

DEPARTMENT OF HEALTH & HUMAN SERVICES

FDA, Center for Biologics Evaluation and Research

MEMORANDUM

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From: John F. Cipollo, Ph. D., Product Reviewer, DBPAP, OVRR

Through Willie Vann., Lab Chief, LBP, DBPAP, OVRR

Subject: Product Review Memo for BLA 125546/0 (Bexsero)

Applicant: Novartis

To: File for 125546/0

Submissions Reviewed:

Amendment 0.01, received July 10, 2014 (CMC/Quality original submission)

Amendment 0.23, received October 31, 2014 (Response to October 8, 2014 IR CMC/Quality)

Amendment 0.24, received November 7, 2014 (Response to October 24, 2014 IR Quality)

Amendment 0.26, received November 17, 2014 (18 month DP Expiration Dating)

Amendment 0.27, received November 21, 2014 (Response to November 6, 2014 IR CMC/Quality)

Amendment 0.35, received December, 15 2014 (Response to November 26, 2014 Teleconference CMC/Quality)

Amendment 0.36, received December, 15 2014 (Response to December 10, 2014 IR CMC/Quality)

Amendment 0.37, received December, 23 2014 (Response to December 12, 2014 IR CMC/Quality)

Amendment 0.44, received January 15, 2015 (Response to secure email on January 6, January 12 and January 13. 2015, IR CMC/Quality)

Amendment 0.45, received January 20, 2015 (Response to secure email January 16 and 20 2015 CMC/Quality)

Amendment 0.46, received January 21, 2015 (Response to secure email January 14, 16 and 19, 2015 CMC/Quality)

Amendment 0.47, received January 22, 2015 Response to secure email January 21, 2015 CMC/Quality)

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1.0 Background

Novartis (initially as Chiron) submitted IND -(b)(4)- for an investigational vaccine, 4CMenB, indicated for the prevention of *Neisseria meningitidis* serogroup B invasive disease, on February 17, 2004. Novartis was granted Fast Track Designation on May 4, 2006.

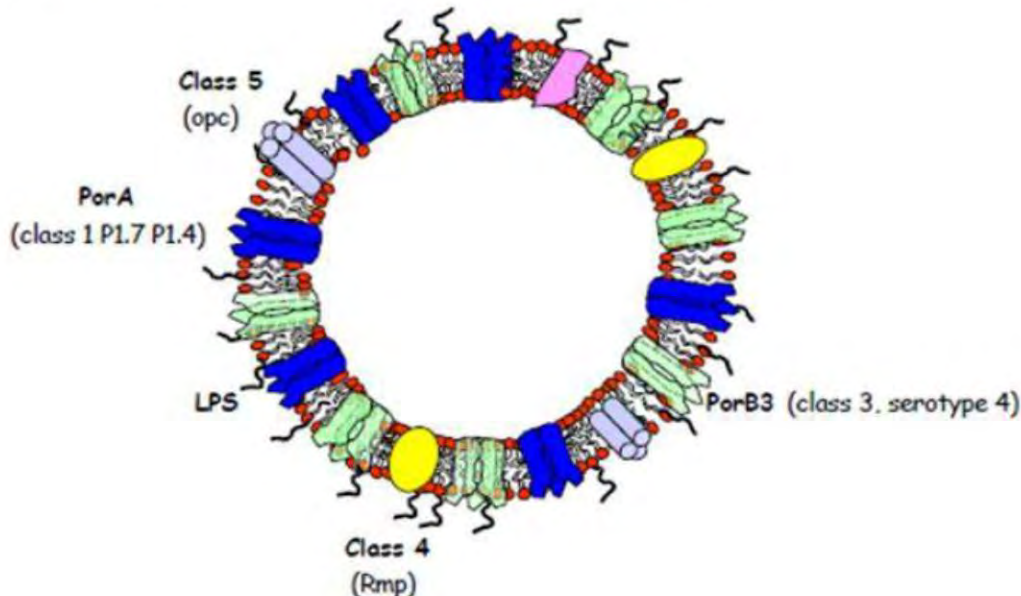
Due to recent outbreaks of *N. meningitidis* infection, CBER requested that Novartis provide an update on the status of their Chemistry, Manufacturing, and Control (CMC)/Quality, manufacturing facility, and clinical data that could support a BLA submission for U.S. licensure under an accelerated approval pathway. A Type C meeting was held on February 12, 2014 (CRMTS #9292, IND #-(b)(4)-) in which CBER responded to Novartis's Clinical/Inspection/CMC/Facility questions to ensure that the information meets the Agency's expectations for licensure under an "Accelerated Approval" pathway. During this meeting, it was suggested that a pre-BLA meeting be scheduled prior to BLA submission. Breakthrough Therapy Designation was granted on April 1, 2014 and approval to submit this BLA as a rolling submission was received on June 17, 2014. A Type C pre-BLA meeting was held on March 27, 2014 (CRMTS #9292, IND #-(b)(4)-) to discuss CMC/Quality contents of the planned BLA submission. Novartis submitted three installments of the rolling BLA for Bexsero (June 16, 2014, July 9, 2014, and July 23, 2014). Novartis completed the BLA submission on July 23, 2014 which initiated the clock for the PDUFA timelines. The CMC/Quality information was included in the July 23, 2014 submission.

Novartis is seeking approval of Bexsero (*Neisseria meningitidis* Meningococcal Group B vaccine: recombinant, adsorbed). The proposed indication of Bexsero is for the active immunization against invasive disease caused by *N. meningitidis* serogroup B strains of individuals from 10 years through 25 years of age. This vaccine is administered as a 2-dose series at least one month apart.

This vaccine is composed of three purified recombinant *N. meningitidis* serogroup B protein antigens, NadA (Neisseria adhesin A) as a single protein, NHBA (Neisseria Heparin Binding Antigen) as a chimeric protein, fHBP (factor H Binding Protein) as a chimeric protein, and PorA P1.4 as the main antigen of Outer Membrane Vesicles (OMV) derived from *N. meningitidis* serogroup B strain NZ 98/254. A diagram of the OMV particle is shown in Figure 3.2.S.1.2.2-1. Bexsero contains 50µg of each of the three purified recombinant protein antigens, 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. The pharmaceutical form is a suspension for intramuscular injection. The vaccine is supplied in 1 mL hydrolytic glass -(b)(4)- prefilled syringes.

Figure 3.2.S.1.2.2-1

Diagram of an OMV Particle



The three recombinant proteins rp287-953 (NHBA chimera), rp936-741 (fHBP chimera), and rp961c (NadA) drug substances (DS) are produced separately at the -----(b)(4)----- facility. Quality control testing of DS is performed at three sites, Novartis Vaccines and Diagnostics Bellaria-Rosia and (b)(4), Italy and -----(b)(4)----- . Batch release of DS is performed at the Bellaria – Rosia site.

The OMV DS is produced at the Novartis Vaccines and Diagnostics Bellaria-Rosia, Italy site. Master and Working seeds for all DS are -(b)(4)- by Novartis Vaccines and Diagnostics at both the Bellaria-Rosia and (b)(4) sites.

Drug product (DP) is formulated, filled, inspected, labeled, packaged, and batch released at the Novartis Vaccines and Diagnostics Bellaria – Rosia, Italy site. Quality control testing of DP is performed at both at Novartis Vaccines and Diagnostics Bellaria – Rosia and (b)(4) sites, Italy. The components of the 4CMenB vaccine are shown in Table 3.2.P.1-1 below. A table summarizing sites of manufacture and responsibilities immediately follows.

Table 3.2.P.1-1 Composition of 4CMenB Vaccine

Component	Quantity per 0.5 mL dose	Function	Reference
rp287-953	50 µg ¹	Active	Internal
rp961c	50 µg ¹	Active	Internal
rp936-741	50 µg ¹	Active	Internal
OMV	25 µg ²	Active	Internal
Aluminium hydroxide	1.5 mg ³	Adsorbent	(b) (4)
Histidine	0.776 mg	Buffering agent	
Sodium chloride	3.125 mg	Tonicity adjusting agent	
Sucrose	10 mg	Tonicity adjusting agent	
Water for Injection	up to 0.5 mL	Solvent	

OMV: Outer Membrane Vesicles; (b) (4) rp: recombinant protein; (b) (4)

¹ Total amount of protein is calculated individually for each protein. The target concentrations are met according to bulks' concentration values, which are determined by (b) (4) assay.

² The target concentrations are met according to bulks' concentration values, OMV is measured as the amount of total protein which is determined by (b) (4)

³ Aluminium hydroxide 1.5 mg corresponds to 0.5 mg of elemental Aluminium.

Sites of Manufacture and Responsibilities

Name and Address	Drug Substance/Product	Responsibility
Novartis Vaccines and Diagnostics S.r.l. Bellaria-Rosia 53018 Sovicille, Italy (also referred to as Rosia)	OMV	----- ----- ----- ----- ----- (b)(4) ----- ----- ----- -----

Novartis Vaccines and Diagnostics S.r.l. ------(b)(4)----- ----- Italy (also referred to as (b)(4))	OMV	----- ----- ----- ----- ----- -----
Novartis Vaccines and Diagnostics S.r.l. Bellaria-Rosia 53018 Sovicille Italy (also referred to as Rosia)	Rp287-953, rp936-741, rp961c	----- ----- ----- ----- ----- ----- ----- ----- -----
Novartis Vaccines and Diagnostics S.r.l. ------(b)(4)----- ----- Italy (also referred to as -(b)(4)-)	Rp287-953, rp936-741, rp961c	----- ----- ----- ----- ----- -----
----- ----- ----- ----- -----	Rp287-953, rp936-741, rp961c	-----, ----- ----- ----- -----
Novartis Vaccines and Diagnostics Bellaria-Rosia 53018 Sovicille Italy (also referred to as Rosia)	(4CMenB)	----- ----- ----- ----- ----- -----

Novartis Vaccines and Diagnostics ----(b)(4)----- ----- Italy (also referred to as (b)(4))	(4CMenB)	----- (b)(4) -----
---	----------	--------------------

2.0 Review of Drug Substance -----(b)(4)-----

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

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

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

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

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

[(b)(4)]

3.0 Review of Drug Product

Multi-Component Meningococcal B Vaccine (4CMenB) is a suspension for injection in pre-filled syringe (PFS), administered intramuscularly, and contains three recombinant proteins (rp), Outer Membrane Vesicles (OMV), and excipients, as listed below in Table 3.2.P.1.1. The sequences of the recombinant protein antigens are derived from *Neisseria meningitidis* (*N. meningitidis*) serogroup B strains and produced in *Escherichia coli* cells by recombinant DNA technology. The specifics of these DS are discussed in detail in the respective sections in this review.

