



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
10903 New Hampshire Ave
Building 71, G112
Silver Spring, MD 20993-0002

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

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

Subject: DMPQ Primary Review for Biologics License Application filed per 21 CFR 601.2
for 4CMenB 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

Overall conclusions and recommendation will be made in my Final Addendum Review Memo.

Responses to the following Information Request will be evaluated in the Addendum Review #1:

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

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

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

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2. -----
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3. -----
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4. ----- (b)(4) -----

[(b)(4)]

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

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

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

Novartis Rosia:

Reference Final Drug Product Container Closure:

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

Reference Processing Equipment

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)

Reference Cleaning Validation

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.
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 203052.” Please provide a summary of Deviation, and when cleaning validation activities are expected to be completed.
10. Please provide your justification for not analyzing (b)(4) on rinse water in Cleaning Validation for --(b)(4)-- and -----(b)(4)-----, as applicable)

Reference CCIT for Prefilled Syringe

11. Reference your new ---(b)(4)---- CCIT method (SOP 295059 / report 296376). You implemented 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?
12. Please provide a complete description of your CCIT ---(b)(4)--- Method outlining all steps and parameters (including Equipment and materials used, vacuum/ pressure stresses, exposure times, (b)(4) detection method, Limit of Detection, etc.).

Review Memo Format and Table of Contents

I have provided a summary of information provided in the submission that is under DMPQ purview as outlined in SOPP 8401.4: In general, my Review Assessment / Comments are provided at the end of review sections in a double lined box. Any information requests (IRs) related to review will be included in these boxes in bolded text. A summary of the firm’s response to that IR will immediately follow in italicized text or in a subsequent Amendment Review memo. My assessment of the response will immediately follow in a double lined box.

Note: -(b)(4)- is a subsidiary of the Novartis Corporation. In this memo in sections detailing the ---(b)(4)--- operations, --(b)(4)-- is named when referring to location related detail, and "Novartis" is named when referring to the Firm.

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1. Amendments related to Review

- 125546/0.3 received 25 Jul 2014 to Information Request on 18 Jul 2014 (in support of Inspection Waiver Memo).
- 125546/0.13 received 24 Sep 2014 to Information Request on 10 Sep 2014
- 125546/0.20 received 24 Oct 2014 to Information Request on 06 Oct 2014
- Information Request expected to be sent on 06 Nov 2014; Response to be evaluated in Addendum Review #1

2. Regulatory History

I was assigned as CMC reviewer in May 2014. The agency received the final components to this BLA in eCTD format on 25 Jul 2014. The application was appropriately filed per 21 CFR 601.2

One Inspection Waiver was submitted and approved for this submission for the Novartis Rosia Facility (approved 12 Sep 2014). For the ----(b)(4)----- facility, CBER requested that ORA perform a PLI inspection as part of the integrated review of this submission. That inspection was performed from -----(b)(4)-----.

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

- 2.3.A.1.2 Facilities & Equipment – --(b)(4)--
- 2.3.P.1 Description/Composition [4CMenB – Suspension for Injection in PFS]
- 2.3.S.2 Manufacture [rp287-953 – --(b)(4)--]
- 2.3.S.2 Manufacture [rp936-741 – --(b)(4)--]
- 2.3.S.2 Manufacture [rp961c – --(b)(4)--]
- 2.3.S.6 Container Closure System [rp287-953 – --(b)(4)--]
- 2.3.S.6 Container Closure System [rp936-741 – --(b)(4)--]
- 2.3.S.6 Container Closure System [rp961c – --(b)(4)--]
- 2.3.S.7 Stability [rp287-953 – --(b)(4)--]
- 2.3.S.7 Stability [rp936-741 – --(b)(4)--]
- 2.3.S.7 Stability [rp961c – --(b)(4)--]
- 3.2.A.1.2.1 Facilities and Equipment Overview – --(b)(4)--
- 3.2.A.1.2.2 Drug Substance – Recombinant Proteins Manufacture
- 3.2.S.2.2 Manufacturing Process & Controls [rp287-953 – --(b)(4)--]
- 3.2.S.2.2 Manufacturing Process & Controls [rp936-741- --(b)(4)--]
- 3.2.S.2.2 Manufacturing Process & Controls [rp961c- --(b)(4)--]
- 3.2.S.2.4 Controls of Critical Steps and Intermediates [rp287-953 – --(b)(4)--]
- 3.2.S.2.4 Controls of Critical Steps and Intermediates [rp936-741 – --(b)(4)--]
- 3.2.S.2.4 Controls of Critical Steps and Intermediates [rp961c – --(b)(4)--]
- 3.2.S.2.5 Process Validation & Evaluation [rp287-953 – --(b)(4)--]

- -----(b)(4)-----
- MenB936-741/23/resins_life_span_study_report/00: Life span study report of MenB 936-741 -----(b)(4)-----
- MenB961c/23/resins_life_span_study_report/01: Life span study report of MenB 961c -----(b)(4)-----
- Personnel, Material, Product , Equipment Flow Diagrams and Air Classification Schematics for -----(b)(4)-----
- PQ 44.211_D, Edition 2.0-Process Validation Report -----(b)(4)----- MenB 287-953
- PQ 44.212_D, Edition 2.0 Process Validation Report -----(b)(4)----- MenB 936-741
- PQ 46.796_D, Edition 2.0-Validation Report of MenB 287-953 Isolation and Purification Process at ---(b)(4)--- (Repetition of the validation)
- PQ 46.797_D, Edition 1.0 Validation Report of MenB936-741 Isolation and Purification Process at ---(b)(4)---
- PV 44.348_0- Validation Report for Fermentation Consistency A validation report for the MenB961 c -----(b)(4)----- process
- PV 83.849 D -Process Performance Qualification Report of the Downstream Manufacturing Process (Isolation and Purification) of MenB961c -----(b)(4)-----
- PV 83.851 D: Stability Study Report for MenB961 c -----(b)(4)-----Time Validation (Small Scale)
- QC3_230710, MenB 287_IM_04 Version 2.0-Laboratory Report QC3-230710_Vers02. Intermediate Stability Report MenB 287_IM_04
- QC3-310810, MenB 936-741_IM_03:Laboratory Report QC3-310810 Intermediate Stability Report MenB 936_IM_03
- QC4 17032011; Addendum ad BP05210 - MenB961 c_ Intermediate Stability Report_IM4_072010
- -(b)(4)-/035/ROAD- -----(b)(4)-----/PQR/00-Validation Report of the refrigerated -----(b)(4)----- Transportation System --(b)(4)---- With ---(b)(4)---- – SI- -----(b)(4)----- To Novartis V&D Srl (Rosia, Italy)
- SP05210; Intermediate Stability Report-MenB 961c 1M 04

3. Environmental Assessment

Novartis requests a categorical exclusion under 21 CFR 25.31(c) from the preparation of an Environmental Assessment as Multicomponent Meningococcal group B Vaccine is a biologic product and a substance that occurs naturally in the environment and the action on STN 125546/0 does not alter significantly the concentration or distribution of the substance, it

metabolites, or degradation products in the environment. Novartis attests that the drug substance and drug product are manufactured according to current local environmental legislations.

Review Assessment / Comments: I am in agreement with the CE.

4. Product Background

Novartis Meningococcal B Recombinant Vaccine (4CMenB or Bexsero) is indicated for active immunization against invasive disease caused by *N. meningitidis* serogroup B strains expressing a sufficiency of one or more of the antigens contained in the vaccine. Novartis is seeking for an indication of 4CMenB in adults and adolescents 11 years of age and older.

4CMenB is multicomponent Meningococcal B Vaccine provided as a suspension for injection in pre-filled 1 mL hydrolytic resistant glass ----(b)(4)---- syringe to be administered intramuscularly.

The drug product is composed of four drug substances; three of the four are recombinant protein antigens produced in *Escherichia coli*:

- Recombinant Protein (rp) 287-953: recombinant *N. meningitidis* serogroup B NHBA fusion protein. The nucleotide sequence of NHBA (Neisserial Heparin Binding Antigen or 287) is derived from Strain NZ98/254 and is fused with the nucleotide sequence of the Accessory Protein 953, which is derived from Strain 2996;
- Recombinant Protein (rp) 961c: recombinant *N. meningitidis* serogroup B NadA protein. The nucleotide sequence of NadA (Neisserial adhesin A or 961c) is derived from Strain 2996;
- Recombinant Protein (rp) 936-741: recombinant *N. meningitidis* serogroup B fHbp fusion protein. The nucleotide sequence of fHBP (factor H Binding Protein or 741) is derived from Strain MC58 and is fused with the nucleotide sequence of the Accessory Protein 936, which is derived from Strain 2996

The three recombinant proteins are produced at the -----(b)(4)-----

The fourth drug substance, Outer Membrane Vesicle (OMV) is derived from *N. meningitidis*, serogroup B Strain NZ98/254. OMV is produced in Building --(b)(4)-- at the Novartis Rosia facility in Italy.

Formulation of the drug substances (3 recombinant proteins and OMV) with Aluminium Hydroxide and buffers, aseptic filling, visual inspection and packaging, occurs at the Novartis Rosia site, Buildings --(b)(4)--.

The 4CMenB vaccine contains 50µg of each of the three purified recombinant protein antigens, with 25µg of OMV measured as amount of total protein containing the PorA P1.4, and 1.5 mg of aluminum hydroxide per 0.5 ml dose.

