Project Name: MNNZ_050-127301-1 **Process Order: 000100332877**

Product: MNNZ_050 - Men B Recombinant Vaccine 287-953, 961c, 936-741+ OMV NZ - Inspected Product (Prefilled Syringes) **Batch: 127301**

SAP Material: RMEB20005 - MEN B TETR LUER LOCK 72L SPER(OMV 11) **LIMS Lot: 106431**

SAP Lot Number: 30000307533

Relative potency	Result >= 0,5	0,983439
305566_COMB_936 - ELISA anti recombinant proteins 936-741		
Upper Confidential Limit 95%	Result >= 1,0	3,59929
Relative potency	Result >= 0,5	1,75893
305566_COMB_961 - ELISA anti recombinant proteins 961c		
Upper Confidential Limit 95%	Result >= 1,0	3,62488
Relative potency	Result >= 0,5	0,976334
305566_RUN1_287 - ELISA anti recombinant proteins 287-953		
Sample executed		Eseguito
Reference		Eseguito
305566_RUN1_936 - ELISA anti recombinant proteins 936-741		
Sample executed		Eseguito
Reference		Eseguito
305566_RUN1_961 - ELISA anti recombinant proteins 961c		
Sample executed		Eseguito
Reference		Eseguito
305566_RUN2_287 - ELISA anti recombinant proteins 287-953		
Sample executed		Eseguito
Reference		Eseguito
305566_RUN2_961 - ELISA anti recombinant proteins 961c		
Sample executed		Eseguito
Reference		Eseguito
305567_COMBINED - ELISA anti OMVZ		
Upper Confidential Limit 95%	Result >= 1,0	2,11289
Relative potency	Result >= 0,5	1,19579

Sample Review Date: 08/11/2013
Last Changed Date: 08/11/2013

Sample Reviewed by: Dr. Massimo Mancini
Quality Control Manager

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CofA Printed on: 13/11/2013

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Via Fiorentina, 1
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Template
Summary Protocol

Documento No.	**306168-03**
Prodotto	**BEXSERO**
Fase di processo	**Final product (Filled/inspected)**
Tipo di contenitore	**Pre-filled syringe**
No. dosi per contenitore	**1**
Ambito operativo	**Europe** ***(see attached table)***

Riferimento WF ID	**55061258**
Sostituisce revisione	**02**
Motivo della revisione	**Pag.2:** Added Liechtenstein in the list of countries **Pag.3:** Added "Proteins" in the description of the vaccine **Pag.3:** Deleted *"or"* between the Centralized procedure numbers since all of them are applicable **Pag.3:** Deleted *"with or without needle "* since the container is always a Pre-filled syringe without needle **Pag.10:** Changed abbreviation for Relative Potency from *"rP"* into *"RP"* **Pag.18:** Changed *Bioburden* specification from ≤15 CFU/100 mL to ≤10 CFU/100 mL, as per CR182298; added explanatory note **Pag.25:** Added *Unspecified Impurities* test, as per CR191342 **Pag.31:** Changed *Residual E. coli HCP* specification from ≤ 200 ppm to ≤ 50 ppm, as per CR206962 **Pag.32:** Changed *Bioburden* specification from ≤17 CFU/100 mL to ≤10 CFU/100 mL, as per CR182298; added explanatory note **Pag.40:** *Appearance* specification reviewed for a greater clarity

Template ID Number : 306168-03

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List of countries where this Template is applicable (as per MA number table):

Austria	Greece	Norway
Belgium	Hungary	Poland
Bulgaria	Iceland	Portugal
Croatia	Ireland	Romania
Cyprus	Italy	Slovakia
Czech Republic	Latvia	Slovenia
Denmark	Liechtenstein	Spain
Estonia	Lithuania	Sweden
Finland	Luxembourg	United Kingdom
France	Malta	
Germany	Netherlands	

The Marketing Authorisation Holder is Novartis Vaccines & Diagnostics Srl Via Fiorentina, 1 – 53100 Siena (Italy)

MA (EU) number	(Invented) name	Strength	Pharmaceutical Form	Route of Administration	Immediate Packaging	Content (concentration)	Pack size
EU/1/12/812/001	Bexsero	--[1]	Suspension for injection	Intramuscular use	pre-filled syringe (glass)	0.5 ml	1 pre-filled syringe with needle
EU/1/12/812/002	Bexsero	--[1]	Suspension for injection	Intramuscular use	pre-filled syringe (glass)	0.5 ml	1 pre-filled syringe without needle
EU/1/12/812/003	Bexsero	--[1]	Suspension for injection	Intramuscular use	pre-filled syringe (glass)	0.5 ml	10 pre-filled syringes with needle
EU/1/12/812/004	Bexsero	--[1]	Suspension for injection	Intramuscular use	pre-filled syringe (glass)	0.5 ml	10 pre-filled syringes without needle

