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MESA DE ENTRADAS

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Product Quality and Disposition Department

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 197/211

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Bacterial and fungal sterility

Method	:	Membrane filtration	
Media	:	Thioglycollate medium	Soybean Casein Digest medium
Temperatures	:	30-35° C	20-25° C
Volume tested	:	**20** ml	
Inoculum per Steritest	:	**10** ml	**10** ml
Volume of medium per Steritest	:	100 ml	100 ml
Test on	:	**24.10.08**	
Test off	:	**07.11.08**	
Result	:	**No microbial growth – Conforms**	

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 198/211

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PART 2

FINAL BULK PRODUCT

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 199/211

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FINAL BULK

TESTS	SPECIFICATIONS
OSMOLALITY	300 - 400 mosmol/kg
FREE FORMALDEHYDE CONTENT	≤30 µg/mL
BACTERIAL AND FUNGAL STERILITY	No microbial growth
HISTAMINE-SENSITIZING ACTIVITY	≥95% survival
NON ADSORBED POLYRIBOSYL RIBITOL PHOSPHATE (PRP) DEPOLYMERIZED PRP	≥8.0 µg/dose <20.0%
PERCENT ADSORPTION – DIPHTHERIA TOXOID	≥23% At time of release, this acceptance criterion was not defined
PERCENT ADSORPTION – HEPATITIS B	≥64% At time of release, this acceptance criterion was not defined
DIPHTHERIA POTENCY	Activity ≥30 IU/dose Lower confidence limit (P = 0.95) of the estimated potency ≥ 20 IU/dose
TETANUS POTENCY	Lower confidence limit (P = 0.95) of the estimated potency ≥ 40 IU/dose
IMMUNOGENICITY PERTUSSIS IN MICE	Anti-PT and anti-FHA antibody GMTs for the vaccine are not significantly lower than those of the reference vaccine (analysis of variance) at the level 5%.
D-ANTIGEN CONTENT	TYPE 1 : 20.0 – 43.0 DU/DOSE TYPE 2 : 5.0 – 9.0 DU/DOSE TYPE 3 : 17.0 – 36.0 DU/DOSE
HEPATITIS B IN VITRO RELATIVE POTENCY (IVRP)	≥0.70 At time of release, this acceptance criterion was not defined

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 200/211

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FINAL BULK

Lot number : FDV01420

Date of manufacture : **02.12.2009**
Storage temperature : + 5°C ± 3°C
Expiry date : **02 September 2010**

Composition

INGREDIENT	Lot number	Volume (ml)
Purified Diphtheria Toxoid	**FA320479**	**2 728**
Purified Tetanus Toxoid	**FA309471**	**1 112**
Adsorbed Pertussis Toxoid	**FA326714**	**18 554**
Adsorbed FHA Pertussis	**FA360425**	**17 278**
Concentrated Polio Trivalent (5C)	**FA331636**	**50 000**
Hepatitis B Surface Antigene C	**AC005** **AC013**	**1 724** **1 656**
Haemophilus Polysaccharide Conjugate	**FA327148** **FA328210**	**16 155** **15 000**
Aluminium hydroxide	**FA367904**	**35 500**
Buffer solution (Disodium hydrogen phosphate and potassium dihydrogen phosphate)	**FA367891**	**20 000**
Essential Amino acids solution	**FA367893**	**25 000**
Buffer solution (trometamol and saccharose)	**FA368886**	**6 269**
Water for injections	**ABS1E335A** **ABS1E336A**	**35 543**
APPROXIMATE TOTAL VOLUME		**242 800**

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MEDICAMENTOS

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CONTROLS :

Osmolality

Method	: Measure of the freezing point reduction
Date	: **15.12.2009**
Result	: **336** mosmol/kg - **Conforms**

Free formaldehyde content

Method	: Spectrophotometry / colorimetric assay
Date	: **30.12.2009**
Result	: **1.36** µg/ml - **Conforms**

Bacterial and fungal sterility

Method	:	Membrane filtration	
Media	:	Thioglycollate medium	Soybean Casein Digest medium
Temperatures	:	30-35° C	20-25° C
Volume tested	:	**20** ml	
Inoculum per Steritest	:	**10** ml	**10** ml
Volume of medium per Steritest	:	100 ml	100 ml
Test on	:	**11.12.2009**	
Test off	:	**28.12.2009**	
Result	:	**No microbial growth – Conforms**	

Histamine-sensitizing activity

Injection (Day 0)

