Diagnostics, Inc. (Novartis) (License Number 1751)

Facility 1. Novartis Vaccines and Diagnostics S.r.l., Bellaria-Rosia, Sovicille Italy.
FEI# 3006738517

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

ADD: 24 Mar 2015

Conclusion and Recommendation

This is the final DMPQ review memo; No more addendum reviews will follow.

I recommend approval of this submission. At both the Novartis Rosia and ---(b)(4)---- facilities, the qualification, validation, and control activities as related to facility, equipment, and container closure appear to be adequate for the drug substance and drug product manufacturing of Meningococcal Group B Vaccine. From my purview of the original application, there appears to

be no evidence that the identity, strength, safety, quality and purity of the product produced in the facilities would be adversely impacted based on the completed development data and experience.

ORA/CDER performed the pre-license inspection (PLI) of the ---(b)(4)---- facility, initiated on --- (b)(4)---- and concluded on ---(b)(4)-----. The PLI has been classified as Voluntary Action Indicated. A PLI at the Novartis Rosia DS/DP Facility was waived on 12 Sep 2014.

Review Memo Format and Table of Contents

I have evaluated the responses to my Information Request (IR) to my Primary Review in this Addendum Review #1. The IRs are in bolded text. A summary of the firm's response to that IR immediately follow in italicized text. My assessments of the response immediately follow in a double lined box.

The table of contents of this review is as follows (major sections numbered, subsections lettered):

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1. Amendments related to Review

- 125546/0.33 received 05 Dec 2014 to Information Requested for clarity of Responses for Question #3 and 5 via Teleconference with the firm on 11/26/14
- Email Response (dated 02 Dec 2014) from ---(b)(4)----- related to Information Requested for clarity of Response for Question #5 via Teleconference with the firm on 11/26/14

Additional Note: 125546/0.5 received 01 Aug 2014 to Information Request on 30 Jul 2014 (evaluated in support of the Inspection waiver for Rosia Facility)

2. Regulatory History

The following documents were reviewed related to the ---(b)(4)---- facility:

- Amendment 125546/0.24 received 07 Nov 2014
- Amendment 125546/0.26 received 17 Nov 2014

3. Amendment Information

Regarding Your -----(b)(4)---- Facility

Reference your -----(b)(4)-----:

Question 1: Please confirm that -----(b)(4)----- are dedicated to the 4CMenB Recombinant proteins only. Please provide a summary of the sanitization procedures and storage conditions of the (b)(4) and the qualification of those procedures and conditions.

4 pages determined to be not releaseable: (b)(4)

[(b)(4)]

[(b)(4)]

Review Assessment / Comment: It is confirmed that all the -----(b)(4)----- used in the purification processes of the three Recombinant Proteins Drug Substances are product dedicated.

-(b)(4)- provided a list of the -(b)(4)- and the summary of sanitization procedures, storage conditions and qualification/validation of those procedures/conditions. (b)(4) reports that

s

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

**Regarding Your -----(b)(4)----- Facility
Reference Processing Filters**

Question 2: Please confirm that processing filters are ---(b)(4)--- to the 4CMenB Recombinant proteins only. Please provide a summary of the sanitization procedures, storage conditions, reuse of processing filters and the qualification of those procedures and conditions.

Novartis Response:

The Company would like to confirm that all the processing filters used in the manufacturing process of the Recombinant Proteins Drug Substances are product ---(b)(4)--.

The list of the processing filters and details are reported in Table 2-1 for rP936-741, Table 2-2 for rP287-953 and Table 2-3 for rP961c, respectively. For -----(b)(4)-----, cleaning and storage are performed after use and the appropriate validation studies have been carried out and details have been provided in STN 125546 – Information Request sequence 0024 response to question 32.

[(b)(4)]

[(b)(4)]

Review Assessment / Comment: It is confirmed that all the processing filters used in the manufacturing process of the Recombinant Proteins Drug Substances are product ---(b)(4)--. Filters are either ----(b)(4)----- or after production campaign as indicated. I have no further concerns.