Table 3.2.P.1-1 Composition of 4CMenB Vaccine

Component	Quantity per 0.5 mL dose	Function	Reference
rp287-953	50 µg ¹	Active	Internal
rp961c	50 µg ¹	Active	Internal
rp936-741	50 µg ¹	Active	Internal
OMV	25 µg ²	Active	Internal
Aluminium hydroxide	1.5 mg ³	Adsorbent	(b) (4)
Histidine	0.776 mg	Buffering agent	
Sodium chloride	3.125 mg	Tonicity adjusting agent	
Sucrose	10 mg	Tonicity adjusting agent	
Water for Injection	up to 0.5 mL	Solvent	

OMV: Outer Membrane Vesicles; (b) (4) recombinant protein; (b) (4)

(b) (4)

¹ Total amount of protein is calculated individually for each protein. The target concentrations are met according to bulks' concentration values, which are determined by (b) (4) assay.

² The target concentrations are met according to bulks' concentration values, OMV is measured as the amount of total protein which is determined by (b) (4) assay.

³ Aluminium hydroxide 1.5 mg corresponds to 0.5 mg of elemental Aluminium.

The vaccine is supplied in a 1-mL hydrolytic glass pre-filled syringe without a pre-affixed needle. Syringes are sealed with a ----(b)(4)---- rubber plunger stopper and tip cap. Syringes are Luer Lok™ types.

3.1 Pharmaceutical Development

A summary of lots used in clinical development studies is provided in Table 3.2.P.2.2.1-1 below. Details of the lot composition are provided in Table 3.2.P.2.2.1-2 below.

Table 3.2.P.2.2.1-1 Summary of Clinical Study Lots

Clinical Lot	Phase I	Phase II	Phase III	Used in Clinical Study
V38D18N1	X	-	-	V72P5
W38D19N1		X	-	V72P6, V72P9, V72P4
X38D27N1	-	-	X	V72P10, V72P13, V72P12
X38D28N1	-	-	X	V72P13, V72P12E1, V72P13E1, V72P16
X38D29N1	-	-	X	V72P13
090101	-	-	X	V72P13E2, V72_29, V72_41, V72P12E1, V7212E2, V72P16
101601			X	V72_29, V72_41
112801			X	V72P12E2

The composition of the 4MenB formulation has changed during development. Formulation for Phase I and II lots was the same. During this period the amount of sucrose in DP rp287-953

varied and --(b)(4)-- was balanced with addition of a concentration range of sodium chloride solution. Aluminum hydroxide was released according to internal specifications. Later (b)(4) specification was used. Moving from Phase II to III processes, sucrose in 287-953 (b)(4) was ----(b)(4)----- and, therefore, the concentration of sodium chloride was set to 6.25 mg/mL. Moving from Phase III to the commercial composition, the concentration of aluminum hydroxide was adjusted to align with -(b)(4)-.

The 4CMenB vaccine is a preservative free, sterile, opalescent liquid (white suspension) for injection. The pH of the drug product is pH -(b)(4)- to optimize antigen --(b)(4)-- to the ----(b)(4)-- and to assure product stability. The ----(b)(4)--- of the drug product is ----(b)(4)-----

Studies in mice, guinea pigs, and rabbits demonstrate that the vaccine formulation elicits bactericidal antibodies. Passive protection was demonstrated for each of the recombinant proteins in the infant rat passive protection model, in which murine immune sera protected infant rats from intraperitoneal meningococcal infection.

The immune response in humans is elicited by producing bactericidal antibodies in adults, adolescents, and infants; no safety concerns have been identified. Throughout the immunogenicity studies, the 4CMenB vaccine elicits responses in the serum bactericidal antibody assay using human complement and clinical studies have demonstrated the efficacy of this vaccine against systemic meningococcal disease.

3.1 Manufacturing Process Development

A summary of the clinical lots and lots used for validation of the manufacturing process is provided in the table below in Table 3.2.P.2.3.1-1.

Table 3.2.P.2.3.1-1 4CMenB Vaccine Lots for Use in Clinical Studies and for Validation of Manufacturing Process

Lot Number	Formulation Date	Building (Rosia)	Use	Bulk Formulation Size (L)	Container Closure	No. Pre-filled Syringe
V38D18N1	(b) (4)	(b) (4)	Phase I (V72P5)	(b) (4)	(b) (4)	(b) (4)
W38D19N1			Phase II (V72P6, V72P9, V72P4)			
(b) (4)			Process validation			
X38D27N1			Phase III (V72P10, V72P13, V72P12)/ Process validation			
X38D28N1			Phase III (V72P13, V72P12E1, V72P13E1)/ Process validation			
X38D29N1			Phase III (V72P13)/ Process validation			
090101			Phase III (V72P13E2)			
(b) (4)			Process validation (Formulation)			
			Process validation (Formulation)			
			Process validation (Formulation)			
			Process validation (Formulation)			
101601			Phase III (V72P13E2)			
(b) (4)			Process validation (Filling (b) (4))			
			Process validation (Filling (b) (4))			
			Process validation (Filling (b) (4))			

Lot Number	Formulation Date	Building (Rosia)	Use	Bulk Formulation Size (L)	Container Closure	No. Pre-filled Syringe
(b) (4)	(b) (4)	(b) (4)	Process validation (Filling (b) (4))	(b) (4)	(b) (4)	(b) (4)
			Process validation (Filling (b) (4))			
			Process validation (Filling (b) (4))			

NA: Not applicable

¹: Please note that validation of the formulation of final bulk only was performed due to a failure of the filling validation. Lots used in filling validation are not shown.

For Phase I and II Manufacturing Process Formulation the manufacturing formulation process was the same for Phase I (Lot V38D18B) and Phase II (Lot W38D19B) clinical lots. Lot formulations were performed at Building (b)(4) at the Rosia, Italy site.

The drug substances, Recombinant Proteins (rp) 287-953, rp961c, and rp936-741 used to produce Phase I/II clinical lots were aseptically produced by Novartis at the (b)(4), Italy site according to the production process described in Section 3.2.P.2.2. The-----
----- (b)(4) -----

For Phase III clinical lots, the formulation process was modified. The three recombinant proteins, provided by ----- (b)(4) -----
----- . Moreover, addition of a sucrose solution was implemented to normalize the amounts of sucrose and sodium chloride in the vaccine composition.

As described in Section 3.2.P.2.2.1, in the formulation of Phase I and II lots, the amount of sucrose was derived from the rp287-953 buffer only and the concentration of sodium chloride in the final vaccine was dependent on the concentration of rp287-953. In the formulation of Phase III lots, the amount of sucrose derived from rp287-953 buffer is normalized to -(b)(4)-, by addition of a sucrose solution. Following this change, the concentration of sodium chloride was set at 6.25 mg/ml in the final vaccine composition, independent of rp287-953 concentration. The proteins and solution ----- (b)(4) ----- were performed by using an -----
----- (b)(4) ----- . The transfer of WFI into the -----
----- (b)(4) ----- .

For commercial manufacturing, in order to comply with the bioburden limit of --- (b)(4) -----
----- to sterile filtration, an improved formulation process was implemented to be in compliance with the current ----- (b)(4) -----
----- Before the improved process, the bioburden limit for the phase, ----- (b)(4) ----- . For the improved formulation process, minor changes with respect to the previous formulation process used to produce Phase III clinical lots have been implemented. These include sterile -----
----- (b)(4) -----
----- .

The filling process is described in Section 3.2.P.3.3.2. The activities of filling and stoppering for the Phase I and Phase II lots were performed in Building (b)(4) at the Rosia, Italy site. The activities of filling and stoppering for the Phase III and commercial lots were performed in -- (b)(4) -----
----- in Building (b)(4) at the Rosia site (up to (b)(4) filling batch size). Starting from 2014, -----
----- (b)(4) ----- in Building --- (b)(4) --- has been validated and used for filling and stoppering activities. Validation of the filling process at the (b)(4) scale is reviewed elsewhere.

A number of improvements were introduced into the filling process post-validation. A quality risk assessment was performed and it was concluded that the proposed improvements did not

require repetition of process validation at (b)(4) scale. In summary, the differences from the original and improved (b)(4) filling processes include implementation of a pre-defined -----
----- (b)(4) ----- samples for release and validation testing are taken after visual inspection.

For proper validation of the original --- (b)(4) --- fill, and in response to OOS results for two validation lots ----- (b)(4) -----, a number of changes were made to the process. These changes served to optimize for ----- (b)(4) ----- . These included adjustment of ----- (b)(4) ----- of the bulk, collection of release and validation samples after ---- (b)(4) ---- Measurement. In 2011 the -- (b)(4) --- process was validated with improvements in ---- (b)(4) ---- . All predefined acceptance criteria were met. Validation is presented in Section 3.2.P.3.5.

A validation study has been performed to validate the filling process at a scale of (b)(4) in Module -(b)(4)- in Building (b)(4) at the Rosia site. The results of the validation study for the filling process in ---- (b)(4) ----- filling line are described in detail in Section 3.2.P.3.5. All results from the filling process validation met predefined acceptance criteria and demonstrate that the filling process (including improvements previously implemented for -- (b)(4) -- to improve robustness of the process with respect to ----- (b)(4) -----) is able to produce a homogeneous product.

3.2 Container Closure

The Drug Product is presented as a suspension for injection in a pre-filled syringe. During development three pre-filled syringes have been used including Luer -- (b)(4) ----, Luer ----- (b)(4) --- and Luer Lok -(b)(4)-. The Luer -- (b)(4) -- model was used to present the product for Clinical Phases I, II and III. The first stability studies were initiated on three full-scale consecutive final product 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.