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

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

- 3.2.A.1.4.2 Drug Substance – OMV Manufacture (Rosia) [4CMenB – Suspension]
- 3.2.A.1.4.3 Drug Product – Formulation-Filling-Finish [4CMenB – Suspension]
- 3.2.P.2.3 Manufacturing Process Development
- 3.2.P.2.4 Container Closure System
- 3.2.P.2.5 Microbiological Attributes (CCIT)
- 3.2.P.3.1 Manufacturer(s)
- 3.2.P.3.3 Manufacturing Process and Controls [4CMenB – Suspension for Injection in PFS]
- 3.2.P.3.4 Controls of Critical Steps and Intermediates
- 3.2.P.3.5 Process Validation and/ or Evaluation [4CMenB – Suspension for Injection in PFS]
- 3.2.P.5.1 Specifications [4CMenB – Suspension for Injection in PFS]
- 3.2.P.5.6 Justification of Specifications [4CMenB – Suspension for Injection in PFS]
- 3.2.P.7 Container Closure System
- 3.2.P.8.2 Post-Approval Stability
- 3.2.P.8.3 Stability Data
- 3.2.S.2.2 Description of Manufacturing Process and Process Controls [OMV – Rosia]
- 3.2.S.2.4 Control of Critical Steps & Intermediates [OMV – Rosia]
- 3.2.S.2.5 Process Validation and / or Evaluation [OMV-Rosia]
- 3.2.S.4.1 Specification [OMV – Rosia]
- 3.2.S.4.5 Justification of Specification [OMV – Rosia]
- 3.2.S.6 Container Closure System [OMV – Rosia]
- 42-058-PVR-00-Validation Report for the Formulation Process to be performed with a
----- (b)(4) ----- Solution in the Formulation Area of --(b)(4)- Located in Building (b)(4)-
Final Processing
- ----(b)(4)----- Layout and Floor Plan, Building (b)(4)
- ----(b)(4)----- Personnel Flow, Building (b)(4)
- ----(b)(4)----- Material Flow, Building (b)(4)
- ----(b)(4)----- Product Flow, Building (b)(4)
- ----(b)(4)----- HVAC Boundaries, Building (b)(4)
- ----(b)(4)----- Room Air Classification, Pressures and Air Flow, Building (b)(4)
- ----(b)(4)----- Equipment Layout, ---(b)(4)---
- ----(b)(4)----- Personnel Flow, ---(b)(4)---
- ----(b)(4)----- Material Flow, ---(b)(4)---
- ----(b)(4)----- Product Flow, ---(b)(4)---
- ----(b)(4)----- Personnel Flow, ---(b)(4)---
- ----(b)(4)----- Material Flow, ---(b)(4)---
- ----(b)(4)----- Air Flow/Pressures & Room Air Classification, ---(b)(4)---
- ----(b)(4)----- HVAC AHU Boundary Lines, ---(b)(4)---
- ----(b)(4)----- Layout and Floor Plan, Building ---(b)(4)---
- ----(b)(4)----- Personnel Flow, Building ---(b)(4)---
- ----(b)(4)----- Product Flow, Building ---(b)(4)---
- ----(b)(4)----- Material Flow, Building ---(b)(4)---
- ----(b)(4)----- Personnel Flow, Building ---(b)(4)---
- ----(b)(4)----- Material Flow, Building ---(b)(4)---
- ----(b)(4)----- Room Air Classification, Building ---(b)(4)---

Floor	Floor Manufacturing Activity
----(b)(4)---- ----(b)(4)-----	------(b)(4)----- -----
----(b)(4)----	<ul style="list-style-type: none"> • -----(b)(4)----- <ul style="list-style-type: none"> ➤ -----(b)(4)----- ----- ➤ -----(b)(4)----- ➤ -----(b)(4)----- ----- • -----(b)(4)----- <ul style="list-style-type: none"> ➤ -----(b)(4)----- ----- ➤ -----(b)(4)----- ----- • -----(b)(4)----- • -----(b)(4)-----
----(b)(4)----	<ul style="list-style-type: none"> • -----(b)(4)----- <ul style="list-style-type: none"> ➤ -----(b)(4)----- ➤ -----(b)(4)----- • -----(b)(4)----- <ul style="list-style-type: none"> ➤ -----(b)(4)----- • -----(b)(4)----- • -----(b)(4)-----

Review Assessment / Comment: Novartis provided no information about the receipt and verifications performed on the Recombinant Proteins received at Rosia.

The following Information Request was sent to the firm:

Please provide a summary of the verifications performed at receipt for the --(b)(4)-- Recombinant Proteins; Reference any applicable Standard Operating Procedures.

Novartis Response:

--(b)(4)-- Recombinant Proteins (drug substances) are verified upon receipt according to SOP 201332. Personnel perform the following checks on the received goods:

- Quantity according to the delivery documents
- Physical appearance and general condition of goods (integrity, cleanliness)
- Conformity of the containers
- Conformity of the labels according to the delivery documents:
 - product name
 - product code
 - batch number

All the checks, performed at ---(b)(4)---, are recorded in Attachment 1 to SOP 201332. Once the batches are accepted, they are booked into the -----(b)(4)----- and stored in designated -----(b)(4)-----.

--(b)(4)-- Recombinant Proteins (drug substances) are released for further manufacturing by Quality department, according to SOP 202121. Quality personnel perform the following verifications:

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

Once the verifications are completed the -(b)(4)- Recombinant Proteins are released for further manufacturing.

Review Assessment / Comment: Receipt Process appears to be controlled. No objectionable findings noted.

b. Facilities Overview

Rosia Building --(b)(4)--

(b)(4) is a multi-product facility. The ----(b)(4)----- is dedicated to OMV manufacture and chemistry of MenACWY polysaccharides for Glycoconjugate vaccines. Glycoconjugates are manufactured on the -----(b)(4)-----.

Novartis performs the manufacture -----(b)(4)----- of the Outer Membrane Vesicles (OMV) on the ----(b)(4)----. The following rooms are used to formulate OMV:

[(b)(4)]

Rosia Building --(b)(4)--

Formulation, filling and inspection operations of 4CMenB are performed on the ----(b)(4)-----
in the following rooms:

[(b)(4)]

Rosia Building ---(b)(4)----

Novartis performs final packaging and labeling Bexsero operations performed on the -----
----- (b)(4) -----

Facility Flow Patterns

(b)(4) Personnel Flow: Gowning requirements are specific for each area. Card restricted access is provided to gowning and work areas. All must be qualified by training to enter the different work areas. Gowning and working techniques for employees working in Class (b)(4) and (b)(4) areas are described in a written. Approved, and controlled procedure. A hygiene program is established for all classified clean room areas. General room hygiene requirements and behavior in clean rooms, including the clothing matrix are described in in SOPs. Novartis provided a plant diagram ----(b)(4)----- illustrating the personnel flow in the manufacture of OMV.

(b)(4) Waste Flow: Bacterial cells are concentrated at the end of fermentation by ---(b)(4)-
----- and then inactivated by DOC addition. -----
----- (b)(4) -----

-----.

Novartis provided plant diagram ---(b)(4)--- showing the flow of waste resulting from the manufacture of OMV.

(b)(4) Materials Flow: Novartis provided a plant diagram ----(b)(4)---- illustrating the materials and equipment flows used in the 4CMenB manufacture.

(b)(4) Personnel flow: The gowning requirements are specific for each area. Card restricted access is provided to gowning areas and work areas and individuals must be qualified by training to enter the different work areas. For the Class (b)(4) areas, such individuals must demonstrate effective gowning through performance testing. Gowning in the aseptic area includes uniforms covered by sterile jumpsuits, shoes dedicated to the sterile area covered by sterile shoe covers, a sterile hood with face covering, sterile gloves, and safety glasses. Hands disinfectant is supplied within the aseptic room. Personnel working in the area surrounding the aseptic core are gowned appropriately in uniforms and sterile jumpsuits, dedicated shoes/shoe covers and sterile head coverings. Novartis provided a plant diagram - ---(b)(4)----- showing the personnel flow in the 4CMenB manufacture.

(b)(4) Materials flow: Novartis provided a plant diagram ---(b)(4)----. illustrating the materials and equipment flow used in the 4CMenB manufacture.

(b)(4) Waste Diagram: Waste is handled and disposed of in accordance with SOPs by personnel who are trained and qualified to perform these operations. Waste generated from various rooms throughout the building is removed from the ---(b)(4)--- via the -----
------(b)(4)-----
------. Waste exists the building for disposal. Novartis provided plant diagram ---(b)(4)----- showing the waste flow resulting from the manufacture of 4CMenB.

Review Assessment / Comments: The diagrams appear to correspond with the description in the supplement. No tortuous paths appear evident, no objectionable findings noted.

c. Contamination Control

For all Rosia buildings, Product changeover, equipment cleaning and room clearance procedures are in place to avoid mix-ups and cross-contamination. Line clearance occurs prior to the start of a manufacturing operation. 4CMenB is manufactured on a campaign schedule. No two different products may be handled simultaneously.

In the submission, Novartis reports to incorporate the same contamination features as listed for the Novartis -(b)(4)- facility.

Review Assessment / Comment: Standards practices for prevention of cross-contamination appear to be in place. No objectionable finding noted.

d. General Cleaning and Disinfection

In all Rosia Buildings, Room, equipment and area cleaning are described in production area specific procedures. The procedures define the rules and responsibilities for cleaning as well as the frequency and the detergents/disinfectants to be used for cleaning. According to Novartis, different cleaning agents are used at the Rosia site, all of which are qualified for the control of microbial contamination. To prevent an adaptation of microorganisms, the disinfectants are alternated on a routine basis. Cleaning is performed at the -----(b)(4)-----, and -(b)(4)- during the shutdown.

(b)(4) cleaning is performed on pass through boxes, the seats and floors in the dressing rooms, the laminar flow hood surfaces, all horizontal surfaces in work areas, machines and carts in work areas and all floors and floor drains. The interior surfaces of pass-through chambers and the laminar flow hoods are cleaned separately. --(b)(4)-- cleaning (within -(b)(4)- for Class, -----(b)(4)-----) and -(b)(4)- cleaning is performed on walls, doors, hoods/carts/seating in dressing rooms, horizontal bench surfaces, machines, floors and floor drains. --(b)(4)-- cleaning (performed within -(b)(4)-, from previous --(b)(4)-- cleaning, for Class -(b)(4)- rooms) and -(b)(4)-- cleaning is conducted as a routine operation and includes ceilings, walls, doors, covers for the HVAC intake, hoods internal to work areas, all hoods/carts/seating in dressing rooms, external surfaces of all stainless steel surfaces, horizontal bench surfaces, machines, floors and floor drains.

Qualified disinfectants are used with validated exposure time ranges from -----(b)(4)-----, as detailed in current procedure, followed by a wipe down with -----(b)(4)-----.

Novartis has taken the same approach to the qualification of detergents and disinfectants as described in the --(b)(4)-- facility.