Reference Processing Equipment

Question 3: Please provide a list, in table format, of the product contact equipment or containers (including Glass) used in 4CMenB Recombinant Proteins manufacturing and specify any other products that are manufactured in that same equipment /container. (Note: you have not distinctly identified what other products are shared on specific product contact equipment /containers in the submission or any other previous communication)

Novartis Response:

Details of product contact equipment used in the 4CMenB Recombinant Proteins manufacturing is provided in the respective tables below.

The request product-specific information is provided in the ----(b)(4)----- . A letter of Access to the DMF is included in Section 1.4.1 Letter of Authorization.

Equipment used in Fermentation

The equipment in the fermentation facility plant (b)(4) currently used for ----(b)(4)----- as well as equipment in the fermentation facility plant (b)(4) used for (b)(4) is shown in Table3-1. Generally all fermentation equipment is potentially shared.

[(b)(4)]

Equipment in (b)(4) Facility

*The equipment in the ----(b)(4)----- currently used for ----(b)(4)----- purification is shown in Table 3-2. Generally all (b)(4) equipment is potentially shared as this a multi-product manufacturing facility. Product specific information requested is provided in the ----(b)(4)-----
-----.*

[(b)(4)]

Equipment in (b)(4) Facility

*The equipment in the -----(b)(4)----- currently used for --(b)(4)-- purification is shown in Table 3-4. Generally, all (b)(4) equipment is potentially shared as this a multi-product manufacturing facility. Product specific information requested is provided in the -----
------(b)(4)-----.*

[(b)(4)]

Review Assessment / Comment: I need further clarity of product shared equipment. In a teleconference with Novartis on 11/26/14, I asked Novartis to update the previously provided table with the other products produced on shared equipment for each line-item piece of equipment, to verify the Product types, and to confirm that Cleaning procedures are established for all associated products. A response was received post teleconference.

Novartis Response:

Details of product contact equipment used in the 4CMenB Recombinant Proteins manufacturing are provided in the respective tables below. Specific details of the other products manufactured using the same equipment is coded in this document (due to client confidentiality) and the

respective date of manufacture are provided in the parenthesis. The details of the code designation are provided in a separate document provided by (b)(4).

(b)(4) provided the following table in an email on 02 Dec 2014:

[(b)(4)]

Equipment used in Fermentation

The equipment in the fermentation facility plant (b)(4) currently used for -----(b)(4)----- fermentation as well as equipment in the fermentation facility plant (b)(4) used for (b)(4) is shown in Table3-1. Generally all fermentation equipment is potentially shared.

[(b)(4)]

(b)(4) confirms that the cleaning procedure is validated for all products on all equipment listed above.

Equipment in (b)(4) Facility

The equipment in the ----(b)(4)----- currently used for -----(b)(4)----- purification is shown in Table 3-2. Generally all (b)(4) equipment is potentially shared as this a multi-product manufacturing facility.

[(b)(4)]

[(b)(4)]

(b)(4) confirms that the cleaning procedure is validated for all products on all equipment listed above with some --(b)(4)-- cleaning being verified during product change-over.

Equipment in (b)(4) Facility

The equipment in the ----(b)(4)----- currently used for (b)(4) purification is shown in Table 3-4: Equipment in ----(b)(4)----- production-4. Generally all (b)(4)--- equipment is potentially shared as this a multi-product manufacturing facility.

[(b)(4)]

[(b)(4)]

(b)(4) confirms that the cleaning procedure is validated for all products on all equipment listed above with some --(b)(4)-- cleaning being verified during product change-over.

Review Assessment / Comment: As indicated, most of the product contact equipment is shared. It appears that no equipment is shared with any potent compounds, and Novartis/ (b)(4) has confirmed that Cleaning Procedures are established for all equipment. Additionally, no concerns with equipment sharing and cross contamination were raised during inspection. I had no issues with cleaning as related to removal of product residues from review, and none were raised during inspection, as well. I have confirmed that resins, membranes, and filters are product dedicated and/or single use. I have no further issues.