The -- (b)(4) -- model syringe was discontinued. Therefore the Luer -- (b)(4) ---- and Luer Lok -(b)(4)- were identified as replacements. For each model the syringe is -(b)(4) glass, the plunger is Latex free rubber, and the cap is -- (b)(4) -- rubber --- (b)(4) ---. These models consist of the same material construction of the syringe and plunger as the original Luer --- (b)(4) ----- model differing only in the tip-cap, which in both cases is made from -- (b)(4) -- rubber.

Leachable studies were contracted to the contract ----- (b)(4) ----- . As the construction of the Luer --- (b)(4) ----- and Luer Lok -(b)(4)- are essentially the same, only the Luer -- (b)(4) ---- syringe was studied. Only model Luer Lok -(b)(4) is requested for approval for use with the drug product. The study evaluated volatiles and semi-volatiles but did not investigate non-volatile leachable compounds or extractables. The study is summarized in 3.2.P.2.4 Container Closure System [4CMenB – Suspension for Injection in PFS]. Under conditions of the leachables study the samples were screened for the semi-volatile lead marker ----- (b)(4) ----- and it was not detected above the limits of method detection by -(b)(4)- analysis after up to (b)(4) months

storage in final containers. Study of semi-volatile organic compounds revealed a range of leachables most notable after 24 months of storage. All detected levels were below safety thresholds for leachables in orally inhaled or nasally delivered pharmaceuticals developed by the -----(b)(4)----- . In Information Request Question 19 communicated on October 8, 2014 Novartis was asked to provide study data that uses an appropriate non-volatile matrix based on this drug product or a similar one, or justify the absence of this study and also to provide an appropriate extractables study or justify the absence of this study. In the response the requested information was presented. The information was adequate to demonstrate no toxicological or safety concerns with the proposed containers. See Information Response and Interactions section of this review for more details.

Microbial attribute studies of the final container are presented in Section 3.2.P.2.5 Microbiological Attributes [4CMenB – Suspension for Injection in PFS]. A container closure integrity test (CCIT) was conducted to test the suitability of the container and closure systems. The principle of the test consists of the -----(b)(4)----- .

The CCIT study was carried out at time points over the shelf life of the DP. Samples were stored at 2-8°C, the same temperature conditions as the final product. The 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 all provided good closure integrity results.

3.3 Manufacturers

The sites of DP production responsibilities are listed in Section 3.2.S.1 Manufacturers. Formulation, filling, inspection, labeling, packaging, and batch release of DP are performed by Novartis Vaccines and Diagnostics Bellaria – Rosia (also referred to as Rosia). Quality control testing is carried out by Novartis Vaccines and Diagnostics at both the Rosia and -- (b)(4) ----- site.

3.4 Batch Formula

In Section 3.2.P.3.3, the manufacturing formula for batch size is provided in the table below. The final formulation batch size ranges from --- (b)(4) ---.

Table 3.2.P.3.2-1 Batch Formula

Component	Quantity per mL	Reference
Recombinant <i>Neisseria meningitidis</i> Protein 287-953	100 µg ¹	Internal
Recombinant <i>Neisseria meningitidis</i> Protein 961c	100 µg ¹	Internal
Recombinant <i>Neisseria meningitidis</i> Protein 936-741	100 µg ¹	Internal
OMV	50 µg ²	Internal
Al(OH) ₃	3 mg	(b) (4)
NaCl	6.25 mg	
Sucrose	20 mg	
Histidine	1.552 mg	
WFI	To 1 mL	

¹ Total amount of protein concentration is calculated individually for each protein. The target concentrations are met according to the bulks' concentration values, which are determined by (b) (4) protein assay.

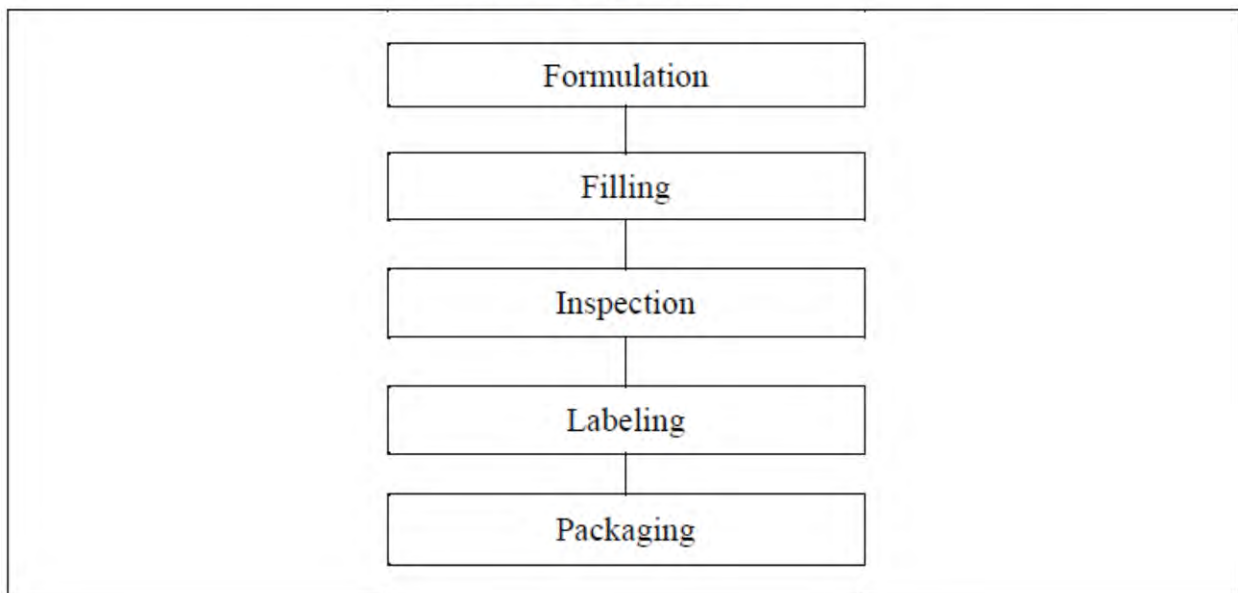
² The target concentrations are met according to bulks' concentration values, OMV is measured as the amount of total protein which is determined by (b) (4) protein assay.

3.6 Manufacturing and Process Controls

The manufacturing process for the drug product involves formulation of the -----

Figure 3.2.P.3.3-1

General Overview of Manufacturing Process for 4CMenB Drug Product



Specifics of the formulation process are provided in 3.2.P.3.3 Manufacturing Process and Controls [4CMenB – Suspension for Injection in PFS]. Briefly, the formulation process is

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

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

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

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

3.5 Control of Critical Steps and Intermediates

In process controls for manufacture of solutions and 4CMenB are provided in Table 3.2.P.3.4.1-1 below taken from Section 3.2.P.3.4 Controls of Critical Steps and Intermediates [4CMenB – Suspension for Injection in PFS]

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

[(b)(4)]

Methods of analysis, compendial of compliance, and specifications are shown.

3.6 Process Validation

Process validation of the formulation and filling process for the production of the 4CMenB vaccine is described in Section 3.2.P.3.5 Process Validation and/or Evaluation [4CMenB – Suspension for Injection in PFS]. It was performed in November 2007 at a scale of up to (b)(4). In April 2010 the formulation scale was --(b)(4)-- and validated up to (b)(4). For the latter validation studies, operational parameters have been defined for control of the process performance, and can be categorized into two groups – critical and noncritical.

Critical Process Parameters (CPPs) are defined as process parameters for which the range is established in such a way as to guarantee the reproducibility of the process. A deviation from the pre-determined limits has significant potential to cause failure of a critical quality attribute (CQA). Failure to meet a CPP results in an investigation to determine potential impact on the Critical Quality Attributes (specifications).

Non-Critical Process Parameters are defined as process variables which have no impact or potentially low impact on the critical quality attributes of the resulting product. Limits for non-critical process parameters in any case are established and monitored during process validation activity but are not used to demonstrate the reproducibility of the process.

In-process controls (IPCs) are performed during manufacture of the drug product to monitor the process. For IPCs, specific acceptance criteria have been defined or in some cases it is used for monitoring the process and alert limits are applied. Failure to meet these acceptance criteria results in a deviation/investigation and appropriate decision regarding the acceptance or rejection of the batch is made based on the conclusion of the investigation.

In addition to the process validation studies, media simulation and media fill runs have been performed to demonstrate the aseptic nature of the processes. Validation of the --(b)(4)--- filter has been performed in order to ensure that the filter is compatible with the product and produces a sterile filtrate following bacterial challenge.

Validation of the Formulation Process

(b)(4)

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

3.7 Transport Validation

Transportation validation was covered in detail in the following reports: process-validation reports oqr272809rev01, oqr268062rev01, prq002810, pqr01709, and pqr017109. Transport was tested for winter and summer conditions under worst case conditions. The transport can be considered validated.

3.8 Control of Excipient

Aluminum Hydroxide

Novartis states that Aluminum hydroxide (-(b)(4)-) is fully compliant with specifications listed in the current ----- (b)(4) -----, for adsorption. The battery of tests performed in the compound are presented in Section 3.2.P.4.1 Table 3.2.P.4.1-1 in the file.

For ----- (b)(4) ----- method was used. Internal methods were validated for use in the quantitation of ----- (b)(4) ----- content. All test specifications required by the --- (b)(4) --- to characterize the aluminum hydroxide have been met, although not all methods are the same as those recommended in that --- (b)(4) --- document. A description of methods used and justifications are presented below in Table 3.2.P.4.2-1. All non-compendial assays were validated. Validation parameters, acceptance criteria, and validation results for ----- (b)(4) -----, summarized in the file in Tables 3.2.P.4.3-1 through 3.2.P.4.3-3.

[(b)(4)]

For all aluminum hydroxide lots manufactured beginning November 2010, specifications for the excipient aluminum hydroxide are fully compliant with the current -----
------(b)(4)----- test has also been implemented. An example Certificate of Analysis (CoA) was provided in the Attachment Titled Aluminum Hydroxide CoA. The $\text{Al}(\text{OH})_3$ is produced by Novartis ------(b)(4)----- An Information Request (Question 21) was submitted for clarification on the site of this excipient qualification on October 24, 2014. Novartis was requested to provide details of the manufacture and stability. The applicant provided details of the manufacturing process, testing procedures and stability data. Follow-up interactions requested process validation information. All the requested information was submitted. The response was satisfactory. The issue was closed.