<p><u>Review Comments/ assessment:</u> Cleaning and disinfection practices appear to be adequate for their intended use. No objectionable finding noted.</p>
--

e. Pharmaceutical Gases

Clean Steam (CS)

In both ---(b)(4)---, Novartis performed IQ/OQ for the CS Generation and CS Distribution Systems. Piping for CS distribution is made of -----
------(b)(4)-----

(b)(4)

The (b)(4) CS Generation System is composed of: a CS Generator -----(b)(4)-----
----- with a productive capacity of ---(b)(4)---: CS is generated at a minimum

pressure of -(b)(4)-. The generator is fed with --(b)(4)-; producing steam of the same quality as WFI. The System is composed of:

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

The -----(b)(4)----- provides continuous water supply to the generator. The operating parameters are controlled by -----(b)(4)----- CS is generated with a pressure of -(b)(4)-. Distribution of the CS is via a -----(b)(4)----- system which has connections to each point of use ((b)(4) total).

For PQ, During Phases 1 and 2, Novartis collected data for all POU's for a period of (b)(4) consecutive days (-(b)(4)- each Phase) prior to release of the system for production. During Phases 1 and, the (b)(4) that feeds the CS generator was also sampled. In tables, Novartis reported ---(b)(4)--- sampling frequency PQ with minimum of (b)(4) samples taken. The acceptance criteria for CS were as follows:

[(b)(4)]

Novartis reported that all acceptance criteria were met.

(b)(4)

The (b)(4) CS distribution system is divided as follows:

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

Novartis performed the PQ in the same manner as (b)(4). All Acceptance criteria were met.

Review Assessment /Comments: Systems appear to be of standard pharmaceutical design and operation. Acceptance criteria and sampling scheme for validation appear acceptable. Novartis has provided references to the associated qualification documents in the submission.

Process Air (PA)

Compressed Air generated in the Utilities Building ((b)(4)) is distributed in ---(b)(4)--- as “Process Air.” The Instrumental Air distribution system is made of -----(b)(4)-----

Novartis executed PQ of the (b)(4) Process Air system by sampling all points ((b)(4) POU) for (b)(4) consecutive days. Novartis executed PQ of the (b)(4) Process Air system sampling points (b)(4) POU) in all) as follows:

[(b)(4)]

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

[(b)(4)]

All acceptance criteria were met.

Nitrogen

Novartis executed the PQ of the ----(b)(4)---- Nitrogen system sampling the points as follows:

[(b)(4)]

Novartis met all Acceptance Criteria as follows:

[(b)(4)]

Oxygen System ((b)(4))

An oxygen distribution system feeds the (b)(4) fermenters, located in fermentation -(b)(4)- fermentation -(b)(4)-. Oxygen is provided from the external Oxygen storage tank. Oxygen pressure from the storage system is reduced to -(b)(4)- before distribution to the fermenters. Piping of distribution system is made in ----(b)(4)----- . Novartis has validated the oxygen distribution system.

Routine Monitoring

Novartis performs routine monitoring of process compressed gases (nitrogen and compressed air) out every (b)(4) months and, if deemed necessary, after any technical work or changes made to the distribution lines.

SOP 201515 “ General Monitoring for Compressed Gases” defines the sampling points on the distribution lines of compressed gases (compressed air and nitrogen). The monitoring consists of running the following tests:

- Verification of dew point; acceptability limit ----(b)(4)----
- Verification of the bioburden; as described in SOP 241981

Review Assessment/Comments: IQ / OQ were performed, which appear to have standard verifications addressed. Novartis has provided references to the associated qualification

documents and SOP in the submission. Acceptance Criteria appears to be based on the Guidance for Industry: "Sterile drugs Products Produced by Aseptic Processing" Current Good Manufacturing Practice. Some clarification on the extent of use of process air in the Class - (b)(4)-- areas is needed; Novartis provided no validation specs for these room classes. Rationale for Micro specs is needed.

Information Request sent to the firm:

Reference your Process Air Systems in ---(b)(4)---:

Please confirm that no Process air is used in Class (b)(4) or Class (b)(4) areas.

Reference Table 3.2.A.1.4.2.5.2.3-2, Performance Qualification Results for (b)(4): How did you establish the acceptance criteria for Microbiological GAS? Why are they considerably higher than what your system appears to be able to maintain?

Novartis Response:

In reference to pharmaceutical gas usage in Building (b)(4) for the Bexsero manufacturing process; the Company confirms that no Process Air and no Nitrogen is exposed to the product or product contact surfaces in Class -----(b)(4)----- . There are no Class (b)(4) areas in (b)(4) for Bexsero manufacturing process.

In reference to pharmaceutical gas usage in Building (b)(4) for the Bexsero manufacturing process; the Company confirms that no Process air is exposed to the product or the product contact surfaces in Class ---(b)(4)--- areas, however, during formulation activities of Bexsero - --(b)(4)-- vaccine the following process steps required use of sterile Nitrogen:

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

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

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

*The Company would like to state that the Novartis Group Quality Manual has established specifications for aseptic and sterile production based on international guidelines for the Pharmaceutical industry, such as: -----(b)(4)-----
-----*

The microbiological gas limits takes into account the classification of the area where the gas sampling point is located, and also where limits for microbiological active air monitoring apply.

As such the microbiological content of the gas (expressed in CFU/cubic meter) used in a given classified area should not exceed the recommended limit for microbiological monitoring of that given area. For instance, for a gas point of use located in a grade (b)(4) room the limit for the microbial content of the gas is the same as the limit dictated by -----(b)(4)----- for

grade ---(b)(4)--- CFU/cubic meter; in conjunction Novartis apply a stricter limit for molds which is -----(b)(4)-----.

For microbiological monitoring of sampling points located in non- classified areas, internal limits are used (these limits being respectively (b)(4) CFU/cubic meter and (b)(4) molds/cubic meter).

In conclusion, the microbial acceptance criteria for gas has been set based on the processing area concerned to ensure that the state of compliance of that area from a microbiological active air monitoring standpoint is not compromised. Hence the acceptance criteria are therefore not set according to the process capability of the gas production and distribution system, but are those indicated by the -----(b)(4)----- for active air monitoring.

Review Assessment/Comments: Confirmed no product is exposed to process air or nitrogen; rationale for specs appears acceptable. I have no further concerns.

f. Water Systems

(b)(4) is supplied with Purified Water (PW), Water for Injection (WFI), and Clean Steam (CS). (b)(4) is supplied with Reverse Osmosis Water (ROW), WFI, and CS. Novartis performed IQ/OQ on all systems. Piping for the distribution loops are made of ----(b)(4)----- with surface roughness ---(b)(4)----. Welding connections are made by -----(b)(4)----- (b)(4)----- are of the -(b)(4)- type. At user points are installed ----(b)(4)-----

(b)(4) PW System

The PW system ---(b)(4)--- is composed of:

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

The (b)(4) PW generators are fed with softened water from (b)(4). PW coming out from the reverse osmosis (RO) second stage is collected in the PW storage vessel. PW conductivity (return flow loop) is ----(b)(4)----- . Circulating pumps ensure a continuous water flow in the distribution loop that feeds the PW to (b)(4) user points.

A dedicated automatic sequence is periodically executed in order to sanitize the distribution loop, the storage vessel, and the circulating pumps by means of overheated water circulating in the distribution loop.

Pumps can also be sanitized manually by means of clean steam. The Process Automation System (PAS) records temperature trend during the sanitization period. The specification for PW PQ and Routine Testing:

[(b)(4)]

Piping for the distribution loop is made from ----(b)(4)----- with surface roughness --(b)(4)----- . Welding connections are made by an -----(b)(4)-----

Novartis divided the validation of the production, storage, and distribution of the PW system into (b)(4) parts. During -----(b)(4)----- . Using the same sampling plans, data was acquired for the PW production and distribution systems for an additional ----(b)(4)----- to complete the Performance Qualification (PQ) of the entire PW system.

Novartis reports that the results of the analysis ((b)(4) samples) performed during PW PQ Phase met acceptance criteria.

(b)(4) ROW System

In (b)(4), the ROW System --(b)(4)- is a (b)(4) stage -----(b)(4)----- unit capable of removing ionic salts with a productive capacity of ---(b)(4)--. It consists of the following major equipment:

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

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

Novartis provided a detail description of the operation of the ROW system in the submission. The specification for ROW PQ and Routine Testing are the same as the -----(b)(4)----- listed for (b)(4) PW. All tests for the ROW System sampling points for Phases 1, 2 and 3 during the period corresponding to the WFI and CS qualification studies complied with the acceptance criteria. All deviations were investigated, resolved satisfactorily and closed prior to completion of the IOQ Report.

(b)(4) WFI Distribution System

In (b)(4), PW from the distribution loop is collected in dedicated --(b)(4)-- that feed the WFI and CS generators. The two WFI generators feed the WFI storage and distribution system ----(b)(4)----- that it is composed of:

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

Novartis provided a detail description of the operation of the (b)(4) WFI system in the submission. Specification for WFI PQ and Routine Testing are the same as PW with the change to -----(b)(4)-----:

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

Sampling /Testing Frequency for WFI were:

[(b)(4)]

Novartis reports that the results of the analysis ((b)(4) samples) performed during WFI PQ Phase met acceptance criteria with the exception of one out of specification result (DR 22628).

(b)(4) WFI Production System

The WFI includes equipment for the distillation, storage and distribution. -----
----- (b)(4) -----

The System ---(b)(4)---- is composed of a -----(b)(4)-----
----- with a productive capacity of -----
----- (b)(4) -----

-----:

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

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

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

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

For (b)(4) PQ, during ----(b)(4)----, Novartis collected data for all POUs for a period of -(b)(4)- for each phase) consecutive days prior to release of the system for production. Using the same sampling plans, data was acquired for the WFI generation and distribution systems for an additional ----(b)(4)----- to complete the performance qualification of the entire WFI system. During Phases 1, 2 and 3 the ROW water point of use that feeds the WFI generator was also sampled, following the frequency and testing for the WFI system.

Acceptance Criteria is the same as (b)(4) Qualification specifications. Novartis reports that the results of the analysis (b)(4) samples) performed during (b)(4) WFI PQ met acceptance criteria with the exception of one (b)(4) out of specification result (DR 232767), which was investigated and resolved with no impact to validation.

Routine Monitoring of the WFI Systems:

WFI quality is constantly monitored by means of ----(b)(4)----- probes installed on the return part of the loops. (b)(4) control system generates a “warning” signal when (b)(4) value exceeds (b)(4) and a “very high (b)(4)” alarm when (b)(4) value exceeds -----(b)(4)----- control system generates a “high ----(b)(4)-----” alarm when ----(b)(4)---- value exceeds -----(b)(4)-----. The WFI distribution system goes automatically in “Out of Service” state in case of “warning” signal for (b)(4) or “high ----(b)(4)----” alarm presence.