Animals and sex	: mice CD1 - Female
Number of animals	: **20**
Route	: Intraperitoneal
Dose tested per mouse	: 2 human doses (1ml)
Date of injection	: **22.01.2010**

Histamine challenge (Day 5)

Challenge dose per mouse	: 2 mg histamine base
Route	: Intraperitoneal
Date of injection	: **27.01.2010**

Reading date (Day 6)	: **28.01.2010**
Result	: **100** % of survival – **Conforms**

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 202/211

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Polysaccharide content :

Method	: High Performance Anion Exchange Chromatography with Pulsed Amperometric Detection method (HPAEC-PAD)
Standard	: CP09E055
Date	: **10.12.2009**
Non adsorbed PRP	: **10.5** µg/dose
Depolymerized PRP	: **7.3 % - Conforms**

Percent adsorption – Diphtheria toxoid:

Method	: Rocket Immunoelectropheresis method
Date	: **17.12.2009**
Result	: **49 %**

Percent adsorption – Hepatitis B:

Method	: ELISA
Date	: **10.12.2009**
Result	: **98 %**

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 203/211

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Diphtheria potency

Method : European Pharmacopoeia
Strain and sex of animals : Guinea pigs - Dunkin-Hartley - female
Weight : 250 - 350 g
Number of animals per dose : 8

Immunization
Date : **08.12.2009**
Volume tested : 1 ml
Route : Subcutaneous

Challenge
Date : **05.01.2010**
Challenge dose : 0.0512 - 0.0128 - 0.0032 - 0.0008 0.0002 and 0.00005 Lf/0.2 ml
Route : Intradermal
Reading date : **07.01.2010**

Results	Dilutions	Score	Log ED_{50}
Reference toxoid **BRP – D4** **97 IU/ml**	**1/16**	**31/48**	**- 1.514**
	1/32	**29/48**	
	1/64	**18/48**	
	1/128	**5/48**	
Product tested **FDV01420**	**1/17.5**	**34/48**	**- 1.711**
	1/35	**27/48**	
	1/70	**24/48**	
	1/140	**12/42**	

Potency : **76** IU/dose
Confidence limits (P=0.95) : **57 - 113** IU/dose

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 204/211

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Tetanus potency

Method	: European Pharmacopoeia
Strain and sex of animals	: Mice Swiss OF1 - Female
Age	: 5 weeks
Number of animals per dose	: 16

Immunization

Date	: **07.12.2009**
Volume	: 0.5 ml
Route	: Subcutaneous

Challenge

Date	: **04.01.2010**
Challenge dose	: **1/320**
Volume	: 0.5 ml
Route	: Subcutaneous
Reading date	: **08.01.2010**

Results	Dilutions	Score/Total	Log ED_{50}
Reference toxoid **NIBSC-T 98/552** **250 IU/ml**	**1/25**	**16/16**	**- 2.009**
	1/50	**15/16**	
	1/100	**7/16**	
	1/200	**2/16**	
Product tested **FDV01420**	**1/150**	**16/16**	**- 2.760**
	1/300	**10/16**	
	1/600	**9/16**	
	1/1200	**4/16**	

Potency : **705** IU/dose
Confidence limits (P=0.95) : **485 – 1 017** IU/dose

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 205/211

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Immunogenicity Pertussis in mice

Animals and sex	: Mice Swiss OF1- Female
Weight	: 20 - 22 g
Number of animals per group	: 10

Immunization

Date	: **11.12.2009**
Volume	: 0.5 ml
Route	: Intraperitoneal
Reference vaccine	: **PFAGI003-03**
Dose per mouse	: 1/5 human dose

Bleeding date : **08.01.2010**

Titration

1. Anti-PT titers

Method	: ELISA
Pertussis toxin for coating	: **FA287985**
Standard anti-PT serum	: **BRP BATCH1**
Date	: **26.01.2010**
Results	
Reference vaccine	: **269** EU/ml (**196 - 367**)
Product tested	: **219** EU/ml (**133 - 361**)
Probability	: **0.452 (p >0.05)**

2. Anti-FHA titers

Method	: ELISA
FHA for coating	: **FA088651**
Standard anti-FHA serum	: **BRP BATCH1**
Date	: **02.02.2010**
Results	
Reference vaccine	: **206** EU/ml (**130 - 328**)
Product tested	: **257** EU/ml (**134 - 496**)
Probability	: **>0.50 (p >0.05)**