It was noted that in neither Section 3.2.P.3.5 Process Validation and/or Evaluation or in the Formulation Validation Report MNNZ_FORMULATION-02342PVR03, in-process control results for the -----(b)(4)----- were not provided. This was the subject of Information Request Question 18 sent to Novartis on October 24, 2014. Novartis responded with the --(b)(4)-- data requested.

The aluminum hydroxide used in the formulation of the 4CMenB DP is manufactured by Novartis in ---(b)(4)---. The original submission contained no detailed description of the production process, process validation, specifications, or stability data. These deficiencies were the topic of IR Question 21 conveyed to Novartis on October 24, 2014 and an issue discussed during a teleconference with the applicant dated November 26, 2014. In response to these interactions Novartis submitted production process description, the process validation study, release and stability specifications and stability data. The response was satisfactory. The issue can be considered closed.

Justification for DP (b)(4) and Filled and Packaged Product release specifications for Aluminum Hydroxide -----(b)(4)-----, and pH were not adequate. These issues were the topic of Question 18 in the October 8, 2014 IR conveyed to the applicant. The response contained in Amendment 0.23, included data and summary of the analysis of (b)(4) DP lots. These data supported the proposed specifications for all tests listed. The issue can be considered closed except for Aluminum Hydroxide (b)(4) as the analytical method is not considered validated in accordance with DBSQC review (see DBSQC review for further information).

The original submission material did not provide in-process control results for the -(b)(4)- Test of Aluminum Hydroxide or for the -(b)(4)- Test of Histidine in Process Validation Studies. This issue was the topic of Question 18 in the IR conveyed to the applicant on October 24, 2014. The response received in Amendment 0.24 contained the missing information. All process validation lots passed -(b)(4)- testing. The issue can be considered closed.

On January 12, 2015 an Information Request was sent by secure E-mail to the applicant requesting clarification concerning the role of aluminum hydroxide in the drug product. Throughout the dossier the component has been referred to as -----(b)(4)----- . The Applicant acknowledged the inconsistency in Amendment 0.44. In that document the applicant designated aluminum hydroxide as an ---(b)(4)---.

Histidine

Analytical procedures are performed according to the methods described in the --(b)(4)----- Histidine. An example CoA is presented in Histidine CoA attachment in Section 3.2.P.4 Histidine. There are no excipients of human or animal origin used in the manufacture of 4CMenB vaccine.

Sodium Chloride

Specifications for sodium chloride meet -----(b)(4)----- requirements. An example CoA for sodium chloride is included in Section 3.2.P.4 Attachment Sodium chloride CoA. There are no excipients of human or animal origin used in the manufacture of 4CMenB vaccine.

Sucrose

Specifications for sucrose are compliant with those recommended in the -(b)(4)-. Specifications include all parameters described in the ---(b)(4)----- Sucrose. An example of Certificate of Analysis of this excipient (CoA) is provided in Attachment Sucrose CoA in Section 3.2.P.4 Sucrose. There are no human or animal source components in the sucrose used in 4CMenB.

Water for Injection

Water for Injection (WFI) is supplied from a qualified loop at the Novartis Rosia, Italy site. The specifications for WFI are provided in Table 3.2.P.4.1-1 in the file. Analytical procedures are performed according to the methods described in the -----(b)(4)----- for Water for injection.

3.9 Control of Drug Product.

Specifications and Justification

Specifications for 4CMenB final bulk are shown in Table 3.2.P.5.1-1 below.

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

[(b)(4)]

During the filling process a series of in process tests are performed. Aluminum hydroxide and histidine are tested for --(b)(4)--. The -(b)(4)- containing the three recombinant proteins, WFI, Sucrose (b)(4) and NaCl solution are tested for -----(b)(4)----- WFI used to rinse the -----(b)(4)----- is tested for -----(b)(4)----- and the filter is integrity tested. Finally, OMV sterile filtrate is sampled for QC tests for ----(b)(4)-----.

The specifications are set based on clinical trials and process performance. The justification of specifications for the release of --(b)(4)--, filled and packaged 4CMenB product are provided in Table 3.2.P.5.6-1 in the file and summarized below. During evaluation of the dossier submitted in 2010-2012, Health Authorities recommended to improve sensitivity and reduce variability of the ---(b)(4)--- immunogenicity assay and bacterial endotoxin assay. Novartis introduced assay modifications for both Drug Product release and stability testing. Assay development and validation for the improved immunogenicity assay -----(b)(4)----- and bacterial endotoxin assay were completed in October 2012, during the review of the marketing applications in Europe, Canada, Australia and Brazil. Detailed discussions are provided in Sections 3.2.P.5.2 and 3.2.P.5.3 for endotoxins and Sections 3.2.P.5.2 and 3.2.P.5.3 for mouse immunization. The endotoxin and -(b)(4)- immunogenicity assay are reviewed elsewhere as these were assigned to other reviewers. All release tests methods are briefly described below.

Release Tests Filled Product (in Pre-filled Syringes)

Aluminum Hydroxide ---(b)(4)----- and filled syringe): The specification for aluminum hydroxide (b)(4) reflects the NVD standard for this parameter which has proven safe and effective for similar --(b)(4)- products produced by Novartis. The target --(b)(4)-- is the amount defined during formulation development to assure for each antigen an ---(b)(4)-----

Sterility: As for any injectable product, sterility is insured by testing representative product sample according to pharmacopoeia requirements. The test is ---(b)(4)-- and conforms to -----
------(b)(4)-----.

Identity: Identity by ---(b)(4)--- is intended to assure that the Drug Product contains each of the 4 drug substance components

Volume: This test ensures that the prescribed 0.5 mL dose can always be extracted from the monodose vaccine containers and is performed according to -----(b)(4)-----.

Appearance: The Drug Product is described as an opalescent liquid with white suspension. The aluminum hydroxide is responsible for that appearance.

Aluminum Hydroxide ---(b)(4)---: The specification is designed to ensure that suitable -----
------(b)(4)-----
------. This specification is also in alignment with other ---(b)(4)---- products produced by NVD.

Aluminum Hydroxide ---(b)(4)---: Content --(b)(4)-- is also assessed on -----
------(b)(4)----- have been filled with the required amount of drug product, in terms of Aluminum Hydroxide, since each antigen is adsorbed to the -----(b)(4)-----

pH: The pH specification is designed to demonstrate that the final formulation has been performed properly and that the drug product is maintained in a buffer system where stability has been demonstrated.

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

Endotoxin: Due to the presence of -----(b)(4)-----, the Drug Product has some endotoxin activity. Specifications are based on data from (b)(4) clinical lots of 4CMenB. A detailed explanation of the approach employed is presented in Section 3.2.P.5.6-1 and reviewed elsewhere.

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

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

Immunogenicity: Specifications at release and end of shelf-life are based on non-inferiority of the tested lot to a full dose of clinically qualified reference standard that is assumed to have a relative potency of (b)(4). This approach is consistent with the approach used for -----
----- (b)(4) ----- For this reason the specification has been set based on Upper Confidence Limit for relative potency estimate ---- (b)(4) ----- . This test is reviewed elsewhere by another reviewer.

Visible Particles: The test is intended to provide a simple procedure for the visual assessment of the quality of parenteral solutions as regards visible particles. The test is performed according to --(b)(4)--.

Test for Packaged Product

Identity: Identity by ---(b)(4)----- is intended to ensure that the Drug Product contains each of the 4 drug substance components.

General Safety: The test was discontinued from the release panel after demonstration of product safety in (b)(4) batches release during the period 2005 -2010 (Section 3.2.P.5.6.3). After interactions with the firm Novartis agreed to continue this test (see Information Request and Responses Section of this review).

Protein Content: There is a justification for non-inclusion - Total protein content is not performed due to the physical-chemical properties of the Aluminum Hydroxide, hydrated for --- (b)(4) ----. Detailed explanation appeared in Section 3.2.P.5.6.4. Absence of a protein content test is justified.

Justification of Specifications

During review of the file it was noted that justification of specifications for -----
----- (b)(4) -----
----- and pH Tests were not provided or were inadequate. Information Request (Question 18) was sent to Novartis on October 8, 2014 addressing this deficiency. The firm provided the information that follows.

[(b)(4)]

Test	Method of Analysis	Current Specification	Proposed Specification	Justification of Specifications
				(b) (4)
pH	(b) (4)		6.4 -6.7 for release (b) (4)	See justifications below

Justification of -----(b)(4)-----

Novartis has re-assessed (b)(4) released lots including clinical batches. Based on these data the proposed specification for -----(b)(4)----- The --(b)(4)- clinical batches falls within this range with release data ----(b)(4)----- As the data was not normally distributed, calculations were performed using the --(b)(4)--- percentile range. This is considered to be comparable to a 3-sigma approach for normally distributed data.

The complete dataset was provided in Attachment 18.1 submitted with the response.

Justification of -----(b)(4)-----

Novartis has re-assessed (b)(4) of released lots including clinical batches. This available data does not support tightening the proposed specification, as shown in process capability plot and data distribution in Figure 18-1 and 18-2 below. The --(b)(4)-- which means that +/- 3 standard deviation fits within the

specification range and tightening specification would lead to a suboptimal process capability lower than 1. The complete dataset was provided in Attachment 18.2 submitted with the response.

Justification of -----(b)(4)-----

The assay for -----(b)(4)----- is based on and fully compliant with --(b)(4)-- requirements -----(b)(4)-----” test A related to suspension for injection. The individual content of Aluminum Hydroxide is determined on -----(b)(4)----- Novartis believes that this specification is justified. Aluminum Hydroxide - -----(b)(4)-----.

Justification of -----(b)(4)-----

----(b)(4)----- is a limit test, whereby the -----(b)(4)-----.

The preparation complies with the test if each individual content is between --(b)(4)---- and ---(b)(4)---- of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of -----(b)(4)----- of the average content.

The test provides the evaluation of conformity with the --(b)(4)---- requirement and the test results cannot be used retrospectively to provide further information on process consistency or capacity. The proposed limit provides sufficient assurance that the adsorbed product elicits a sufficient immunoresponse, as demonstrated in a clinical setting.