For routine monitoring, -----(b)(4)----- are tested. For ROW, (b)(4) points are tested --(b)(4)--. For WFI, sampling is performed (b)(4) and sites are rotated so that the complete set of sampling sites (b)(4) total) is tested (b)(4). At the sampling point closer to the return to the WFI tank; sampling is performed additionally every (b)(4) weeks. For Clean Steam, sampling is performed -(b)(4)- and sites are rotated such that the complete set of sampling sites ((b)(4) total) is tested ---(b)(4)---

<p><u>Review Comments/Assessment:</u> Novartis provided simplified schematics for all Water storage and distribution systems along with detail descriptions of their operation. Diagrams appear to correspond with the description. Relevant P&ID are referenced. Water and CS systems appear to be of standard design and operation. The deviation reported for (b)(4) PQ was an OOS for (b)(4). According to Novartis, the valve that resulted in the OOS was improperly cleaned, and the quality of the WFI was not implicated. The deviation does not appear to impact the qualification. The WFI system qualifications appear to be comprehensive with standard verifications addressed. Novartis has provided the associated qualification documents and SOPs in the submission. Acceptance Criteria appears to correlate with --(b)(4)-- standards for WFI. Routine Monitoring samples are tested at the same acceptance criteria as PQ. No objectionable findings noted.</p>
--

g. HVAC and Environmental Monitoring

Overview of (b)(4):

(b)(4) HVAC system for the OMV manufacturing areas is built with an external air pre-treatment unit (b)(4) that feeds (b)(4) systems (----(b)(4)-----) dedicated to different process areas and a system (b)(4) that feeds one cold room. The design of all (b)(4) HVAC systems (for the processing areas) is nearly identical, but they serve different classified areas. The --(b)(4)-- is equipped with dedicated systems for the control of temperature and humidity.

Novartis limited the data summary to the HVAC systems that serve the OMV processing areas as follows:

[(b)(4)]

HVAC systems ----(b)(4)----- are designed as ---(b)(4)----- units, ----(b)(4)----- uses ----(b)(4)----- air, and are equipped with a (b)(4) filter in the exhaust, serving the Fermentation Areas. Design ranges for Air Changes: Class -----(b)(4)-----
In the fermentation areas, (b)(4) has negative pressure to ensure containment, while the other units serving additional manufacturing areas are positive pressure units. Laminar Air Flow Cabinet (LAF) – used for transfer of -----(b)(4)-----
Novartis provided an air flow and pressure differential (DP) plant diagram, ---(b)(4)---, and HVAC Zones diagram, ---(b)(4)-----.

Overview of (b)(4):

The (b)(4) HVAC systems that supply air to the formulation, filling, and inspection areas (first floor) is composed of an external air pre-treatment unit that feeds --(b)(4)-- HVAC systems. The --(b)(4)-- systems are made up of --(b)(4)-- air handling units (AHU). Novartis provided an air classification and DP plant diagram, ---(b)(4)---, and HVAC Zones diagram, -----(b)(4)-----
The HVAC Systems are as follows:

[(b)(4)]

[(b)(4)]

For Filling Operations, Novartis incorporates Grade_{(b)(4)} Laminar Air Flow (LAF) devices within Grade_{(b)(4)} rooms. In --(b)(4)--, LAF surrounds the ----(b)(4)----- and the -----(b)(4)----- with air pulled from the surrounding Grade_{(b)(4)} area. In --- (b)(4)---, LAF surrounds the -----(b)(4)----- and the -----(b)(4)----- with air pulled from the surrounding Grade_{(b)(4)} area, as well.

According to Novartis, for both buildings, containment features are in place for areas with different clean room classifications and/or for areas that are utilized for different functions. These features include higher pressure differential from more controlled (higher classified) areas to less controlled (less classified) areas. Personnel and material airlocks are in place to assist in containing areas. Negative pressure differentials are maintained in fermentation areas to ensure biological containment. Additionally, each of the HVAC units serves a different processing area to maximize containment of these areas. A humidity of approximately --- (b)(4)----- is maintained in the controlled areas of the facility. Critical differential pressures are continuously monitored by -----(b)(4)-----.

Overview of (b)(4):

The area of Building_{(b)(4)} in which the packaging line is located is unclassified. The packaging area is served by_{(b)(4)} HVAC units, providing temperature control only. Conditions throughout_{(b)(4)}, both packaging and other functional areas, are monitored and controlled through a -----(b)(4)----- . No environmental monitoring is conducted for the packaging area. Novartis provided_{(b)(4)} Room Classification diagram, -----(b)(4)-----.

Review Comments / Assessment: Novartis provided a description of the mechanics of the HVAC systems; the systems appear to be standard pharmaceutical design and operation. DP, Temperature, and Humidity specification were provided in the submission in tables for each room supplied by each HVAC unit; the specs appear to correlate with Plant drawing. Specifications appear to be adequate for the intended use of the rooms.

System Qualification

For systems in both --- (b)(4)-----, Novartis performed IQ/OQ for the HVAC Systems. IQ OQ included verification of:

- Accurate Technical drawings
- Identification of HEPA filter casings

- ID and Calibration of Critical measuring devices
- ID and connection of Utilities
- Determination of air exchanges
- The HEPA filters DPs and filter leak tests
- Room classification according to ---(b)(4)-----in static condition “at rest”
- Smoke study for airflow visualization under static conditions for all clean room classification
- Installation of DP measuring devices
- Temperature and relative humidity
- DPs between different rooms
- Particle Recovery times

For IQ/OQ of the LAF units, supplied by (b)(4), included the following verifications:

- Main components meeting specification
- Operational Documentation
- Air Classification
- Smoke study demonstrated that the air flow from the HEPA filters and LAF Units are unidirectional under static and dynamic conditions including during the monitoring and set-up of equipment, and critical intervention simulations (e.g. environmental simulations and equipment assembly/disassembly)
- Alarm functionality
- Filter integrity testing
- Determination of air flow speed

For PQ (both Buildings), Novartis checked the performance of the air handling systems as an operative unit together with the clean room area or LAF supplied by the system. All classified clean rooms / LAF were monitored for viable particles, airborne particles and surface microbial contaminants for three days. Monitoring of the clean rooms for PQ occurred during normal production activity, “in operation” (dynamic) conditions.

HVAC PQ included:

- (b)(4) successive media fills during the Performance Qualification of each filling line
- Temperature, air pressure, humidity monitoring by the (b)(4) system
- Viable and non-viable particle testing, contact plate and settle plate testing
- Continuation of the environmental monitoring program by SOP
- Simulation of worst-case conditions for the media fills, by including:
 - 100% coverage of the usable filling time and machine stops to extend the media fill runs.
 - Inclusion of maintenance simulated interventions in the media fill simulation.
 - Replacement of staff, to mimic normal shift operations

The acceptance criteria were as follows:

[(b)(4)]

[(b)(4)]

*In (b)(4), Novartis applied tighter specs for PQ in Grade --(b)(4)-- for dynamic non-viable with counts rounded down to the nearest thousandth place (i.e. -----(b)(4)-----)

For review of PQ, Novartis provided data reports for:

- Two PQ studies (Jan 2012 and Sep 2013) for --(b)(4)--. All acceptance criteria were met with the exception of two viable surface monitoring excursions in Jan 2012.
- Five PQ studies (Aug 2008, Nov 2010, Nov 2013, Jan 2014, and Mar 2014) for --(b)(4)--. All acceptance criteria were met with the exception of one viable surface monitoring excursion in Aug 2008, and two in Nov 2010.
- Three PQ studies (Jan 2012, Aug 2013, and Dec 2013) for ---(b)(4)-----. All acceptance criteria were met with the exception of one viable surface monitoring excursion in Jan 2012, one in Aug 2013, and two in Dec 2013)
- One PQ study (March 2007) for --(b)(4)----. All acceptance criteria were met with the exception of two viable surface monitoring excursions
- One PQ study (May 2010) for --(b)(4)----. All acceptance criteria were met with the exception of five viable surface monitoring excursions
- One PQ study (Mar 2007) for --(b)(4)----. All acceptance criteria were met with the exception of one viable surface monitoring excursion and one non-viable airborne particulate monitoring excursion.
- One PQ study (Mar 2007) for --(b)(4)----. All acceptance criteria were met with the exception of one airborne viable monitoring excursion.
- One PQ study (Mar 2007) for --(b)(4)----. All acceptance criteria were met with no excursions.
- One PQ study (Mar 2007) for --(b)(4)----. All acceptance criteria were met with no excursions.
- Three PQ studies (Jan 2007, Jan 2013, Mar 2013) for --(b)(4)----. All acceptance criteria were met with no excursions.
- One PQ study (Mar 2007) for ---(b)(4)-----. All acceptance criteria were met with no excursions.

- One PQ study (Mar 2007) for --(b)(4)----. All acceptance criteria were met with one viable surface monitoring excursion.

Routine Monitoring

Novartis controls the clean rooms by the routine monitoring program, per SOP 201430 “*General Procedure for Environmental Control*,” designed to comply with current health authority standards. The SOP establishes the environmental control requirements according to the area classifications and use. Personnel monitoring requirements for employees working in classes --(b)(4)-- areas and the environmental monitoring sampling plan (location of sampling points, frequencies of monitoring) for each processing area are described by SOPs.

According to Novartis, Environmental monitoring is performed under dynamic operating conditions with sampling for viable and non-viable particulates and on critical surfaces. The general environmental monitoring procedure includes viable active air monitoring, viable passive air monitoring, non-viable air monitoring surface monitoring, and personnel monitoring with acceptance criteria identical to qualification specs.

Each medium is previously tested for growth promotion according to SOP. Novartis applies the following Media and Incubation Specifications:

[(b)(4)]

Results of routine monitoring are summarized in trend reports. The environmental monitoring locations are evaluated and reviewed on a -(b)(4)- basis and adjustments to the program are implemented where appropriate. Monitoring frequencies depend on the environmental classification of the area (grade/class) and criticality of the process. The monitoring frequencies for each classified area grade and the sampling method used for both viable and non-viable monitoring under operating conditions are:

[(b)(4)]

[(b)(4)]

Novartis also employs the following procedures to ensure the quality of environmental monitoring:

- Microbiological samples are evaluated in the microbiological laboratory.
- Excursions from action limits are identified to the species of organism according to validated procedures.
- If an action limit is exceeded, a deviation report and immediate corrective actions will be initiated according to defined procedures.