--[1] One dose (0.5 ml) contains:

Recombinant *Neisseria meningitidis* group B NHBA fusion protein [1,4,3]	50 micrograms
Recombinant *Neisseria meningitidis* group B NadA protein [1,2,3]	50 micrograms
Recombinant *Neisseria meningitidis* group B fHbp fusion protein [1,2,3]	50 micrograms
Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 measured as amount of total protein containing the PorA P1.4[2]	25 micrograms

[1]produced in *E. coli* cells by recombinant DNA technology
[2]adsorbed on aluminium hydroxide (0.5 mg Al^{3+})
[3]NHBA (Neisseria Heparin Binding Antigen), NadA (Neisserial adhesin A), fHbp (factor H binding protein)

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Lot ----
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SUMMARY PROTOCOL FOR PRODUCTION AND TESTING

OF MENINGOCOCCAL GROUP B RECOMBINANT PROTEINS + OMV NZ VACCINE

FINAL LOT ----------

Name and address of marketing authorization holder	Novartis Vaccines and Diagnostics Srl Via Fiorentina, 1 - 53100 Siena (Italy)
Proprietary name of product	BEXSERO
Centralized procedure number (EU)	EU/1/12/812/001 - EU/1/12/812/003 EU/1/12/812/002 - EU/1/12/812/004
Final lot	----------
Type of container	Pre-filled syringe
No. of final containers (after inspection)	----------
No. of doses per final container	One
Volume of single human dose	0.5 mL
Date of start period of validity	----------
Expiry date	----------
Storage conditions of final lot	2 – 8°C. Do not freeze

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COMPOSITION OF THE MEDICINAL PRODUCT

Qualitative and quantitative composition per human dose

Recombinant N. meningitidis group B protein 936 - 741 (measured as total protein)	50 mcg
Recombinant N. meningitidis group B protein 287 – 953 (measured as total protein)	50 mcg
Recombinant N. meningitidis group B protein 961c (measured as total protein)	50 mcg
OMV antigen from *N. meningitidis* group B, strain NZ 98/254 (measured as total protein)	25 mcg
Aluminium hydroxide	1.5 mg
Sodium chloride	3.125 mg
Sucrose	10 mg
Histidine	0.776 mg
Water for injection	up to 0.5 mL

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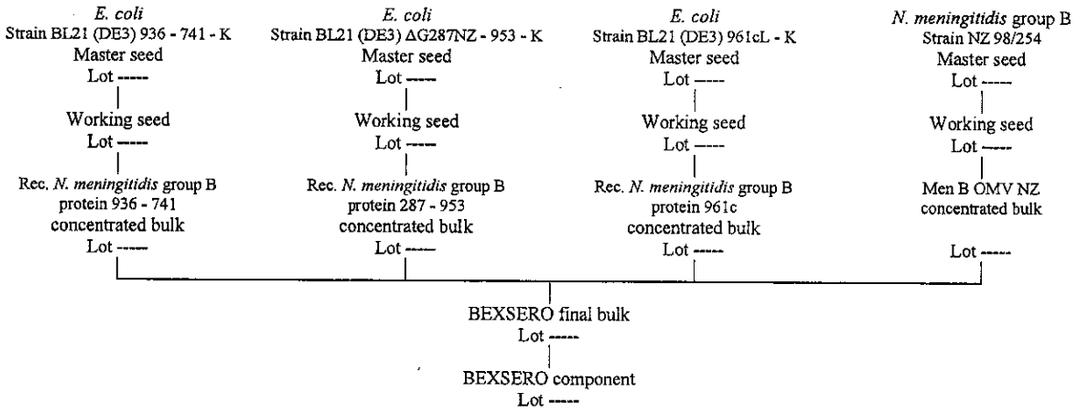
PRODUCTION PLAN



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FINAL BULK VACCINE LOT ----------