Reference Cleaning Validation

Question 4: Please provide justification for your acceptance criteria for Purification Equipment as follows:

[(b)(4)]

Novartis Response:

The Company would like to state that the (b)(4) limit is based on experiments during which caustic ----(b)(4)----- was (b)(4) and the (b)(4) was correlated to the concentration of the solution. At a (b)(4) concentration of (b)(4)- the correlating (b)(4) is (b)(4). The requirement for the residues of non-toxic cleaning substances is (b)(4). The (b)(4) of non-toxic (b)(4), correlating to (b)(4), is (b)(4)-- lower than this limit, which provides a comfortable safety margin.

The acceptance criterion for --- (b)(4) ---- was set to --- (b)(4) ---- which correlates to less than --- ----- for non-toxic substances. This limit is chosen higher than (b)(4) because it might be influenced by -----
----- (b)(4) -----.

The acceptance limit for --- (b)(4) ----- is based on established industry limits for the transfer of substances during cleaning.

The limits for microbial counts in the final rinse, ----- (b)(4) -----, respectively, are the criteria defined in --- (b)(4) -----.

<u>Review Assessment / Comment:</u> Justification of specifications appears acceptable for this upstream processing. I have no further concerns.
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Question 5: refer to 3.2.S.2.5 Process Validation & Evaluation [rp961 – (b)(4)]; Page 58 of 66: You performed a ----(b)(4)----- study (rp961c ----(b)(4)----- with full scale batches) to confirm the ability to (b)(4) the tested --(b)(4)--- for at least (b)(4) hours within their respective process containers with no significant increase in (b)(4)---. Were similar studies performed for rp287-953 and rp936-741?

Novartis Response:

The detailed response to this question is provided in the STN 125546 – Information Request sequence 0024 response to Q13 submitted 7th November 2014.

<u>Review Assessment / Comment:</u> Novartis did not give me a direct response, and I need clarification /confirmation from Q13. A teleconference with Novartis on 11/26/14, was conducted for follow-up. A response was received post telecon.

Novartis Response:

The study performed for ----(b)(4)----- reported for rp961c has not been executed for rp287-953 or rp936-741.

The Company would like to clarify ----(b)(4)----- data (for all three recombinant protein antigen manufacturing processes) is reported only for --- (b)(4) ----- that require a (b)(4) until the completion of analytical in-process tests necessary for further processing. During routine manufacturing samples for ----- (b)(4) ----- analyses are taken at the latest possible time point prior to proceeding on to the next processing step. Hence (b)(4)---

----- (b)(4)----- is a concurrent strategy involving continuous in-process monitoring which applies to all stages of (b)(4) processing where applicable. The Company believes that this matrix approach (b)(4) stability data from small scale studies supported by (b)(4) in-process data from full scale (b)(4) holds) undertaken is valid with regards to demonstrating (b)(4) stability and (b)(4) control.

<p><u>Review Assessment / Comment:</u> Novartis' response is acceptable. (b)(4) control of the DS appears to be adequately monitored. I have no further concerns.</p>

Regarding Your Novartis Rosia Facility

Reference Final Drug Product Container Closure

Question 6: Please provide a summary of the Incoming Testing / Release Requirements for the Syringe and Stoppers

Novartis Response:

Details of the incoming test for the syringe and stoppers used for Bexsero drug product are provided in the following tables. Please note batch sampling size/quantity is based on the criteria defined in the (b)(4) sampling index.

Tests for Syringes

[(b)(4)]

1 page determined to be not releaseable: (b)(4)

[(b)(4)]

Review Assessment / Comment: Specification for syringes appears acceptable with standard verifications. AQL level appear appropriate for relevant criteria. Novartis reports incoming and (b)(4) testing requirements. No objectionable findings noted.