Review Assessment / Comments: The qualifications appear to be comprehensive with standard verifications addressed. Relevant PQ Reports are referenced in the submission. Acceptance criteria appear adequate for the intended room classifications. The data provided appears to correspond to the design specifications, in accordance with the -----
------(b)(4)----- which recommends minimum air changes per hour to be (b)(4). Areas appear to be adequately classified for their intended use. Differential Pressures are depicted in directions of higher grade to lower grade areas. The acceptance criteria appear to correlate with acceptable conditions in cleanroom environments according to the -----(b)(4)-----

Since the rooms of the Washing and Dirty Corridor area, served by (b)(4), are unclassified, Novartis does not perform Environmental Monitoring PQ studies for those areas. However, pressure, humidity and temperature of each room are continuously monitored and controlled by the (b)(4) system. I have no objections to this approach.

Routine Monitoring and Periodic Requalification appear adequate to support environmental control, with limits identical to validation specs.

PQ studies deviations seem to have a trend to viable surface monitoring, and the resolution is unclear. PQ Report for -----(b)(4)---(Formulation and Filling Area) were not provided in the summary.

The following Information Request was sent to the firm:

- 1. Reference 3.2.A.1.4.2 Drug Substance – OMV Manufacture (Rosia), Section 3.2.A.1.4.2.4, HVAC Systems and 3.2.A.1.4.3 Drug Product – Formulation-Filling-Finish Section 3.2.A.1.4.3.4, HVAC Systems:**
 - a. For the PQ studies for -----(b)(4)-----, numerous excursions to Surface environmental monitoring excursions were reported. Were root causes identified for these events and have you recognized a trend in these deviations?**
 - b. For each deviation, you state a subsequent resampling as a resolution and then reference closing of DRs on some previous date. For example in Table 3.2.A.1.4.2.4-15 HVAC System (b)(4) Test Results - Closed on January 09th 2012, you reference “Deviation --(b)(4)-- -Surface environmental monitoring’s out of limit on point -----(b)(4)----- CFU/plate, upper than acceptance criteria. Subsequent resampling within limits permitted closing of DRs on February 13th 2008.” Please explain what the date (in this example Feb 13th 2008) is referencing.**
 - c. You have provided no EMPQ data for (b)(4) HVAC System serving the Class (b)(4) Cold Room. Do you perform EMPQ for this room?**
 - d. In Table 3.2.A.1.4.2.4-20 & -21, you cite areas that are Class (b)(4) (Exposed Product). Please identify the specific rooms where exposed product occurs, the extent of product exposure, and mitigation of risk that has been performed.**
- 2. Please confirm that ---(b)(4)--- Formulation and Filling Areas supplied HVAC systems ----(b)(4)---- will not be used for Bexsero operations.**

Novartis Response

I(a)(b)The Company would like to confirm that investigation were undertaken to identify the root cause following the surface environmental monitoring excursions reported in the PQ studies and that the appropriate CAPAs were implemented.

Some of these excursions relate to historical PQ data (original PQ data from 2008). The evaluation of the environmental monitoring data performed to date in these areas, has not identified any underlying trend for such excursions.

With regards to resampling following an excursion, the Company would like to stress that this was necessary as all other environmental monitoring sample points within the specified area were in conformance. Therefore resampling was undertaken to confirm the result. In all cases where there is such an excursion a root case analysis was undertaken and appropriate action

implemented as stated above. A summary of the deviation reports (DR) are provided in the following sections:

1. Excursions on areas covered by HVAC Systems -----(b)(4)----- in Building (b)(4) (Drug Substance OMV Manufacture)
2. Excursions measured in areas covered by HVAC System --(b)(4)-- in Building (b)(4) (Drug Product – Formulation-Filling- Finish)

1. Analysis of Environmental Monitoring Excursions on Areas Covered by HVAC Systems -----(b)(4)----- in Building (b)(4) (Drug Substance OMV Manufacture)

For areas of Building (b)(4), Rosia, covered by HVAC systems ----(b)(4)-----, a total of (b)(4) OOL (Out Of Limit) in environmental monitoring were noted from the PQ studies of the system until today. (as Novartis outlined in a table 2.2 in the response) The PQ studies were performed between 2008 and 2014. Novartis reported the details of the PQ studies were performed between 2008 and 2014 in table 2.1 in the response.

Overall Evaluation on Excursions of areas covered by Systems -----(b)(4)-----

The environmental monitoring excursion investigated relate to different periods (starting from 2008 to 2013) and areas (Fermentation, Media and Buffer Preparation and Purification). Subsequent to the respective investigations no potential trends or repetitive environmental OOL were observed.

To complete the evaluation data from January 2012 to June 2014 is presented in the Tables 2-3 to 2-9 below to demonstrate that these specific areas and systems are able to operate consistently within the respective acceptance criteria for the specific areas.

Viable samplings include all types of microbiological samplings: active and passive air monitoring, surface monitoring

Period	Type of sampling	Total # of samplings	Samplings within action limit	% of samplings within action limit
Table 2-3 Summary of EM Data for -(b)(4)- Area, HVAC System (b)(4) Fermentation (b)(4)				
Year 2012	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
Year 2013	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	99.96
Jan-Jun 2014	Non-viable	(b)(4)	(b)(4)	99.42
	Viable	(b)(4)	(b)(4)	99.88
Table 2-4 Summary of EM Data for (b)(4) Area, HVAC System (b)(4)				
Year 2012	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
Year 2013	Non-viable	(b)(4)	(b)(4)	99.67
	Viable	(b)(4)	(b)(4)	100
Jan-Jun 2014	Non-viable	(b)(4)	(b)(4)	99.17
	Viable	(b)(4)	(b)(4)	100
Table 2-5 Summary of EM Data for (b)(4)Area, HVAC System (b)(4)				
Year 2012	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	99.95
Year 2013	Non-viable	(b)(4)	(b)(4)	100

<i>Period</i>	<i>Type of sampling</i>	<i>Total # of samplings</i>	<i>Samplings within action limit</i>	<i>% of samplings within action limit</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
<i>Jan-Jun 2014</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
Table 2-6 Summary of EM Data for (b)(4)Area, HVAC System (b)(4) – Purification (b)(4)				
<i>Year 2012</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>99.94</i>
<i>Year 2013</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>99.97</i>
<i>Jan-Jun 2014</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
Table 2-7 Summary of EM Data for (b)(4)Area, HVAC System (b)(4)				
<i>Year 2012</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
<i>Year 2013</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
<i>Jan-Jun 2014</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>00</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
Table 2-8 Summary of EM Data for (b)(4)Area, HVAC System (b)(4)– Buffer & Media Preparation/Sterilization and Clean Corridor				
<i>Year 2012</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
<i>Year 2013</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
<i>Jan-Jun 2014</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
Table 2-9 Summary of EM Data for (b)(4)Area, HVAC System (b)(4)				
<i>Year 2012</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
<i>Year 2013</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>99.95</i>
<i>Jan-Jun 2014</i>	<i>Non-viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>100</i>
	<i>Viable</i>	<i>(b)(4)</i>	<i>(b)(4)</i>	<i>99.95</i>

2. Analysis of EM Excursions on Areas Covered by HVAC Systems ---(b)(4)---- in Building (b)(4), Rosia (Drug Product Manufacture)

Building (b)(4) – General Area and Inspection (b)(4) (HVAC (b)(4)) – Formulation -(b)(4)- --- (b)(4)----- . Novartis provided a summary of the Deviation reports for OOLs that occurred in (b)(4) Rosia during the validation in Table 2-10.

From their overall evaluation, Novartis excluded any connection between ---(b)(4)----- considering:

- Different Module and Area.
- Different room and Grade classification.
- Different microorganism origin and species ----- (b)(4)-----
- Different days of EM Excursion.
- Trend analysis on points ----- (b)(4)-----.
- Value of all other sampling results linked to impacted area.
- Re-sampling outcome – All points were conform after further sampling monitoring.

The environmental monitoring deviations discussed in the Table 2-10 are historical (from 2006), the Company is confident of the compliance and quality standard of HVAC (b)(4) and (b)(4).

To complete the evaluation data from January 2012 to June 2014 are presented in the Tables 2-11 to 2-15 below to demonstrate that these specific areas and systems are able to operate consistently within the respective acceptance criteria for the specific areas.

Period	Type of sampling	Total # of samplings	Samplings within action limit	% of samplings within action limit
Table 2-11 EM Data for General Area and Inspection PFS1 (b)(4), serviced by HVAC (b)(4)				
Year 2012	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	99,86
Year 2013	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
JAN/JUN 2014	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
Table 2-12 EM Data for Area Formulation ----(b)(4)----, Serviced by HVAC (b)(4)				
Year 2012	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
Year 2013	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	99,74
JAN/JUN 2014	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	99,25
Table 2-13 EM Data for Formulation ----(b)(4)----, serviced by HVAC (b)(4)				
Year 2012	Non-viable	(b)(4)	(b)(4)	99,9
	Viable	(b)(4)	(b)(4)	99,93
Year 2013	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
JAN/JUN 2014	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	99,91
Table 2-14 EM Data for Formulation ----(b)(4)--- Area, serviced by HVAC (b)(4)				
Year 2012	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	99,93
Year 2013	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
JAN/JUN 2014	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
Table 2-15 EM Data for Formulation -----(b)(4)---- Area, serviced by HVAC (b)(4)				
Year 2012	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
Year 2013	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100
JAN/JUN 2014	Non-viable	(b)(4)	(b)(4)	100
	Viable	(b)(4)	(b)(4)	100

I(c) The Company would like to confirm that EMPQ for the class --(b)(4)-- room has been performed. Novartis provided details of the historical and current PQ data for HVAC system (b)(4) which serves (b)(4) room --(b)(4)--- (room number (b)(4)) are provided in Tables 2-16 to 2-18.

- *Table 2-16 Results of Performance Qualification Executed for HVAC System ---(b)(4)--- Room ---(b)(4)----- Generated in 2008*
- *Table 2-17 Results of Performance Qualification Executed for HVAC System (b)(4) in 2010*
- *Table 2-18 Results of Performance Qualification Executed for HVAC System (b)(4) in 2013*

No deviations were recorded during the execution of the above mentioned studies; all the results met acceptance criteria demonstrating that the (b)(4) HVAC system ensures the (b)(4) classification of ----(b)(4)-----.