Justification of pH

Novartis has re-assessed (b)(4) released lots, including clinical batches. Based on this data a re-assessment of pH specification range has been proposed. The new proposed pH range specification is 6.4 – 6.7 for release. The thirteen clinical batches fall within this range with release data 6.5 – 6.7.

As the data was not normally distributed, calculations were performed using the ---(b)(4)--- percentile range. This is considered to be comparable to a 3-sigma approach for normally distributed data.

In addition, analysis of the stability data indicates an increase of pH value of ----(b)(4)----- which corresponds to an -----(b)(4)-----.

Considering the multiple testing approach performed at stability, an upper limit of (b)(4) is proposed. This value is based on the 99% probability that no OOS during stability occurs. The complete data set was provided in Attachment 18.2 in the response.

These responses were adequate. However, validation for -----(b)(4)----- Test was not adequate in accordance with an IR conveyance to Novartis dated September 18, 2014 the response in Amendment 0.14 dated September 26, 2014. The reader is directed to those correspondences for further detail on validation of the -----(b)(4)----- Test.

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

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

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

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

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

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

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

3.10 Characterization of Impurities

Characterization of Impurities is summarized in Section 3.2.P.5.5 Characterization of Impurities [4CMenB – Suspension for Injection in PFS]. In general, possible impurities found in the drug substances are controlled at an earlier stage, in part because of the difficulty performing a

[(b)(4)]

Criteria used for Qualification of reference standards for the Identity and -----(b)(4)----- Tests are summarized in Tables 3.2.P.6.2.2-1 and 3.2.P.6.2.3-1 in the file. Acceptance criteria used and reported results are appropriate. Reference standards for the Potency Assay are reviewed elsewhere. Qualification is based on a comparison with the current reference standard(s).

Stability testing is performed to establish the suitability of the qualified reference standard by re-verification against the original qualification protocol. Stability testing is performed in comparison to the previous standard. Results are reported in a qualification report. Expiration dates are assigned based on the results per SOP 203642.

3.13 Stability of 4CMenB in Pre-filled Syringes

The final product, 4CMenB, is composed of three recombinant proteins (961c, 936-741, and 287-953) and OMV, adsorbed to aluminum hydroxide. The proposed shelf-life of the filled product is 24 months, when stored at 2-8°C and protected from light.

The proposed 24 month shelf life is based on immunogenicity data from clinical trials conducted with lots with a median age longer than 24 months and supported by ICH stability programs using the panel of release assays. Three studies are presented as the confirmatory stability studies; these are executed with the release assay panel presented in Section 3.2.P.5.1. Data from all executed studies are included in Section 3.2.P.8.3.

After adjustments were made to the immunogenicity and bacterial endotoxin assays, (b)(4) additional lots were placed on stability after Health Authorities review in 2012. Twelve months of stability data from these new lots were submitted with the file. Twelve months of validation lots from 4CMenB produced on the (b)(4) filling line (b)(4) are available.

During clinical trials 4CMenB of various aged lots were used as shown in Table 3.2 P.8.3.1-1. As Novartis concludes that all trials listed in the table were successful, the ages of these lots are put forth as supportive of the requested expiry.

Table 3.2.P.8.3.1-1 Overview of 4CMenB Lots and Age of the Drug Products Used in Clinical Trials

Lot	Date of Manufacture	Clinical Trial (Population)	Age of lot at first injection (months)	Age of lot at last injection (months)	Median Age (months)
X38D27N1	(b) (4)	V72P12 (Ph2b) Infants	9	23	16
X38D28N1		V72P16 (Ph2) Infants	20	34	27
090101		V72_41 (Ph3) Adolescents	28	30	29
101601		V72_41 (Ph3) Adolescents	14	16	15
112801		V72P12E2 (Ph3) Children	16	23 (naïve subjects)	19
				26 (booster dose)	21

The batches used in stability studies prior to bacterial endotoxin and potency assay revision (October 2012) are presented in Table 3.2.P.8.3.1-2 in the file. These are not discussed further in the dossier.

Three studies are identified as confirmatory stability studies. Key information concerning these studies is presented in Table 3.2.P.8.3.1-3 below and manufacturing details are provided in Tables 3.2.P.8.3.1-4 – 3.2.P.8.3.1-6. The first study was initiated following an upscale of the filling process from --(b)(4)----- . The three Process Validation batches ----(b)(4)----- and ----(b)(4)----- were included. Data obtained from this study also served as confirmation for the final primary packaging, Luer Lok™ syringes with -(b)(4)- tip. This study was implemented prior to implementation of the (b)(4) Endotoxin and Potency assays. The (b)(4) assays were introduced at the (b)(4) month time point. The current methods are described in Sections 3.2.P.5.2 and 3.2.P.5.3 for endotoxins and Sections 3.2.P.5.2 and 3.2.P.5.3 for (b) (4) .

[(b)(4)]

The second study was initiated with introduction of the current endotoxin and potency assay and was performed with batches -----(b)(4)----- . The third and latest full scale stability study was initiated in October 2012 to confirm the comparability of three validation lots filled in the -----(b)(4)----- in ---(b)(4)--- of Building (b)(4) at the Rosia site. For further details see Section 3.2.P.3.5.1.2. The study includes three batches -----(b)(4)----- . Genealogy of the lots is shown in Tables 3.2.P.8.3.1-4 through 3.2.P.8.3.1-6 below.

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

[(b)(4)]

[(b)(4)]

All stability studies are designed in accordance with ICH guidelines including samples stored at the proposed shelf life at 2-8°C protected from light and at accelerated conditions at --(b)(4)--- and at --(b)(4)----- for a shorter period of time. Before samples are stored at the selected

conditions they are -----(b)(4)----- according to internal procedures to mimic the maximum potential exposure -----(b)(4)----- during packaging activities. The test panel used for the stability programs is the same used for release, in place at the time point for testing the stability samples. Foot notes are added to the results if method changes have taken place during the study. All test methods were validated according to current guidelines. Test schedules for the three studies are presented in Table 3.2.P.8.3.2-1 through 3.2.P.8.3.2-5 in the file.

Table 3.2.P.8.3.2-4 Confirmatory Stability Study 3

**Test Plan for Long Term Stability Study on (b) (4) Validation
Lots of Filled Product Stored at 2-8°C (b) (4)**

Test	Method	Specification	Test Intervals (months)							(b) (4)
			0	3	6	9	12	18	24	
Appearance	Visual	Opalescent liquid (white suspension)	R	X	X	X	X	X	X	(b) (4)
Visible Particles	Visual	Conform (absence of foreign particles)	R	X	X	X	X	X	X	
pH	(b) (4)	(b) (4)	R	X	X	X	X	X	X	
Identity	rp287-953	(b) (4)	R	X	X	X	X	X	X	
	rp961c	(b) (4)	R	X	X	X	X	X	X	
	rp936-741	(b) (4)	R	X	X	X	X	X	X	
	OMV	(b) (4)	R	X	X	X	X	X	X	
Endotoxin Content		(b) (4)	R	-	X	-	X	-	X	
(b) (4)		(b) (4)	R	X	X	X	X	X	X	
Immunogenicity	rp287-953	(b) (4)	R	-	X	-	X	X	X	
	rp961c	(b) (4)	R	-	X	-	X	X	X	
	rp936-741	(b) (4)	R	-	X	-	X	X	X	
	OMV	(b) (4)	R	-	X	-	X	X	X	
Sterility	Direct Inoculation	Sterile	R	-	-	-	-	-	X	

(b) (4)

(b) (4)

OMV: Outer Membrane Vesicles; R: Results reported are from release; rp: recombinant protein; RP: Relative Potency; (b) (4)

(b) (4)

(b) (4) data performed at release

(b) (4)

(b) (4) may also be referred to as (b) (4)

* Immunization method and immunogenicity test were modified from (b) (4)

methodology starting from the (b) (4) time point. The specifications were not changed.

Table 3.2.P.8.3.2-5 Confirmatory Stability Study 3

**Test Plan for Accelerated and Stress Stability Studies on (b) (4)
Validation Lots of Filled Product, Stored at (b) (4)**

(b) (4)

Test	Method	Specification	Test Intervals (months)				
			Release	(b) (4)			
			0	1	2	3	6
Appearance	Visual	Opalescent liquid (white suspension)	R	X	X	X	X
Visible Particles	Visual	Conform (absence of foreign particles)	R	X	X	X	X
pH	(b) (4)	(b) (4)	R	X	X	X	X
Identity	rp287-953	(b) (4)	R	X	X	X	X
	rp961c		R	X	X	X	X
	rp936-741		R	X	X	X	X
	OMV		R	X	X	X	X
Endotoxin Content			R	-	X	-	X
(b) (4)			R	X	X	X	X
Immuno- genicity	rp287-953	(b) (4)	R	X	X	X	X
	rp961c		R	X	X	X	X
	rp936-741		R	X	X	X	X
	OMV		R	X	X	X	X

(b) (4)

(b) (4)

OMV: Outer Membrane Vesicles; R: Results reported are from release; rp: recombinant protein; RP: Relative Potency; (b) (4)

(b) (4) Upper Confidence Limit;

(b) (4) may also be referred to as (b) (4)

Study design for the third study for product storage and accelerated conditions are shown in Tables 3.2.P.8.3.2-4 and 3.2.P.8.3.2-5.

For study 1 long-term stability results through results for the following tests: Identity for each antigen, Appearance, pH, ----(b)(4)----- and Sterility confirmed that batches -----(b)(4)----- were within specification for all time points up to and including the proposed shelf life (24 months) when stored at 2-8°C. Throughout the old Potency method is referred to as (b)(4) and the new method as the -(b)(4)-, tests. The Potency assay was adjusted during the time schedule. The original (b)(4) test was highly variable with limited sensitivity. The new endotoxin

assay was also implemented at the 18 month mark. All results for endotoxin time points, using old (b)(4) and new -(b)(4)- testing methods, were within specifications.