Reference Processing Equipment

Question 7: Please provide a list, in table format, of the product contact equipment or containers (including Glass) used in OMV manufacture and 4CMenB Formulation /Fill and specify any other products that are manufactured in that same equipment or container. (Note: you have not distinctly identified what other products are shared on specific product contact equipment /containers in the submission or any other previous communication)

Novartis Response:

The list of product contact equipment and containers for 4CMenB formulation/fill is provided in Table 7-1.

[(b)(4)]

[(b)(4)]

Review Assessment / Comment: Some shared equipment for Formulation and Fill; Cleaning procedure established and evaluated in my Primary Review. I found the cleaning validation and associated residual limits to be acceptable in the Primary Review. Filling Needles are dedicated. All OMV equipment including glassware is dedicated. I have no further concerns.

Reference Cleaning Validation

Question 8: Reference Table 3.2.A.1.4.2.6.1.9.2-4 Cleaning Validation Results for Fermenter ---(b)(4)---- After the Restart of the Area: Please explain why (b)(4) was not tested and /or reported.

Novartis Response:

*The Company would like to state that (b)(4) was tested -----(b)(4)----- as part of the -----
----- (b)(4)----- cleaning re-validation study for ---(b)(4)-- following -----(b)(4)-----
----- . The cleaning re-validation was not completed at the time of submitting
the BLA 125546. .*

*The study has been completed and reported in OMVZ/40/071/(b)(4)----/CVR/02.
The table below shows the summary of the results for the -----(b)(4)-----
of the area:*

[(b)(4)]

*The (b)(4) limit of (b)(4) is a revised criteria documented in protocol OMVZ/40/071/-----
-(b)(4)---/CV/02 which was changed from a previous value of (b)(4).*

Question 9: You state that “Cleaning Revalidation activity, demonstrating the cleaning procedure efficacy to remove residual product processing OMV-NZ from the fermenter (b)(4)-----, is still on-going due to DR 303052.” Please provide a summary of Deviation, and when cleaning validation activities are expected to be completed.

Novartis Response:

Details of the deviation are summarized in the following sections. This deviation is the same which is discussed in the response to Question 8.

Event Description:

Deviation 203052 was opened due to the total (b)(4) not meeting the acceptance criteria during Cleaning Revalidation on the fermenter ---(b)(4)-- (OMVZ manufacturing, Fermentation Area, ----(b)(4)-----, Protocol ref OMVZ/40/071/---(b)(4)-----/RCV/00). -----(b)(4)----- performed on ---(b)(4)--- on the same date/batches are in conformance with acceptance criteria (as reported in OMVZ/40/071/--(b)(4)--/CVR/01 and in the submitted dossier Table 3.2.A.1.4.2.6.1.9.2-4 “Cleaning Validation Results for Fermenter ---(b)(4)----- after the Restart of the Area”).

Root Cause and Corrective Actions

An in depth root cause investigation identified two primary factors related to the sampling and testing materials and not related to the equipment cleaning itself. The cleaning treatment for glass vials used for (b)(4) analysis in the QC lab was found to be insufficient in the complete removal of low level (b)(4) contaminants originating from the empty vials. This resulted in a variable low level contamination of the ---(b)(4)-- when analyzed on the (b)(4) machine. As a corrective action, a new (b)(4) vial treatment procedure was implemented per CAPA 272449 and Change Request 268235 (closed on 22 April 2014).

An additional potential contributing factor to the results was a variable (b)(4) contribution from the (b)(4) themselves used in the validation sampling. To improve the consistency and reliability of the (b)(4) utilized for this sampling,----(b)(4)----- was introduced which is certified (b)(4) free from the manufacturer. This was implemented as part of the same CAPA and CR mentioned above.

The reason these issues were identified during the fermenter cleaning validation was due to the exceptionally tight cleaning validation acceptance criterion. Because of the tight limits (based on downstream expectations for upstream fermentation operations), the low level contaminants were enough to exceed the acceptance criterion.