I(d) The Company would like to clarify that the expression “Class (b)(4) (exposed product)” identifies areas where production activities which cannot be considered completely closed are carried out. In particular these processing activities are undertaken in laminar flow or biohazard hoods located within the clean room environment. A more frequent EM routine monitoring is undertaken for the areas where these class (b)(4) open activities are performed (laminar and biosafety hood)

Table 2-19 below summarizes the activities on each of the area where exposed product processing occurs.

Table 2-19 Summary of Open Processing Operations in Bldg. (b)(4)

[(b)(4)]

The exposure of the product is limited to the short duration needed to perform the activity (e.g. the filling of the bottles). The risk is mitigated as the operation is performed in a dedicated qualified laminar flow hood which is situated in a clean room environment, thus providing a greater protection for the product.

2. The Company would like to clarify that ---(b)(4)- Formulation and Filling Areas, ---(b)(4)-----is executed into ---(b)(4)-- areas (----(b)(4)-----) as reported in the relevant section 3.2.A.1.4.3.1.1.

<i>---(b)(4)----</i>	<i>---(b)(4)----</i>
<i>------(b)(4)-----</i>	<i>------(b)(4)-----</i>
<i>-----</i>	<i>-----</i>

Also ---(b)(4)--- Formulation and Filling Areas will not be used for ----(b)(4)-----, Bexsero formulation, filling and inspection operations. Details of the rooms where these operations are executed are provided in the Table 3-1 below.

Table 3-1: Details of Process Areas for Bexsero Drug Product Manufacture

[(b)(4)]

Review Assessment / Comments: Table 2.1 for “PQs performed on Systems -----(b)(4)----- showed most recent PQs performed in Sep 2014, Dec 2013, and March 2014 for -----(b)(4)----- respectively. Requalification appears to be consistently performed as required.

Table 2.2 for OOL Deviation Report Summary for Areas of Building (b)(4), Rosia, covered by HVAC systems ----(b)(4)----- showed that all excursions were in Grade --(b)(4)-- areas. The highest count observed was (b)(4) CFU/plate (Limit was (b)(4) CFU/plate) in a Grade (b)(4), Wash Room. All eight events appear to be investigated thoroughly with microorganisms identified, and CAPAs applied to each event.

Table 2.10 Deviation reports for OOLs that occurred in (b)(4) Rosia during the validation, the three events appear to be investigated thoroughly with microorganisms identified, and CAPAs applied to each event.

Novartis has provided evidence of no trend in their analysis.

The acceptance criteria for the qualification of the ----(b)(4)----- correlate with the acceptance criteria for the other Class (b)(4) areas.

Formulation and filling does not occur in --(b)(4)-- areas. The Class (b)(4) (exposed product) activities appear to be lower risk; the DS is a ----(b)(4)---- material at this point, and is subsequently sterile filtered. I have no further concerns. No objectionable findings noted.

h. Processing Equipment Overview

Product Contact Equipment for OMV Production (b)(4) is:

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

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

[(b)(4)]

Novartis performed equipment qualification according to requirements to SOP 247293, SOP 220820 & SOP 247293 and outlined in the validation master plan and included, where appropriate, installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) components. Commercial off-the-shelf (COTS) equipment is subjected to reduced documental flow (SOP 202026), but is subject to full operating test. All required documentation has been QA approved and are on file at the site.

Separately from Process Validation, Novartis performed PQ on the following equipment:

[(b)(4)]

<p><u>Review Assessment/Comments</u>: Equipment appears adequate for its intended use, no novel technology appears evident. Some further clarification on shared equipment is needed.</p>

Filling Equipment

Filling Dosage ---~~(b)(4)~~--- and Filling Dosage ---~~(b)(4)~~---

The filling volume applied for Bexsero is --~~(b)(4)~~-- (target) with acceptance range (safety range) of ----~~(b)(4)~~-----; considering the density of the product, the filling volume corresponds to -

-(b)(4)-- with acceptance range (safety range) of ----(b)(4)----- . The filling volume with the product has been checked during the process validations every (b)(4) minutes. In addition, before the process validations, the filling machines ----(b)(4)----- have been qualified to demonstrate their ability to dose the required volume using WFI that was considered representative of all the products for that purpose. The qualification consisted of -----
------(b)(4)-----
----- . Novartis summarized the results obtained during the relevant filling machine qualifications:

[(b)(4)]

Novartis reports that all PQ tests passed for filling dosage.

<u>Review Assessment/ Comments:</u> Fill Volume PQ appears adequate. No objectionable findings noted.

Automatic Inspection Equipment --(b)(4)-- and --(b)(4)--

Filled syringes are -(b)(4)- visually inspected on an automatic inspection machine in order to detect and reject any cosmetic and particulate defects. The following parameters are checked by the inspection machine ----(b)(4)----:

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

The automatic inspection machines can inspect impurities in transparent products that have a clear and limpid aspect, like water, and opalescent or opaque products having aluminum hydroxide or aluminum phosphate contents up to a minimum --(b)(4)---- concentration of Al³⁺.

For validation tests, the following PFS Kits are prepared with faulty vials taken during production or prepared manually, if not available:

- -----(b)(4)----- for transparent and opalescent products, aimed to detect particle defects
- Volume and Sample Review Kits: syringes prepared for the Form Test Kit

These kits are used to validate the reliability and reproducibility of the checks carried out by the machine. These checks are re-verified at each production batch start and end by means of a form test (cosmetic defects) and a verification test (particle defects).

The controls on the machine are able to detect possible defects present in production. The defects are subdivided in 2 main categories, Critical and Non-Critical), in relation to the gravity of the damage that has to do with the quality of the product.

The first category (Critical) defects can damage the product by altering its therapeutic characteristics or quality. The second category (Non-Critical) defects, defined as cosmetic (major or minor), do not alter the therapeutic characteristics of the product, but can make it inadaptable for its commercialization.

The following defects relative to the ones mentioned above are taken into consideration and analyzed:

Types of Defect	Criticality	
Particle Dispersed in the Liquid	Critical	Level 1
Filling Level High/Low	Critical	Level 1
Cracks on the Syringe	Critical	Level 1
Defective Plunger	Critical	Level 2
Product Opacity	Critical	Level 2
Needle Cover Missing	Critical	Level 2
Bent Needle	Critical	Level 2
Broken Flange	Major (Non Critical)	Level 3

Novartis provided detailed description of the configuration of the description of Inspection Automatic Machines ----(b)(4)----- . Both systems are automated and consist of --- --(b)(4)----- as well as the -----(b)(4)----- . Novartis provided tables of the Control units versus Defect Inspection performed for each unit on each machine. --(b)(4)-- consists of a -----(b)(4)----- detection sensor that reads the intensity of the light. Each syringe to be inspected passes between the transmitter and the receiver.

Novartis performed PQ consists of (b)(4) phases. The first --- (b)(4) -- phase, referred to as --- (b)(4) ----, is aimed at checking the capacity of the machine to consistently discriminate among different types of defects. In particular, the performance qualification tests can be summarized as follows:

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

Novartis carried out the second phase, named -----(b)(4)----, on -(b)(4)- batches processed for opalescent product. The validation is carried out through the automatic inspection of a number of pre-filled syringes -----(b)(4)-----

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

lots used for Phase III clinical trials with the Luer ---(b)(4)--- presentation (X38D27N1, X38D28N1, and X38D29N1); these lots also served as consistency lots for the manufacturing process.

Due to the discontinuation of production of the rubber formulation --(b)(4)-- (present in the syringe tip cap), Novartis initiated a replacement plan. Two syringes (Luer ---(b)(4)--- and Luer Lok -(b)(4)-) were identified to replace the Luer ----(b)(4)---

Novartis reports that the plunger stopper ---(b)(4)-----, which is a direct vaccine-contact material, is the same for all three syringes and the Luer ---(b)(4)--- and Luer Lok --(b)(4)-- syringes have the same barrel (1mL short).

To demonstrate the suitability of the container closure system, Novartis conducts a container closure integrity test (CCIT) that consists of the -----
------(b)(4)-----

----- Novartis verified the amount of -----(b)(4)-----, with an acceptance criterion of (b)(4) CFU/ml. Control syringes inoculated with ----(b)(4)----- served as positive controls. Novartis performed the CCIT at Time (b)(4) and at regular time points (every (b)(4) months up to (b)(4) months then --(b)(4)-- over the entire shelf life of the product.

Samples used in the study are stored at the same temperature conditions as the final product (2-8°C). (b)(4) syringes are scheduled to be tested at each time point. At the end of each test, the positive control and test syringes were evaluated for microbial growth. Novartis reported results obtained up to (b)(4) months for the Luer ---(b)(4)----- and Luer --(b)(4)--- test syringes, and up to (b)(4) months for the Luer Lok -(b)(4)- test syringes. The test results for all syringe types met the acceptance criterion for container closure integrity testing. All positive controls showed growth confirmed as ---(b)(4)---

Review Assessment / comments: I defer review of the Leachable Studies to the Product Specialists. No reference or evidence of CCIT validation was provided in the submission.

The following information request was sent to the firm:

- 1. Please confirm that the Luer Lok -(b)(4)- syringe will be used solely for commercial product, or do you plan to use the Luer ---(b)(4)-- syringe alternatively, as needed?**
- 2. Please provide a summary of the syringe CCIT validation with reference to relevant protocols.**
- 3. Was functionality testing of the syringe system(s) performed?**

Novartis Response

1. The Company would like to confirm that the primary packaging Luer Lok -(b)(4)- syringe presented in section 3.2.P.7 is the only primary packaging that will be used for Bexsero commercial product.

2. Historically the validation of closure integrity test (CCIT) has been executed using a ---(b)(4)--- test according to SOP 201635. This qualification requires the integrity test at different time points up to (b)(4) years. Following interaction with CBER related to container closure issues relating to other Novartis products, the Company has made improvements to its container closure procedures to include a ---(b)(4)--- method.

The ---(b)(4)--- method (SOP 295059) will be introduced for new container closure validations and the repetition of the already executed studies. The existing studies that were initiated with the --(b)(4)--- method, only, will go ahead for the following time points with the same method.