The second study batches were all within specification for all time points up to and including the 12 month time point when stored at 2-8°C except for batch --(b)(4)--, which was out of specification at the 1 month time point. Overall, the results did not reveal any decreasing trend in the stability profile of the product. The Endotoxin Test OOS measured at the 1 month time point for batch --(b)(4)-- moved back in specification at subsequent 3, 6, 9 and 12 month time points. The analysis of (b)(4) Relative Potency results were supplemented with the analysis of the geometric mean titers (GMTs) obtained for each antigen at specific doses. Analysis of GMT data was provided as supportive information invalid Relative Potency results.

All the (b)(4) lots ((b)(4) lots for antigen rP936-741) were tested for homogeneity of the slopes (homogeneity is accepted if the relative p-value is greater than 0.25). If the values were not homogenous, a “full model” was applied, otherwise, slopes were pooled and a “common slope model” was used. Then data were tested for homogeneity of the intercepts and, if the values were homogeneous the intercepts were pooled and a “common slope & common intercept model” was applied. Weighting was used because the old test was used for some data points. This analysis was viewed as showing no significant downward trend in potency based on the limited data set. It was concluded that the 4CMenB DP was stable for up to 12 months based on the available data.

Study 3, also serving as stability validation for (b)(4) filling line in Rosia building (b)(4), using lots ----(b)(4)-----, showed in specification ranges for assays: Identity for each antigen, Appearance, pH, -----(b)(4)----- and Sterility up to and including 12 months. The new --(b)(4)-- Potency test was implemented at the 6 month time point. For all lots, the results remained within specifications at the 6 and 12 month time points.

The (b)(4) results were evaluated by considering -----(b)(4)-----

The results from the variance decomposition showed that the variability observed in this stability study is lower than the variability obtained during validation, suggesting that no other factors, such as time (i.e.: a decrease in potency), are contributing to the total variability.

The results from stability studies from studies 1-3 were generally positive. Those for study 1 demonstrate stability for assays Identity for each antigen, Appearance, pH,---(b)(4)-----

---(b)(4)--- and Sterility but were not applicable for the current Endotoxin and Potency assays. Studies 2 and 3 also demonstrated stability for Identity for each antigen, Appearance, pH, ---(b)(4)----- and Sterility assays and demonstrated less variability of the Endotoxin assay. The (b)(4) Potency assay demonstrated better sensitivity and reduced variability compared to the (b)(4) version and no downward trend in stability in either study was observed.

Post-approval Stability Protocol and Stability Commitment

A minimum of one lot of filled product for 4CMenB vaccine will be placed on stability ---(b)(4)- and monitored for the time length of the shelf-life of 24 months when stored at 2-8°C and protected from light. The annual stability program will include the following tests: Appearance, Visible Particles, pH, Identity, Endotoxin, ---(b)(4)-----, Immunogenicity, and sterility. Confirmed out-of-specification results up to and including the proposed shelf-life of 24 months will be reported. The Stability Protocol is summarized in Table 3.2.P.8.2-1 below.

Table 3.2.P.8.2-1 Test Plan for (b) (4) Stability Program for Filled Product Stored at 2-8°C

Test		Specification	Test Intervals (months)							(b) (4)
			0	3	6	9	12	18	24	
Appearance		Opalescent liquid (white suspension)	R	TBD	TBD	TBD	TBD	TBD	TBD	(b) (4)
Visible Particles		Conforms (absence of foreign particles)	R	NR	TBD	NR	TBD	NR	TBD	
pH ¹			R	TBD	TBD	TBD	TBD	TBD	TBD	
Identity	rp287-953		R	TBD	TBD	TBD	TBD	TBD	TBD	
	rp961c		R	TBD	TBD	TBD	TBD	TBD	TBD	
	rp936-741		R	TBD	TBD	TBD	TBD	TBD	TBD	
	OMV		R	TBD	TBD	TBD	TBD	TBD	TBD	
Endotoxin			R	NR	TBD	NR	TBD	NR	TBD	
(b) (4)			R	TBD	TBD	TBD	TBD	TBD	TBD	
Immunogenicity	rp287-953		R	NR	TBD	NR	TBD	TBD	TBD	
	rp961c		R	NR	TBD	NR	TBD	TBD	TBD	
	rp936-741		R	NR	TBD	NR	TBD	TBD	TBD	
	OMV		R	NR	TBD	NR	TBD	TBD	TBD	
Sterility			R	NR	NR	NR	NR	NR	TBD	

IU: International Units; (b) (4) NR: Not required; OMV: Outer Membrane Vesicles;

R: Results reported are from release; rp: recombinant protein; RP: Relative Potency; TBD: To be determined; UCL: Upper Confidence Limit.

¹Specifications for pH were tightened from (b) (4) starting from 2015 on the basis of re-assessment of data from (b) (4) released lots, including clinical batches.

4.0 BLA Review of Lot Release Protocol

I reviewed the Lot Release Protocol (LRP) submitted for 4C Men B (Bexsero) tetravalent vaccine. I found it to be acceptable.

4.0 BLA Review of Batch Production Records

Representative, executed batch records from the manufacture of drug substance batches (one batch each of subfamilies manufactured at ----(b)(4)----- (rp287-953, rp936-741, and rp961c) that were used to produce a drug product process validation lot, were provided and reviewed.

- Rp287-953: Lot numbers -----(b)(4)-----

- Rp963-741: Lot numbers -----(b)(4)-----

- Rp961c: Lot numbers -----(b)(4)-----

Representative, executed batch records from the manufacture of drug substance batches produced at Rosia, Italy, OMV that were used to produce a drug product process validation lot, were provided and reviewed.

- OMV: Lot number -----
----- (b)(4) -----

Executed batch records from the manufacture of a process validation drug product lot manufactured at Rosia, Italy were reviewed.

- Lot No ----- (b)(4) -----
-----.

I found the batch production records to be acceptable.

5.0 BLA Review of Labeling

I reviewed and provided comments on the proposed labeling for 4C Men B (Bexsero) vaccine (container, carton, and package insert).

Kanamycin clearance is based on a calculation estimate as described in Section 3.6 of this review. The issue was covered in Amendments 0.46 and 0.47. The information submitted (as discussed above) support the claim that each dose contains less than 0.01 micrograms kanamycin (by calculation). The CMC review team advised that the label reflect this clearance on calculation basis.

6.0 UNII Code Designation

I reviewed the UNII code designations and found them to be acceptable.

7.0 Component Information Table

For this BLA, I reviewed the components that are used to manufacture the 4C Men B (Bexsero) vaccine. I reviewed the raw materials, ingredients, and components control strategy to make sure

8.0 Information Requests and Interactions

Question 1

Novartis Response:

CBER Response: The requested information was provided. The response is adequate.

--(b)(4)--

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

(b)(4)

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

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

The following comments pertain to the Drug Product.

Question 18

Justifications for the following Drug Product release test specifications for ---(b)(4)---, Filled, and Packaged Product are not adequate: -----(b)(4)----- and pH. The justification provided in Section 3.2.P.5.6 “Justification of Specifications Table 3.2.P.5.6-1” is not adequate. While your justifications accurately state the purpose of these tests, your specifications do not

reflect the analysis of your manufacturing process experience for any of the listed tests. Please revise the specifications to reflect historical performance of lots in the tests or justify how the specifications proposed are adequate to control the quality and consistency of the product. Please provide data and analyses using manufacturing scale lots for justification of specifications for these. Please provide the clinical experience ranges for each.

Novartis Response:

The applicant acknowledged the recommendation with regards to revision of justification of specifications for the Bexxero Drug Product.

Justification of -----(b)(4)-----

The applicant re-assessed (b)(4) released lots including clinical batches. Based on these data the proposed specification for -----(b)(4)----- The --(b)(4)-- clinical batches falls within this range with release data ----(b)(4)----. As the data was not normally distributed, calculations were performed using the ---(b)(4)---- percentile range. This is considered to be comparable to a --(b)(4)-- approach for normally distributed data. The complete dataset was provided in Attachment 18.1

Justification of -----(b)(4)-----

The applicant re-assessed (b)(4) released lots including clinical batches. The applicant indicated that the available data does not support tightening the proposed specification. The (b)(4) was determined to be (b)(4) which means that (b)(4) standard deviation fits within the specification range and tightening specification would lead to a suboptimal process capability ----(b)(4)----. The complete dataset was provided in Attachment 18.2.

Justification of -----(b)(4)-----

The assay for -----(b)(4)----- was based on and fully compliant with --(b)(4)--- requirements -----(b)(4)----- Test A related to suspension for injection. This test is applied to tablets, powders for parenteral use, ophthalmic inserts, and suspensions for injection and establishes a standard for percent of average content. Individual contents of Aluminum Hydroxide are determined on -----(b)(4)----- Based on the compendial nature of the test, Novartis believes that this specification is justified.

Justification of -----(b)(4)-----

----(b)(4)---- is a limit test, whereby the cumulative result of all non-adsorbed proteins is measured. The preparation complies with the test if each individual content is between -----(b)(4)----- of the average content. The preparation fails to comply with the test if

more than one individual content is outside these limits or if one individual content is outside the limits of -----(b)(4)----- of the average content.

The test provides the evaluation of conformity with ---(b)(4)--- requirements and the test results cannot be used retrospectively to provide further information on process consistency or capacity. The proposed limit provides sufficient assurance that the adsorbed product elicits a sufficient immunoresponse, as demonstrated in a clinical setting.

Justification of pH

The applicant re-assessed (b)(4) released lots, including clinical batches. Based on this data a re-assessment of pH specification range has been proposed. The new proposed pH range specification is --(b)(4)-- for release. The thirteen clinical batches fall within this range with release data --(b)(4)--

As the data was not normally distributed, calculations were performed using the ---(b)(4)---- percentile range. This is considered to be comparable to a --(b)(4)-- approach for normally distributed data.

In addition, analysis of the stability data indicates an increase of pH value of --(b)(4)-- per month which corresponds to an increase of ----(b)(4)----- months. Considering the multiple testing approach performed at stability, an upper limit of (b)(4) is proposed. This value is based on the (b)(4) probability that no OOS during stability occurs. The complete data set is provided in Attachment 18.2.

CBER Response:

The response to justification of specifications is adequate. However, validation for --(b)(4)-----Test is not adequate as indicated in IR conveyance to Novartis dated September 18, 2014 and by their response in Amendment 0.14 dated September 26, 2014. Therefore, the ----(b)(4)----- Test specification shall be considered appropriate pending receipt of acceptable validation of the test. Novartis has acknowledged the need for additional data to satisfy validation requirements for the ----(b)(4)----- Assay and committed to submit the required data in Amendment 0.44. As this was requested by another reviewer, I will defer the adequacy of the response.