Information on blending

Name and address of manufacturer	Novartis Vaccines and Diagnostics Srl Bellaria - Rosia, 53018 Sovicille - Siena (Italy)
Date of manufacture	----------
<u>Men B recombinant protein 936 - 741 component</u>	
Purified concentrated bulk lot (*)	----------
Concentration	---------- mcg/mL
Amount	---------- Kg
<u>Men B recombinant protein 287 - 953 component</u>	
Purified concentrated bulk lot (*)	----------
Concentration	---------- mcg/mL
Amount	---------- Kg (**)
<u>Men B recombinant protein 961c component</u>	
Purified concentrated bulk lot (*)	----------
Concentration	---------- mcg/mL
Amount	---------- g
<u>Men B OMV component</u>	
Purified concentrated bulk lot (*)	----------
Concentration	---------- mcg/mL
Amount	---------- Kg
<u>Adjuvant</u>	
Aluminium hydroxide concentrate bulk lot	----------
----- container	
Concentration	---------- mg/mL
Amount	---------- Kg

(*) – *Information on production and testing of concentrated bulks blended in this final bulk vaccine have been recorded in relevant summary protocols.*

(**) – *All antigens can be considered as 1:1, except for 287-953, which is to be calculated as 1.0143 g/L.*

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First formulation buffer

Nature	Saline solution
Amount	---------- Kg

Second formulation buffer

Nature	Sucrose solution
Amount	---------- Kg

Third formulation buffer

Nature	Histidine buffer
Amount	---------- Kg

Diluent

Nature	Water for injection
Amount	---------- Kg

Final amount	---------- Kg
Storage conditions of final bulk vaccine	2 – 8°C
Approved storage period	1 month

Test on final bulk vaccine

Aluminium hydroxide content (Specification: 2.4 - 3.6 mg/mL)

Method	Titration
Date of test	----------
Result	---------- mg/mL

Sterility test (Specification: Sterile)

Method	Eur. Ph./USP, direct inoculation
Media	FTM and SCDM
Volume tested	---------- mL
Date of test	Record date beginning - date end
Result	----------

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FINAL LOT ----------

Production details of final lot

Name and address of manufacturer	Novartis Vaccines and Diagnostics Srl Bellaria - Rosia, 53018 Sovicille - Siena (Italy)
Date of filling	----------
Filled volume	---------- mL
Type of container	Pre-filled syringe
No. of final containers (after inspection)	----------
Expiry date	----------
Storage conditions of final lot	2 – 8°C. Do not freeze

Tests on final lot

Identity test (Specification: Positive for 936 - 741, 287 - 953, 961c and OMV NZ)

Method	Western blot
Date of test	----------
Result	----------

Extractable volume (Specification: ≥ 0.50 mL)

Method	Eur. Ph./USP
Date of test	----------
Result	---------- mL

Aluminium hydroxide content (Specification: 2.4 - 3.6 mg/mL)

Method	Titration
Date of test	----------
Result	---------- mg/mL

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Aluminium hydroxide homogenicity (Specification: ≤ 20 %)

Method	Titration
Date of test	----------
Result	---------- %

Aluminium hydroxide uniformity (Specification: Conforms to Eur. Ph.)

Method	Titration	
Date of test	----------	
Aluminum hydroxide content	Min.:	---------- mg/mL
	Max.:	---------- mg/mL
	Average:	---------- mg/mL
Result	----------	

Appearance (Specification: Opalescent liquid with white suspension)

Method	Visual examination
Date of test	----------
Result	----------

pH (Specification: 6.0 - 7.0)

Method	Potentiometric
Date of test	----------
Result	----------

Osmolarity (Specification: 240 - 360 mOsm/Kg)

Method	Eur. Ph./USP
Date of test	----------
Result	---------- mOsm/Kg

Endotoxin content (Specification: ≤ 9,600 IU/mL)

Method	LAL test
Date of test	----------

1	------- IU/mL
2	------- IU/mL
3	------- IU/mL
4	------- IU/mL
5	------- IU/mL
6	------- IU/mL
Result	------- IU/mL (*)

(*) *The result is the geometric mean of 6 determinations*

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Percentage of vaccine adsorption to aluminium hydroxide (Specification: ≥ 90 %)

Method	SDS - PAGE
Date of test	----------
Result	---------- %

Sterility test (Specification: Sterile)

Method	Eur. Ph./USP, direct inoculation
Media used	FTM and SCDM
No. of containers tested	----------
Date of test	Record date beginning - date end
Result	----------

Pyrogenicity test (Specification: Non pyrogenic)

Method	USP/CFR (*)
Date of test	----------

Temperature rise 1st test	-------		-------		-------
Temperature rise 2nd test	-------	-------	-------	-------	-------