The validation study for the current Luer Lok presentation started in 2008, and the study report “----(b)(4)-----Luer-Lock/Integrity_Closure/PQR/00”, including all the results up to (b)(4) years has been completed and approved. The results demonstrated that the syringe/stopper is able to guarantee the container closure. Details of the study are presented in the dossier section 3.2.P.2.5 Microbiological Attributes for which data analysis has been completed and is presented in this response.

One new CCIT study using the --(b)(4)--- method has been recently executed for the syringe/stopper used for Bexsero on ---(b)(4)-- line and the (b)(4) months results have met the acceptance criteria (study report 92/CCIT/------(b)(4)-----Luer-Lock/PQIR/02).

A second new CCIT study with the ---(b)(4)--- method has been recently executed for the syringe/stopper used for Bexsero on -(b)(4)- line and the (b)(4) months results have met the acceptance criteria (study report 92/CCIT/----(b)(4)----- Luer-Lock/PQIR/01).

The following section provides procedural details of the CCIT studies which have been executed.

---(b)(4)--- CCIT Study

The validation of the Luer Lok syringe was initially performed in 2008 and the description below incorporates improvements in the method that are used evaluate the follow-up time-points

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

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

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

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

[(b)(4)]

----(b)(4)----- **CCIT Method**

Novartis has improved its approach for future CCIT validation procedures by moving to a --(b)(4)--- test. A new method (SOP 295059) has been developed and validated (report 296376). This method implemented a positive control to increase assay sensitivity to detect minute leaks in the closure system. This was accomplished by using a -----(b)(4)----- . As part of the new (b)(4) method introduction, a comparison study between the (b)(4) test and the --(b)(4)----- test has been performed -----(b)(4)----- to demonstrate that the (b)(4) method is at least equal or better than the -(b)(4) method. This method will be performed on containers and the filling line being used to perform the filling in future validation studies.

*This method is now implemented for routine validations and the SOP 295059 has been implemented. As stated above, CCIT studies with the --(b)(4)-- method have been executed for the syringe/stopper used for Bexsero on --(b)(4)-- line and on --(b)(4)-- line. The results (for --(b)(4)-- line) at time point (b)(4) months are reported in the interim report ““92/CCIT/-----
----- (b)(4)-----Luer-Lock/PQIR/02”. The results (for -(b)(4)--- line) at time point 6 months are reported in the interim report ““92/CCIT/----- (b)(4)-----Luer-Lock/PQIR/01”. A Summary of the data are presented in Table 13-2 and Table 13-3*

**Table 13-2: Summary of CCIT study 92/CCIT/----- (b)(4)-----
Intrusion Test**

[(b)(4)]

[(b)(4)]

Table 13-3: Summary of CCIT study 92/CCIT/------(b)(4)----- using -----
--(b)(4)---- Test

[(b)(4)]

3. Functionality testing of the syringe system has been performed by device supplier ----(b)(4)---

The Syringe used by Novartis Vaccines for Bexsero product is a Luer Lok syringe-----
------(b)(4)----- (catalog numbers are -----(b)(4)-----),
supplied from -----(b)(4)----- . The Plunger used by Novartis Vaccines for Bexsero product is
------(b)(4)-----

Details of the test performed by -----(b)(4)----- are provided below:

For the syringe:

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

For the plunger:

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

The executive summary report describing the results of the tests performed by (b)(4) is attached to this document (Attachment Q14)

As part of the Bexsero combination product implementation plan, a design verification protocol is planned to be issued and executed by the Company by the end of Q3 2015. The purpose of this protocol is to confirm that Bexsero combination product system (syringe, plunger, plunger rod and drug product) is performing in accordance to functional requirements expected for this type of device.

Review Assessment/ Comments: Evidence of the completion of a thorough CCIT study is provided with reference to relevant protocols & SOPs, both -----(b)(4)----- tests were performed. Standard functionality testing addressed with design verification planned; requirements of 820s appear to be considered. Novartis' justification for their CCIT Positive control leak aperture size, and better understanding of their ----(b)(4)--Test Method is needed.

Evaluation of the Incoming Testing / Release Requirements for the Syringe and Stoppers is needed.

j. Process Validation (OMV)

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

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

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

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

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

k. Formulation and Filling Process Validation (Drug Product)

Process validation of the formulation and filling process for the production of the 4CMenB vaccine was performed in November 2007 at a scale of up to (b)(4). In April 2010, the formulation scale was increased and validated up to (b)(4). In order to validate the formulation process, and to allow use of a range of volumes that may be necessary for commercial operations, a -(b)(4)- approach was used: (b)(4) runs (batches) at the maximum manufacturing batch size (b)(4) and (b)(4) additional run at the minimum batch size (b)(4) were performed.

Formulation Overview

The major steps of Formulation are as follows:

[(b)(4)]

Formulation Validation

During this validation, Novartis applied a bioburden limit of ---(b)(4)--- mL to the -----
----- (b)(4)-----
----- preparation is performed
in a grade (b)(4) area and is -----(b)(4)----- located in a grade (b)(4) area

Prior to the initiation of the formulation process validation, Novartis performed a Quality Risk Assessment (QRA) to identify critical parameters and process controls for the formulation process. The following were defined in the QRA as critical parameters and were controlled within the ranges identified during the validation study:

[(b)(4)]

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

[(b)(4)]

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

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

[(b)(4)]

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

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

Review Assessment/ Comments: Novartis taken no less than (b)(4) samples per run at --(b)(4)-----, end of the validation runs (----- (b)(4) ----- runs respectively). Acceptance criteria correlate with specification, with exception to the Endotoxin limit. A validation release criterion for endotoxin was --- (b)(4) --- and specification is --- (b)(4) ---. Novartis noted that this spec has been updated (tightened) in their summary. Novartis' justification for the specification is that due to the presence of ----- (b)(4) -----, the Drug Product has some endotoxin activity and the specifications is based on data from five clinical lots of 4CMenB which they supported the number with a statistical calculation. Novartis reports no Endotoxin result from clinical batches or validation batches to exceed --(b)(4)-----. Historically, the endotoxins results appear to range from ----- (b)(4) ----- . Novartis reported no bioburden, endotoxin, or pyrogen OOS. Data in summary document appears to correlate with validation reports. Relevant SOPs are referenced in the protocols. No objectionable findings noted.

I. Drug Product Release Specification

Test	Method of Analysis	SOP	Reference	Specification	
Final Bulk					
------(b)(4)-----	---(b)(4)---	---(b)(4)---	---(b)(4)---	---(b)(4)---	
---(b)(4)---	---(b)(4)---	---(b)(4)---	---(b)(4)---	---(b)(4)---	
Filled Product (in Pre-filled Syringes)					
Identity	rp961c	---(b)(4)---	228563	Internal	Positive
	rp936-741				Positive
	rp287-953				Positive
	OMV				Positive
Volume	Extractable volume	203519	---(b)(4)---	≥ 0.50 mL	
Appearance	Visual inspection	202564	Internal	Opalescent liquid (white suspension)	
---(b)(4)---	------(b)(4)-----	202469	Internal	---(b)(4)---	
---(b)(4)---				---(b)(4)---	
---(b)(4)---				---(b)(4)---	
------(b)(4)----- ---(b)(4)---				---(b)(4)---	
pH	---(b)(4)---	202553	---(b)(4)---	---(b)(4)---	
------(b)(4)-----	------(b)(4)----- -----	202551	---(b)(4)---	---(b)(4)---	
Endotoxin	------(b)(4)-----	201708	---(b)(4)---	---(b)(4)---	
------(b)(4)-----	------(b)(4)-----	235283	Internal	---(b)(4)---	
Sterility	------(b)(4)-----	201631	---(b)(4)---	Sterile	
Pyrogen	------(b)(4)-----	201796	---(b)(4)---	---(b)(4)---	
Immunogenicity	rp961c	------(b)(4)----- ------(b)(4)----- -----	305566	Internal	---(b)(4)---
	rp936-741				---(b)(4)---
	rp287-953		---(b)(4)---		
	OMV		305567		---(b)(4)---
Visible Particles	Visual inspection	286169	---(b)(4)---	Conforms (absence of foreign particles)	
Packaged Product					
Identity	rp961c	------(b)(4)-----	228563	Internal	Positive
	rp936-741				Positive
	rp287-953				Positive
	OMV				Positive

Novartis States that, due to the presence of (b)(4) in the ------(b)(4)-----, the Drug Product has some endotoxin activity. Specifications are based on data from five clinical lots of 4CMenB.

Review Assessment / Comments: Specifications appear to correlate with Process Validation Criteria. Justification for specification for endotoxin appears acceptable but the final assessment is deferred to DBSQC and/or product office reviewer. Final product is required to be sterile and ---(b)(4)---. No objectionable findings.

-----(b)(4)---- for -(b)(4)- Formulation Tank

In April 2010, Novartis started a study to provide data on 4CMenB -----(b)(4)----- to verify the stability (chemical and microbiological) of -----(b)(4)----- 4CMenB liquid (b)(4) in a -----(b)(4)----- . This study has been performed on three validation lots of ----(b)(4)----- . For this study, about -----(b)(4)-----, simulating the formulation tanks.

[(b)(4)]

Samples were tested at one month intervals up to four months, and all met the acceptance criteria as follows:

[(b)(4)]

Review Assessment/ Comments: No objectionable findings noted.

m. Media Simulations

OMV

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

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

[(b)(4)]

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

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

Review Assessment/ Comments: The relevant Cleaning Validation Reports were referenced in the submission. Novartis provided a table of potential residues from the OMV process and cleaning, and states that, when more than one type of residue is present, an assessment is done to identify which is the most difficult to clean and this is the residue that is to be used during validation, but did not identify which residue was used as worst case in the submission. Novartis did not provide cleaning validation data for product contact equipment used for the media and buffer preparation. However, they state that cleaning validation has been performed.

PW rinse limits appear acceptable for intended use. Rationale for (b)(4) limit is not clearly explained adequately. The final WFI Rinse limits are slightly higher than (b)(4) standards, need rationale.

I suggest the following Inspectional Consideration:

Verify that cleaning validation data for product contact equipment used for the media and buffer preparation has been performed and is adequate for its intended use.