Question 19

Regarding your extractable and leachable studies, in Section 3.2.P.2.4.1 you describe extractable/leachable studies performed on Luer --- (b)(4)----- syringes at your contract laboratory --- (b)(4)----- . The study evaluated volatiles and semi-volatiles but did not

investigate non-volatile leachable compounds or extractables. Please provide study data that uses an appropriate non-volatile matrix based on this drug product or a similar one, or justify the absence of this study. Also, please provide an appropriate extractables study or justify the absence of this study.

Novartis Response:

The applicant acknowledged the inclusion of volatile, semi-volatile and non-volatile leachable compounds or extractables in this type of study. Extractables studies on volatile, semi-volatile and non-volatile compounds were performed by ---(b)(4)----- on the plunger stopper and tip cap rubber closure systems in order to identify any chemical compounds that might be subject to leaching when in contact with the pharmaceutical matrix. Both study reports are attached (Attachment 19.1 and Attachment 19.2).

----- (b)(4) ----- was selected as the marker for the leachable study because it was found in both extractable studies ----- (b)(4) ----- . Because (b)(4) is a semi-volatile compound, the preferred analytical technique to monitor its quantity was ----(b)(4)----.

The leachable study investigation on non-volatile compounds was deemed not necessary on the basis of the results of the extractables study executed on aqueous and non-aqueous solvent models. The absence of non-volatile compounds in the Bexsero study is therefore considered justified.

CBER Response:

All required information has been submitted. The response is satisfactory.

The following comment pertains to Comparability Protocols

Question 20

Please confirm that no Comparability Protocols were submitted with this BLA to request a future change to be downgraded to an Annual Report. We note that you submitted a section in each DS subsection for qualification of future reference material (Section 3.2.S.5). The information provided in these sections does not include a detailed Comparability Protocol. A post approval supplement can be submitted to request a Comparability Protocol for downgrading future changes to Annual Report. Please confirm.

Novartis Response:

The applicant confirms that no Comparability Protocols have been submitted with this BLA. We acknowledge the advice from CBER and will submit Comparability Protocols post-approval as appropriate.

CBER Response:

The response is adequate.

The following comment pertains to rp936-741 and rp287-953 DS

--(b)(4)---

(b)(4)

--(b)(4)---

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

8.2 *Information Request Communicated October 24, 2014, Responses Received November 7, 2014, and CBER Responses*

Regarding the (b)(4) Drug Substance

--(b)(4)--

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

(b)(4)

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

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

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

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

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

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

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

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

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

Regarding the Drug Product

Question 18

Please provide a list of all (b)(4) times used in the manufacture of drug product. We note that in Section 3.2.P.3.5 Process Validation and/or Evaluation, formulation validation report MNNZ_FORMULATION-02342PVR03 you did not provide in-process control results for the (b)(4) Test of Aluminum Hydroxide or for the (b)(4) Test of Histidine as outlined in Section 3.2.S.P.3.3 Manufacturing Process and Controls [4CMenB – Suspension for Injection in PFS]. Please provide data to support these In-Process Controls.

Novartis Response:

Novartis would like to clarify that the operations required for the drug product manufacturing process (formulation and filling) are executed consecutively without any predefined --(b)(4)-- between different process steps. Times required for completing each single process step are part of the entire process duration which is less than (b)(4) and are needed to perform the activities to move to the next step. For this reason these times are considered process times rather than (b)(4) times. (b)(4) times used in the formulation and fill were provided with the response.

A -(b)(4)- test of Histidine was not in place at the time of the Formulation Process Validation, which was executed in 2010, but was implemented in October 2012. All the commercial lots have been tested as described in the section 3.2.P.3.3. During the 2010 formulation process validation (refer to MNNZ_FORMULATION02342PVR03 report), Aluminum suspension and

Histidine solution were tested for (b)(4)- at the end of the preparation. The results of these tests were provided with the response.

CBER Response:

The (b)(4)- Tests for Aluminum Hydroxide and Histidine Excipients used in DP formulation have been sterility tested in the 2010 process validation. The response is adequate.

Question 19

Please provide a list of all filters used in the manufacture of drug product. We note in Section 3.2.P.3.5 Process Validation and/or Evaluation, (b)(4)-- Validation Report Project No. 8-28-9786 that you provided extractable and leachable studies on the (b)(4)----- filter. If other filters are used in the manufacture of DP, please provide a justification as to why this filter represents worst case scenario with regard to E/L. Please provide extractable studies with different solvents to include water, ethanol, high pH, and low pH. Alternatively, please provide a justification for not using these solvents. Please provide leachable data using product testing for any material detected during the extractable studies.

Novartis Response:

The list of all filters used in the manufacture of Bexsero was provided in the response.

The (b)(4)----- filter represents the worst case scenario with regard to extractables./ The extractable studies for this filter were reported in Attachment 2.1 which was included with the response. These studies have been performed with (b)(4)----- studies cannot be performed on (b)(4)--- due to the (b)(4)-----.

For both (b)(4)-----, the concentration detected in the Extractable study (b)(4)----- is equal or less than (b)(4). This amount would equate (b)(4)----- in a 0.5 mL vaccine dose (b)(4)-----.

This amount is below the TTC (Threshold of Toxicological Concern) of (b)(4)-- for a genotoxic impurity in chronically administered pharmaceuticals. This amount is also below the current SCT (Safety Concern Threshold) for Parenteral and Ophthalmic Drug Products of (b)(4)--- (PQRI; 2013); a leachable below the SCT would have a dose so low as to present a negligible safety concern due to carcinogenic and non-carcinogenic toxic effects.

TTC and SCT are conservative thresholds in the context of a vaccine because they are proposed for compounds that are expected to be used daily for sub-chronic and chronic treatments while vaccination only occurs once or a few times in a human lifespan and treatments are generally separated by months or years. Thus, -----(b)(4)----- - if they resulted in leachables - at levels below the TTC and SCT, are not expected to cause systemic or local toxicity to vaccines. Due to the low levels of extractables detected in the study, Novartis does not consider it is necessary to quantitate the amount of these compounds as leachables into the final product.

CBER Response:

The requested E/L studies have been submitted. These studies demonstrate that any leachables are below the threshold of toxicological and safety concern. The response is adequate.

Question 20

We note that in Section 3.2.P.5.6 Justification of Specifications [4CMenB – Suspension for Injection in PFS] you have requested an exemption for the General Safety Test (GST) as a release test for drug product. We do not concur with your proposal at this time. Please add the GST as a release test. You may submit a post approval supplement to request exemption from the GST once an adequate amount of lots have been manufactured and tested.

Novartis Response:

Based on CBER's feedback via secure email on November 6, 2014 Novartis will respond to this question in a separate amendment after November 07, 2014. The issue was addressed in Amendment 0.27. Novartis proposed addition of the GST to the lot release protocol. A draft protocol was submitted with the response, which was reviewed elsewhere.

CBER Response:

In amendment 0.44 Novartis agreed to perform the General Safety Test Release Test for the Bexsero Drug Product as a lot release test. The response is acceptable.

Question 21

Please provide the source of Aluminum Hydroxide. If this is not a purchased raw material, please provide details on the manufacture and stability.

Novartis Response:

Aluminum Hydroxide bulk is produced at the Novartis Vaccine site in --- (b)(4) ---. Information on manufacture and stability is provided below.

Manufacturer(s)

Name	Address	Operation(s)
(b) (4)		
Novartis Vaccines and Diagnostics S.r.l.	Bellaria-Rosia 53018 Sovicille (SI) Italy	Quality Control testing

A description of Manufacturing Process and Process Controls was provided with the response.

The manufacturing process consists of 6 steps including -----

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

-----, These were described in sufficient detail. The stability protocol was also discussed as were analytical procedures used in the process.

CBER Response:

Detail of the manufacturing process for aluminum hydroxide at the Novartis -(b)(4)- site has been submitted. The information provided is supportive of the Aluminum Hydroxide manufacturing process. However, no process validation was provided. During a teleconference on November 26, 2014 the absence of validation data was discussed. The validation was subsequently submitted in Amendment 0.23 and was adequate. The response was satisfactory.

9.3 ***Information Request Communicated November 6, 2014, Responses Received November 21, 2014, and CBER Responses***

Regarding drug substance --(b)(4)--

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

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

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

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

8.3 *Information Request Communicated December 12, 2014, Responses Received December 23, 2014, and CBER Responses*

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

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

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

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

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

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

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

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

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

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

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

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

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

8.4 Information Request Communicated by Secure e-mail January 12, 2014, Responses Received November 7, 2014, and CBER Responses (Amendment 0.37)

Throughout your submission, you have referenced the role of aluminum hydroxide as an ----- (b)(4) ----- . We note that you requested that aluminum hydroxide be considered an --(b)(4)--- during the pre-BLA meeting. We commented that we reserve judgment until a complete review of the submitted material. At this time, we do not concur with the role of aluminum hydroxide as an --(b)(4)---. After a complete review and our conversation today, we concur with your suggestion of the role of aluminum hydroxide as an adsorbent. Please submit your official request for the role of aluminum hydroxide as an adsorbent. In addition, please reference the Sections of the BLA that justifies your proposed role. Please note that we do not need a justification on why the aluminum hydroxide does not act as an --(b)(4)--

Novartis Response:

On January 12, 2015 an Information Request was sent by secure E-mail to the applicant requesting clarification concerning the role of aluminum hydroxide in the drug product. Throughout the dossier the component has been referred to as ----- (b)(4) ----- . The Applicant acknowledged the inconsistency in Amendment 0.44. In that document the applicant designated aluminum hydroxide as an ‘adsorbent’.

CBER Response:

The response is acceptable.

8.5 Information Request Communicated by Secure e-mail January 16, 2014, Responses Received January 20, 2015 (Amendment 0.45), and CBER Responses

The applicant submitted revised CMC agreements. Revisions were acceptable. See Section 13.0 of this memo for agreements.