Conclusion : **Conforms**

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 206/211

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D Antigen content

Method : ELISA
Standard : **11.07.07 versus EWS**
Date : **12.01.2010**

	D Antigen unit/dose		
	Type 1	Type 2	Type 3
Product tested	**28.1**	**5.8**	**24.6**

Result : **Conforms**

Hepatitis B in vitro Relative Potency

Method : ELISA
Date : **10.12.2009**
Result : **Conforms**

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003768
DE ENTRADA

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 207/211

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PART 3

FINAL PRODUCT

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A.N.M.A.T. FOLIO 208 FABRICADO

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 208/211

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FINAL PRODUCT

TESTS	SPECIFICATIONS
APPEARANCE	Whitish and cloudy suspension
pH	6.5 - 7.5
EXTRACTABLE VOLUME	At least the nominal volume
ALUMINIUM CONTENT	0.40 - 0.80 mg/dose
BACTERIAL AND FUNGAL STERILITY	No microbial growth
PYROGEN TEST	Conforms to Ph. Eur. criterion
ABNORMAL TOXICITY TEST	No death nor sickness sign At time of release, the test was performed
IDENTITY OF EACH VALENCE : DIPHTHERIA, TETANUS, PERTUSSIS, POLIOMYELITIS, HEPATITIS B, HAEMOPHILUS	Positive

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FINAL PRODUCT

Lot number : S4313

Date of manufacture: **10.02.2010**

CONTROLS :

Appearance

Method	: Visual inspection
Date	: **11.03.2010**
Result	: **Conforms**

pH

Method	: Glass electrode
Date	: **17.03.2010**
Result	: **7.20 - Conforms**

Extractable Volume

Method	: European Pharmacopoeia
Date	: **15.03.2010**
Result	: **Conforms**

Aluminium content

Method	: Complexometry
Date	: **18.03.2010**
Result	: **0.62** mg/dose - **Conforms**

Bacterial and fungal sterility

Method	:	Membrane filtration	
Media	:	Thioglycollate medium	Soybean-Casein Digest medium
Temperature	:	30-35° C	20-25° C
Number of units tested	:	**40**	
Inoculum per Steritest	:	**10** ml	**10** ml
Volume of medium per Steritest	:	100 ml	100 ml
Test on	:	**17.02.2010**	
Test off	:	**03.03.2010**	
Result	:	**No microbial growth - Conforms**	

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Pyrogen test

Method : by intravenous injection 0.1 µg/ml/kg of the rabbit body weight
Date : **11.03.2010**
Number of rabbits : 3

Weight of each rabbits (kg)	Initial temperature in °C (A)	Intravenous dose (ml)	Maximum temperature in °C (B)	Response (B) - (A)
2.5	**39.24**	**0.5**	**39.45**	**0.22**
2.5	**39.13**	**0.5**	**39.22**	**0.10**
2.7	**39.13**	**0.5**	**39.26**	**0.13**

The sum of the 3 individual maximum temperature rises : **0.44** °C
Result : **Conforms**

Diphtheria, Tetanus, Pertussis (FHA and Pertussis toxoid), Poliomyelitis, Hepatitis B and Haemophilus identity

Method : Luminex
Date : **08.04.2010 and 09.04.2010**
Result : **Positive - Conforms**

Abnormal toxicity

Animals	:	Mice	Guinea pigs
Number of animals	:	5	2
Volume injected	:	0.5 ml	5 ml
Route of injection	:	Intraperitoneal	
Test on	:	**08.03.10**	
Test off	:	**15.03.10**	
Result	:	**No death nor sickness sign - Conforms**	

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A.N.M.A.T. FOLIO 006772 MESA DE ENTRADAS

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Product Quality and Disposition Department

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA),poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 210/210

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MANUFACTURER' S CERTIFICATION

I herewith certify that **DIPHTHERIA, TETANUS, PERTUSSIS (ACELLULAR, COMPONENT), HEPATITIS B (RDNA), POLIOMYELITIS (INACTIVATED) AND HAEMOPHILUS INFLUENZAE TYPE B CONJUGATE VACCINE (ADSORBED)**, batch number **S4314**, was manufactured and tested according to cGMP and was submitted in the frame of the CTD submission via the Article 58 of regulation N°726/2004 in july 2011, procedure number : EMEA/H/W/002495.

This includes that, for any materials 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 .

GENERAL CONCLUSION : Conforms

Date : 07 December 2014

Name : A. PASIEU-SEGUELA

R&D QA **Product Quality and Disposition Department**

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