The following Information Request was sent to the firm:

- 1. In Table 3.2.A.1.4.2.6.1.9.2-1 Types of Residues and Method of Detection, you provide the potential residues, but do not state which one was the most difficult to clean, and the Method of detection used for that residue. Please provide this information.**
- 2. Please provide a table of the Clean and Dirty Hold times that you have established for the OMV equipment.**
- 3. Please provide the rationale for your limits for WFI rinse cleaning procedures.**

4. Please provide a rationale for your (b)(4) limit of --(b)(4)-- including how it equates to a parts per billion calculation and why it is acceptable for every piece of equipment even those they have different surface areas.

Novartis Response:

1. The cleaning validation for each piece of equipment was performed with the actual in-process soil at that step, rather than selection of a particular soil that could be more difficult to clean. The only exception to this is in the media and buffer preparation area, where multiple solutions are prepared in a single vessel (aqueous solutions, organic solutions, media). For these solutions, a dedicated cleanability study was performed which demonstrated that the soils evaluated represented equivalent cleaning challenges for the equipment, and that any could be used for validation (additional details in table below).

Table 6-1 below provides additional details on the cleaning validation approach, as well as the methods used for detection of the specific soils.

Table 6-1 Types of ---(b)(4)---, Method of Detection and cleaning validation approach for equipment used in Media and Buffer preparation.

[(b)(4)]

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

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

2. FinalFillDrugProductionbldg.(b)(4).

Regarding product contact equipment used for the fill-finished product (formulation and filling operations), limits for -----(b)(4)----- for rinsing samples are reported as follows:

Final Rinse Condition:	Acceptance Criteria		
WFI rinse	----(b)(4)----	----(b)(4)----	----(b)(4)----
	----(b)(4)----	----(b)(4)----	----(b)(4)----

As an outcome limits for ----(b)(4)----- are the same as WFI limits.

In addition to rinse sampling, as a complementary method, detection of ---(b)(4)----- is performed. In this case -(b)(4)- limits of equipment sampled in (b)(4) class are established at --(b)(4)-----, according to those recommended for --(b)(4)-- by the -----

All the product contact equipment used for the fill-finished product are ----(b)(4)----- prior to use and the cleaning validation sampling -----(b)(4)----- the cleaning cycle, before the sterilization step.

Regarding ---(b)(4)---- the limits of --(b)(4)-- is applied, according to the correlation study performed by the supplier on ---(b)(4)--- residues. Per Novartis SOP, historical limits for ---(b)(4)--- residues have been set at -(b)(4)-. A study has been performed by the ---(b)(4)--- supplier -----(b)(4)----- in order to measure the correlation between ----(b)(4)---- level and the ---(b)(4)--- residues.

Data showed that ----(b)(4)----- value corresponds to less than -(b)(4)----- measured -----(b)(4)-----

volume which will come into contact. For this reason, the potential carryover is calculated on the OMV final bulk volume, which is approximately (b)(4).

Review Assessment/ Comments: Rationale for residual limits appear acceptable; MAC calculation used to determine (b)(4) limits for dedicated equipment is acceptable. Confirmed Clean and Dirty Hold times are established. No objectionable findings.

In (b)(4), Novartis validated cleaning procedures for equipment used to formulate, fill and package multiple vaccine and adjuvant products. Product Contact Equipment and associated cleaning systems are as follows:

[(b)(4)]

¹ Needles and Piping – Dedicated

All cleaning systems are located in a dedicated area on -(b)(4)-. The washing cycles are validated by analyzing water samples and swabbing representative cleaned items. A typical cleaning process includes -----(b)(4)-----

Novartis performed the cleaning validation activities with fixed time frames of (b)(4) hours - (b)(4)- for the storage of unclean equipment, representing the worst-case condition. For automatic cleaning cycles, ----(b)(4)----- runs of cleaning procedures were performed; a visual inspection is executed to observe for the absence of non-soluble residues and equipment dryness after each cycle. For fixed and mobile equipment listed above, Novartis established the ----(b)(4)--- and the -----(b)(4)----- months.

According to Novartis, the ----(b)(4)---- detects product residues on equipment surfaces. The limits set for protein residues are dependent on whether the equipment is dedicated or multiproduct. For dedicated pieces of equipment, the limit is based on a ---(b)(4)-- active residual value of -(b)(4)-. The limit is then calculated taking into account the minimum batch size, the worst case surface contact area and the --(b)(4)-- area. For multiproduct pieces of equipment, the limit is determined taking all products into consideration. The calculation includes the smallest batch size, the lowest total protein per dose, the worst case surface contact area and the -----(b)(4)-----

Novartis provided a step-wise description of the washer and (b)(4) cycles in the submission.

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

Novartis has the following CV Specifications:

[(b)(4)]

Novartis reports that all acceptance criteria were met.

Review Assessment/ Comments: The cleaning validation appears to provide evidence that Novartis' cleaning procedures allow for the removal of contaminants associated with previous batch and residues of cleaning agents, as well as the control of potential microbial contaminants. Novartis reported Cleaning Revalidation study for --(b)(4)-- and -(b)(4)- to include --(b)(4)-----
------(listed in memo). The CV limits appear acceptable, --- (b)(4)--- limits needs some rationale. For --- (b)(4)--- is not required; however, -(b)(4)- for --- (b)(4)----- is required, which is adequate for -----(b)(4)----- . For Filling machine -----(b)(4)-----, Novartis did not establish a ---(b)(4)----- because the equipment, the equipment is ---(b)(4)--- immediately after filling. This approach appears acceptable.

The following Information Request is sent to the firm:

Reference Table 3.2.A.1.4.3.7.1.10-2, Current Specifications for the Cleaning Validation” You state that the (b)(4) cycle ends when the -----
----- (b)(4)-----
-----However, your current CV specification for -----(b)(4)----- Please provide your rationale for this limit.

Novartis Response:

The Company would like to clarify that the acceptance limit for -----(b)(4)----- on the basis of the following rationale. Cleaning procedure for formulation and filling equipment include the use of a --(b)(4)--. Per Novartis SOP, historical limits for ---(b)(4)--- residues have been set at --(b)(4)--. A study has been performed by the ---(b)(4)--- supplier --(b)(4)----- in order to measure the correlation between ----(b)(4)--- level and the ---(b)(4)--- residues.

The data confirmed that --(b)(4)--- rinse --(b)(4)-- value corresponds to less than -----
------(b)(4)-----

Regarding the (b)(4) system, it has been installed on -(b)(4)- line only, and the functioning principle ensure that the cleaning cycle -----(b)(4)-----

Review Assessment/ Comments: Limit rationale is acceptable. Novartis reported cleaning revalidation activities, after the restart of the area in 2012, following (b)(4) years of shutdown. However, reports no (b)(4) results-justification needed. Novartis states 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 203052.”-need to evaluate the deviation, and when cleaning validation activities are expected to be completed. Clarification on omission of (b)(4) rinse testing for Washing Machine and CIP is needed. No objectionable findings noted.

o. Sterilization Performance Qualification

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

Formulation tanks and filling components of Syringe filling machine --(b)(4)-- are steam sterilized in autoclave ----(b)(4)----- . PQ of autoclaves consists mainly in the verification of heat distribution and heat penetration performed in loading conditions. Each load has been individually validated with (b)(4) runs at the maximum configuration and (b)(4) runs at the minimum configuration. During the distribution and heat penetration tests, a number of --- (b)(4)----- were arranged in the ----(b)(4)----- and -----(b)(4)----- with population ----(b)(4)----- . Acceptance criteria for the qualification test are -----(b)(4)----- of BIs. All the results met the pre-defined acceptance criteria.

Novartis made reference to the relevant qualification reports ((b)(4) totals) and reported acceptable results per each autoclave and each load.

Review Assessment / Comments: At least (b)(4) runs of maximum load were performed for each configuration, as recommended per PDA TR 1. Standard approach to sterilization qualification appears evident. No objectionable findings noted.

(b)(4) System Dedicated to Syringe Filling Machine -(b)(4)-

Novartis uses the (b)(4) system installed on filling machine -----(b)(4)----- the product contact parts by flowing steam. To qualify the (b)(4) system, -----(b)(4)-----

Acceptance criteria for the qualification test are -----(b)(4)-----
----- All the results met the pre-defined acceptance criteria. Novartis referenced the relevant PQ Report.

Review Assessment / Comments: Standard approach to sterilization qualification appears evident. No objectionable findings noted.

p. Stability

Novartis has placed the (b)(4) batches -----(b)(4)-----, filled in Luer Lok syringes with -(b)(4)- tip cap and stored at 2-8°C with stability results through (b)(4) months. Novartis is testing as the full release specification in real time for up to (b)(4) months.

Novartis will place a minimum of (b)(4) lot of filled product for 4CMenB vaccine on stability - (b)(4)--- to confirm the shelf-life of 24 months when stored at 2-8°C and protected from light. The -(b)(4)- stability program will include specification tests at specified intervals provided in a table in the submission. Novartis commits to report confirmed out-of-specification results up to and including the claimed shelf-life of 24 months.

Review Assessment/ Comments: For final DP container, sterility is tested at T₀, 24 months, (b)(4) month and (b)(4) month test points. Endotoxin is tested at T₀, 6,9,12, 24, (b)(4) month and (b)(4) month test points. Novartis reports no sterility or endotoxin OOS up to date.

Novartis has indicated that CCIT is performed Time 0 and at regular time points (every_{(b)(4)} months up to (b)(4) months then (b)(4) over the entire shelf life of the product in the stability program. However, it is not outlined in the Post Approval Stability Program. I defer the review of the OMV Drug substance Stability to the Product Office Specialists.

The following information request will be sent to the firm:

Will Container Closure Integrity Testing (CCIT) be included in the Post Approval Stability for Final Filled Product (PFS)? If so, please provide the time intervals.

Novartis Response:

The Container Closure Integrity Testing studies executed for the Bexsero final filled product are summarized in the response to Q13. Based on the CCIT data presented and the scope of studies in progress, the Company believes that in conjunction with the periodic sterility testing undertaken during the stability study program that it is not necessary to include additional CCIT into the post approval stability program.

<p><u>Review Assessment/</u> Comments: Based on CCIT study overview provided in this same response; Novartis is studying CCIT out to (b)(4) months in current ongoing studies. However, the CCIT and other stability testing on ongoing post approval batches support control of the process. This CCIT study is representative of one timepoint; -----(b)(5)----- -----.</p>

7. Inspection Considerations

Note: Line items below are hyperlinked to the applicable section of this review memo

1. [Verify adequate qualification and control of disinfectants used for cleaning of facility.](#)