8.6 Information Request Communicated by Secure e-mail January 14, 16, and 19 2014, Responses Received January 21, 2015 (Amendment 0.46), and CBER Responses

CBER requested clarification concerning the calculation of kanamycin in -----
----- (b)(4) -----

Request from CBER:

Kanamycin levels in commercial lots of Bexsero. The Novartis position: Kanamycin is less than 0.01 mcg /dose, CBER has some confusion with the information in the file and how it supports this statement. The request is for Novartis to provide the basis of what was done to support that statement.

Novartis Response:

The applicant described that it used a worst case scenario calculation approach to estimate residual kanamycin in per dose in drug product based on several assumptions of contributions from ----- (b)(4) ----- . Assumptions included -----
----- (b)(4) -----

CBER Response:

The assumptions and calculation are reasonable but need clarification. Please explain the basis of the --(b)(4)-- retention of kanamycin.

12.8 Information Request Communicated by Secure e-mail January 21, 2015, Responses Received January 22, 2015 (Amendment 0.47), and CBER Responses

CBER requested clarification concerning the calculation of kanamycin in -----
----- (b)(4) ----- Also covered in this Amendment was clarification concerning location of analytical testing.

Comment:

*Please provide the basis of the (b)(4) in the following assumption: -----
----- (b)(4) -----
-----*

----- (b)(4) ----- However, a retention of - (b)(4) - of the antibiotic in the --- (b)(4) --- was assumed as a worst case.

Novartis Response:

Rationale was provided in the response. The applicant made reasonable assumptions about ----- (b)(4) ----- at formulation leading to a worst case scenario calculation where the --- (b)(4) --- step yields a theoretical retention of (b)(4) of the initial kanamycin leading to a conservative estimate of kanamycin at (b)(4) ----- . The (b)(4) retention was based on manufacturer's permeability parameters, which were described in the submitted material.

CBER Response:

The estimate is reasonable. The response is acceptable.

Comment:

We note the following discrepancies. Please comment.

a. For all three recombinant proteins, the table states that testing for release is done at (b)(4) The BLA method/validation state (b)(4)

b. For the -- (b)(4) --, the table states that the testing for identity and endotoxin/protein for release and stability are done at (b)(4) The BLA method/validation state Rosia.

c. For the --- (b)(4) ----- for final product, the table states that testing for ----- (b)(4) ----- for release and stability is performed at Rosia. It is unclear in the BLA where the validation was performed.

Novartis Response:

The applicant discussed conventions used in submitted site location information. The Company has used -- (b)(4) -- as manufacturer when the main manufacture of the product is --- (b)(4) --- For the recombinant proteins all testing is done at the - (b)(4) - site except for ----- (b)(4) -----, and the final release which are performed at Novartis Rosia. Novartis is correcting the site where the ---- (b)(4) ----- for release and stability test is performed in the supplied table. The convention for the use of [OMV, Rosia] was clarified. The table provided clarified sites of performance.

CBER Response:

The response was acceptable

Comment:

Testing performed at each site must be validated/qualified. Please add the following information to the table.

- a. *The validation/qualification report number*
- b. *The site that the validation/qualification was performed.*

Novartis Response:

Novartis has updated the tables “Overview of analytical procedures and executing test site for release and for stability for 4CMenB...” in sections 3.2.S.4.2 and 3.2.P.5.2 Analytical Procedures – Introduction for all DS and for the DP and added the requested information.

CBER Resonse:

Updated tables were verified for sites of validation, cross validation where applicable and alignment with methods validation with sites listed in the table. The response was acceptable.

13. Written Agreements (Amendment 0.45 received January 20, 2015)

1. The Company commits to submit a proposal to update protein content and pH specifications following statistical analysis of a minimum of (b)(4) additional manufacturing scale lots, which will include data from the 2014 manufacturing campaign. The Company expects to have the report concluded by Q1- 2015 and will submit a prior approval supplement, CBE30 supplement, or Product Correspondence, as appropriate, by April 2015. The revised specification will be implemented prior to the start of the next rp936-741 drug substance manufacturing campaign or upon approval.
2. The stability data up to (b)(4) months at ----(b)(4)----- manufactured using the (b)(4) process has been provided as supporting data in updated Sections 3.2.S.7.3- Stability Data, 3.2.S.7.1, Stability Summary, and 2.3.S.7- Stability for -(b)(4) Updates of the approved ----(b)(4)----- stability data will be provided on an on-going basis through (b)(4) months beginning in Q3 2015 and will be submitted as Product Correspondence.
3. The Company commits to submit a proposal for updated ----(b)(4)---- pH Specification following the statistical analysis of a minimum of (b)(4) additional manufacturing scale lots, which will include data from the 2014 manufacturing campaign (batch release expected Q1/2015). The report will be submitted as a prior approval supplement, CBE30 supplement, or Product Correspondence, as appropriate, by Q3 2015. The revised specification will be implemented in the following ---(b)(4)- ----- manufacturing campaign or upon approval.
4. The Company commits to submit a proposal to update ----- (b)(4) ----- Purity Specifications. The updated specifications will separately account for the ----- (b)(4) ----- . The updated specification will also include an update of the Unspecified Impurities specification. Proposed revision will

follow the statistical analysis of a minimum of (b)(4) additional manufacturing scale lots. This will include batches from the 2014 manufacturing campaign for which QA release is expected Q1/2015. The Company will submit the report as a prior approval supplement in Q4 2015. The revised specifications will be implemented in the following ----(b)(4)----- manufacturing campaign and ----(b)(4)----- stability program upon approval.

5. The Company commits to submit a proposal to update the ----(b)(4)----- pH Specification following statistical analysis of a minimum of (b)(4) additional manufacturing scale lots, which will include data from the 2014 ---(b)(4)----- manufacturing campaign; (batch release expected Q1/2015). The Company will submit the report as a prior approval supplement, CBE30 supplement, or Product Correspondence, as appropriate, by Q4 2015. The specification will be implemented in the following ----(b)(4)----- substance manufacturing campaign or upon approval.
6. The Company commits to submit proposed specifications for the rp287-953 Concentrated Bulk ----(b)(4)----- In-Process Control Test following statistical analysis of a minimum of (b)(4) additional manufacturing scale lots, which will include data from the 2014 drug substance manufacturing campaign (batch release expected Q1/2015). The Company will submit the report as a CBE30 supplement by Q4 2015. The specification will be implemented in the following rp287-953 drug substance manufacturing campaign.
7. The Company commits to submit a reassessment of the rp287-953 Purified Bulk --(b)(4)----- Specification following statistical analysis of a minimum of (b)(4) additional manufacturing scale lots which will include data from the 2014 manufacturing campaign. The Company will submit the report as a prior approval supplement, CBE30 supplement, or Product Correspondence, as appropriate, by Q4 2015. The revised specification will be implemented in the following rp287-953 drug substance manufacturing campaign or upon approval.
8. The Company commits to perform Extractables and, if required, Leachables studies for medium risk process filter used in the --(b)(4)-- manufacturing process reported in Table 6-2 seen in response to Question 14 of October 24, 2014 Information request. The report will be submitted as Product Correspondence by Q4 2015.
9. The Company commits to perform Extractable and, if required, Leachable studies for medium risk process filter used in the --(b)(4)-- process as proposed in response to Question 10 of Information Requests from October 24th 2014. The results will be submitted as a Product Correspondence by Q4 2015.
10. The Company commits to perform Extractables and, if required, Leachables, studies for medium risk process filter used in production of -(b)(4)- in line with commitments

taken for ----(b)(4)----- . The results will be submitted as a Product Correspondence by Q4 2015.

11. The Company commits to repeat the ----(b)(4)----- study for -----
----- (b)(4)-----
----- steps at full manufacturing scale. The study will be initiated during the next ----(b)(4)----- manufacturing campaign. Details of the --- (b)(4)----- validation will be provided using the Product Correspondence procedure by Q4 2015.
12. The Company commits to repeat the -----(b)(4)----- study for-----
----- (b)(4)-----
----- (b)(4)-----
at full manufacturing scale. The study will be initiated during the ----(b)(4)-----
----- manufacturing campaign. Details of the --(b)(4)--- validation will be provided using the Product Correspondence procedure by Q1 2016, based on manufacturing campaign schedule, depending on inventory levels and market demands.
13. The company commits to validate the range of the --(b)(4)-- purity assay to include the range for unspecified impurities. Data will be submitted as Product correspondence by Q4 2015.
14. The Company will execute a re-validation of the OMV process in Bldg. (b)(4) according to a pre-defined validation protocol. The activities will be executed in 2015 and the report will be submitted once all data has been compiled and concluded post approval according to the requested communication procedure as Product Correspondence by Q1 2016.
15. The Company acknowledges the advice for the design of the OMV manufacturing process --- (b)(4)- study. A risk-based approach will be undertaken to assess the worst case conditions for the study, which will include the monitoring tests detailed in tables 3.2.S.2.2.2-1 and 3.2.S.2.2.3-1 in the submission with the addition of bioburden testing at the -----(b)(4)----- . The report will be submitted as Product Correspondence by Q1 2016.
16. The Company Commits to repeat the OMV ----- (b)(4)-----
----- validation study post approval which will include sterility testing. Periodic updates will be provided using the Product Correspondence procedure beginning with the first 12 month time point report submission by Q3 2016.

14. Approval Recommendation

After a complete and thorough review of the original BLA submission and all amendments listed on the first page of this memo, I recommend approval of Bexsero. BLA approval was supported

by the above listed written agreements submitted in Amendment 0.44 on January 15, 2015. The drug substances for Bexsero will be manufactured at: Novartis Vaccines and Diagnostics S.r.l. Bellaria-Rosia 53018 Sovicille, Italy; Novartis Vaccines and Diagnostics -----
----- (b)(4) ----- . Bexsero will be formulated, filled, labeled, and packaged at Novartis Vaccines and Diagnostics Bellaria-Rosia 53018 Sovicille, Italy. The expiry of the drug substances rp287-953, rp936-741, and rp961c will be (b)(4) months when stored at the recommended temperature of -(b)(4)- The expiry of the OMV drug substance will be (b)(4) months when stored at (b)(4) The expiry of drug product will be 24 months from the date of initiation of filling when stored at the recommended temperature of 2-8 °C and protected from light.