

Inspection Waiver Memo, September 8, 2014 - BEXSERO

To: DATS: 586296
STN BLA 125546/0
Novartis Meningococcal B Recombinant Vaccine (4CMenB); Bexsero®
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: Decision for a Waiver of a pre-license inspection 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 Novartis Vaccines and Diagnostics S.r.l., Bellaria-Rosia, Sovicille Italy.
FEI# 3006738517

ADD: 23 Jan 2015

John A. Eltermann, Jr., R.Ph, M.S	CONCUR	DO NOT CONCUR
Director, Division of Manufacturing and Product Quality		
Office of Compliance and Biologics Quality		
Center for Biologics Evaluation and Research		

Jay Slater, MD	CONCUR	DO NOT CONCUR
Director, Division of Bacterial, Parasitic & Allergenic Products		
Office of Vaccines Research and Review		
Center for Biologics Evaluation and Research		

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 approval for this product for indication of 4CMenB in adults and adolescents -----(b)(4)-----.

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* (at the ----(b)(4)----- facility in --(b)(4)-):

- 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 factor H Binding Protein (fHBP or 741) fusion protein. The nucleotide sequence of fHBP is derived from Strain MC58 and is fused with the nucleotide sequence of the Accessory Protein 936, which is derived from Strain 2996

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)---.

Supporting Information

Justification for this Inspection Determination is based on criteria outlined in CBER SOPP 8410 "Determining When Pre-Licensing/Pre-Approval Inspections (PLI/PAI) are necessary." As stated in the SOPP, CBER's policy is that a pre-license or pre-approval inspection will generally be necessary for a supplement if:

1. The facility does not hold an active US license.

Novartis Rosia is US approved as a multi-product facility; Novartis holds current U.S. license #1751 for Menveo® and other US approved products.

2. The facility has not been inspected in the last two years by the FDA.

The inspectional history of Novartis Vaccines and Diagnostics S.r.l. [Last two years] at Rosia, Sovicille Italy Site (FEI# 3006738517) is as follows:

Date	Type	Product(s)	Investigators	Classification
10 Jun 2013- 18 Jun 2013	Surveillance; Level 2	Multi-product covered Quality, Production, and Facilities/Equipment.	Team Biologics	VAI

Note: Rosia was inspected by international regulatory agencies for the approval of Bexsero for international markets as follows:

Date Regulatory Agencies

2011 Turkey Ministry of Health

2011 Health Canada's Biologics and Genetic Therapies Directorate (Canada BCTD)

2012 Brazilian Health Surveillance Agency (ANVISA-Brazil)

Compliance Check received on 12 Aug 2014 states that there are no ongoing or pending investigations or compliance actions with respect to the above facility or its product(s).

3. The previous inspection revealed significant GMP deficiencies in areas related to the processes in the application/supplement (similar processes) or systemic problems, such as QC/QA oversight.

The most recent inspection, conducted by Team Biologics, was classified as Voluntary Action Indicated.

Note: Novartis submitted an Electronic Biological Product Deviation Report # 380642 for Menveo® on April 13, 2012 for a “data handling issue” in Building (b)(4) at Rosia. During an investigation of a manufactured lot of MenY polysaccharide, Novartis determined that excursions from the in-process control limits during the ---(b)(4)----- process had not been reported as deviations in all cases. Print outs from the Manufacturing ---(b)(4)--- Control system in Building b(4) were, in some cases, were manually manipulated before their inclusion in the batch records to remove excursions. During the June 2013 FDA inspection, per the EIR, the investigators reported the issue as a 483 observation, and performed a comprehensive audit. Novartis reported that a manager manipulated data and coerced personnel under his supervision to alter data and manipulate samples. Per the EIR, the Agency Investigator “was able to confirm that the firm was very conscientious and diligent in ensuring that the full extent of the data manipulation issue was investigated and corrective action implemented.”

As part of the resolution of this issue, Novartis revalidated their CRM197 and Men Y (b)(4)---- processes (submitted in STN 125300(b)(4) and MenA, MenC, and MenW (b)(4) ----- (b)(4)----- processes (submitted in STN 125300(b)(4)--. The related submissions are pending approval. Accordingly, outstanding issues related to these submissions were discussed in an internal CBER meeting on 18 Aug 2014, and the Product Office Specialists affirmed that the incident and related corrective actions appear to have no impact to Bexsero operations.

4. **Manufacturing Process:**

- a. **The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.**
- b. **The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.**

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Drug Product manufacturing includes formulation of final bulk and filling into syringes and inspection of pre-filled syringes of 4CMenB. Formulation includes -----
----- (b)(4) -----

----- are performed at Rosia Building b(4). Labeling and secondary packaging operations are performed in Rosia Building b(4) These formulation, filling, packaging and inspection areas are approved for multi-product manufacture of US approved products:

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

[(b)(4)]

Recommendation:

This memorandum recommends that a pre-license inspection be waived at the Novartis Vaccines and Diagnostics S.r.l., Rosia Facility. The prior GMP compliance inspection, performed just over 1 year of the present date, was classified as VAI and included auditing of quality systems and support operations related to Building --- (b)(4) -----.

Signed:

LCDR Donald Ertel _____ DATE _____
CMC Facility Reviewer
Division of Manufacturing and Product Quality
Margaret Bash _____ DATE _____
Chair
OVRR/DBPAP/LBP