Result ----------

Immunogenicity (Specification: RP ≥ 0.5 - Upper Confidence Limit (P=0.95) ≥ 1.0)

Method	ELISA
No. and type of animals injected (for each group)	8 mice, 5 – 8 weeks old, CD1 female
Route of injection	Intraperitoneally
No. and volume of injections	Two 0.5 mL injections
Amount of each recombinant antigen injected	20 mcg/injection
Amount of OMV antigen injected	10 mcg/injection
Date of immunization	Record date beginning - date end
Date of test	----------
Result:	

	RP	UCL
936 - 741	----------	----------
287 – 953:	----------	----------
961c:	----------	----------
OMV NZ:	----------	----------

(*) *The pyrogenicity test is performed according to USP/CFR in terms of operative instructions and data interpretation. An inoculum dilution of 1:700 is used on rabbits.*

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Visible particles (Specification: Absence of foreign particles)

Method	Eur. Ph.
Date of test	----------
Result	----------

CERTIFICATION

I herewith certify that Final Lot No. ---------- of Meningococcal Group B Recombinant + OMV NZ Vaccine was manufactured and tested according to the procedures approved by competent authorities and complies with the quality requirements. This includes that, for any material derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.
In addition the OMCL performing OCABR has been notified of all relevant approved variations that have an impact on product specifications or on data supplied in section 3 of this protocol as described in the EU administrative procedure for OCABR.

Dr. --------
Quality Operations / Qualified Person

Date

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SUMMARY PROTOCOL FOR PRODUCTION AND TESTING

OF RECOMBINANT MENINGOCOCCAL GROUP B PROTEIN 936 - 741

CONCENTRATED BULK

LOT ----------

Summary

PRODUCTION PLAN

E. coli
Strain BL21 (DE3) 936 - 741 - K
Master seed
Lot ----------

↓

Working seed
Lot ----------

↓

Men B recombinant protein 936 - 741 concentrated bulk
Lot ----------

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E. COLI STARTING MATERIAL

Production details of master seed

Name and address of manufacturer	Novartis Vaccines and Diagnostics Srl Bellaria - Rosia, 53018 Sovicille - Siena (Italy)
E. coli strain	BL21 (DE3) 936 - 741 - K
Master seed lot	----------
Date of manufacture of master seed	----------
Added preservatives in master seed	None
Storage conditions of master seed	Liquid nitrogen

Tests on master seed

Purity test (Specification: Absence of contaminants)

Method	Inoculation on plates and microscopic observation
Date of test	----------
Result	----------

Identity tests (Specification: Positive)

Method	API identification
Date of test	----------
Result	----------
Method	Western blot
Date of test	----------
Result	----------

Vitality test (Specification: $\geq 10^{8}$ CFU/mL)

Method	Inoculation on plates and colony count
Date of test	----------
Result	--- x 10^{---} CFU/mL

Plasmid retention (Specification: $\leq$ 10 % cells without plasmid)

Method	Plasmid retention test
Date of test	----------
Result	---------- % cells without plasmid

Template ID Number : 306168-03

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Plasmid structural stability (Specification: Conforms to standard)

Method	Plasmid structural stability test
Date of test	----------
Result	----------

Plasmid sequence (Specification: Conforms to standard)

Method	Sequencing of coding region of plasmid
Date of test	----------
Result	----------

Plasmid copy number (Specification: Report result)

Method	Plasmid copy number test
Date of test	----------
Result	---------- copies/bacterium

Bacteriophages (Specification: Conforms to standard)

Method	Inoculation on plates and observation
Date of test	----------
Result	----------

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Production details of working seed

Name and address of manufacturer	Novartis Vaccines and Diagnostics Srl Bellaria - Rosia, 53018 Sovicille - Siena (Italy)
Lot of master seed used in manufacture	----------
Working seed lot	----------
Date of manufacture of working seed	----------
Added preservatives in working seed	None
Storage conditions of working seed	- 80 ± 10°C

Tests on working seed

Purity test (Specification: Absence of contaminants)

Method	Inoculation on plates and microscopic observation
Date of test	----------
Result	----------

Identity tests (Specification: Positive)

Method	API identification
Date of test	----------
Result	----------
Method	Western blot
Date of test	----------
Result	----------

Vitality test (Specification: $\geq 10^{8}$ CFU/mL)

Method	Inoculation on plates and colony count
Date of test	----------
Result	--- x 10^{---} CFU/mL

Plasmid copy number (Specification: Report result)

Method	Plasmid copy number test
Date of test	----------
Result	----- copy/bacterium

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