In other cleaning validation studies with wider acceptance criteria, this variability did not significantly effects the results. Although the variability in the (b)(4) method would have impacted all cleaning validation results, the situation represents a worst-case scenario in terms of (b)(4) measurement therefore there is no impact on previously executed cleaning validation studies.

The deviation 203052 was closed on 21st February 2014. After implementation of the CAPAs described above, the cleaning validation was re-executed. All results from (b)(4) consecutive runs confirmed (as shown in the response for Question 8). The final report was approved on August 18th, 2014.

Review Assessment / Comment: Novartis appears to provide appropriate scientific rationale for the (b)(4) approach to (b)(4) limit for this upstream processing equipment. The investigation appears to be resolved adequately, and completion of cleaning validation has been confirmed. OMV equipment is dedicated to OMV production. I have no further concerns.

Question 10: Please provide your justification for not analyzing ----(b)(4)----- in Cleaning Validation for -----(b)(4)-----, as applicable)

Novartis Response

The Company would like to confirm that the ----(b)(4)----- assay applied to ---(b)(4)----- samples for cleaning validation studies has provided suitable recoveries (see dossier section 3.2.A.1.4.3 Drug Product - Formulation/Filling/Finish) to ensure that the assessment of the cleaning procedure implemented is adequate. To complement -----(b)(4)----- analysis is also undertaken on (b)(4) samples. The Company believes this monitoring approach is robust and provides sufficient level of assurance that eventual residues from manufacturing process are monitored effectively following the cleaning validation procedure.

The company however acknowledges that (b)(4) could also be considered for its use in cleaning validation studies. Implementation opportunity for (b)(4) will be evaluated through use of recovery studies, which are anticipated to be executed by the second quarter of 2015 in due time for routine cleaning revalidation activities.

Review Assessment / Comment: Novartis' response is acceptable.

I recommend the following Inspectional Consideration: For Meningococcal Group B Vaccine operations at Novartis Rosia (FEI# 300673851), verify that (b)(4) testing on rinse water for cleaning with -----(b)(4)----- has been studied and implemented, as needed.

Reference CCIT for Prefilled Syringe

Question 11: Reference your new ----(b)(4)-----CCIT method (SOP 295059 / report 296376). You implemented a positive control to increase assay sensitivity to detect minute leaks in the closure system using a -----(b)(4)----- . How did you determine that a (b)(4) leak defect size is your critical (worst case) leak? To support test sensitivity, we recommend minimum nominal leak diameter at ---(b)(4) of your positive control; have you considered this range of leak diameter for your positive control?

The Company would like to confirm that the (b)(4) leak defect size is considered adequate for use as positive control in the CCIT --- (b)(4) --- test. This has been the Company standard since 2012. As already stated in response to CBER Information Request received on October 6th, 2014, (STN 125546 – Information Request sequence 0020, Question 13), a comparative study between the microbial challenge test and the --- (b)(4) --- test was performed which demonstrated that the --- (b)(4) --- method was more sensitive than the microbial challenge test. This was done using ----- (b)(4) ----- of nominal diameter of --- (b)(4) -----, confirming sensitivity of the --- (b)(4) --- method itself.

Review Assessment / Comment: Novartis' response is acceptable.

Reference CCIT for Prefilled Syringe

Novartis Response:

Preparation of Positive Control

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

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

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

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

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

-----.

Review Assessment / Comment: Standard design approach is evident with -----
----- (b)(4) ----- As noted in Q12, Novartis is implementing a
PC with (b)(4) defect size. Visual Inspection ----- (b)(4) ----- appear adequate
for current method, and has been reported to be validated. No objectionable findings noted.

See Inspectional Consideration in Q12.

Novartis has not included CCIT in their Post Approval Stability Program. Since they are testing
for sterility, we cannot require CCIT to be included as a PMC. However, I am forwarding the
following recommendation to the firm for consideration of CCIT in their Stability Program:

**The Agency has noted that you are not performing Container and Closure Integrity
Testing (CCIT) in your Post Approval Stability Program. I wanted bring to your attention
the following excerpts from -----**

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

- -----

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

-----.”

