

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° S4312 (clinical batch) 153/229

**Bacterial and fungal sterility**


Method used	:	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	:	12.03.08
Test off	:	26.03.08
Result	:	No microbial growth


**Inactivation kinetics**

Method	:	viral titration of polio cytopathogenic effect on sensitive cells
Cell strain used	:	Hep 2
Temperature of incubation	:	36 ± 1° C
Test on	:	21.03.08
Test off	:	28.03.08

TIME	D0	D0 + 24H	D0 + 48H	D0 + 72H	D0 + 96H
Titer (CCID <sub>50</sub> /ml)	10 <sup>9.30</sup>	10 <sup>5.80</sup>	≤10 <sup>2.30</sup>	≤10 <sup>1.30</sup>	≤10 <sup>1.30</sup>

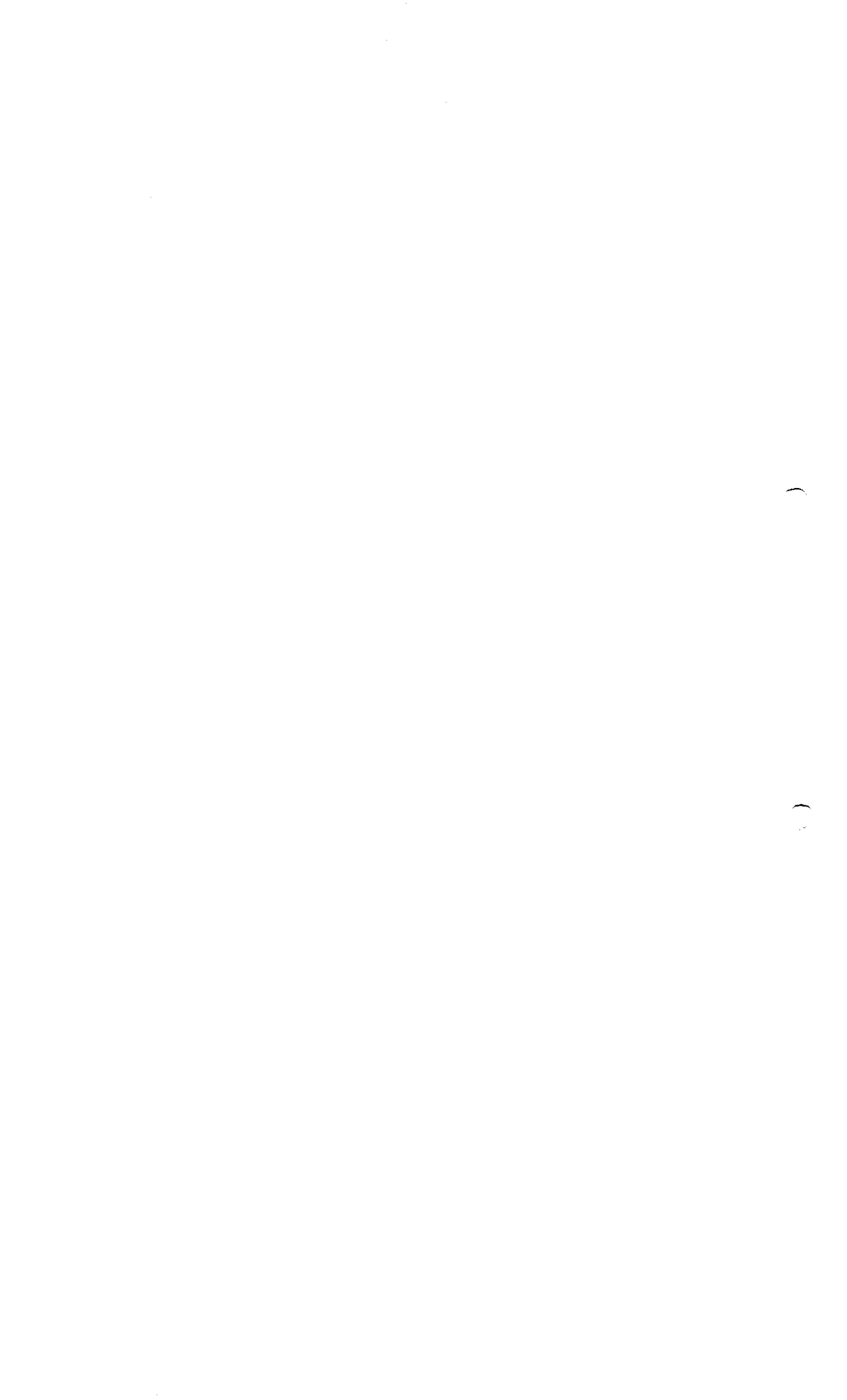
Slope calculation : - 0.1458, Conforms

  
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 DIRECTORA TÉCNICA  
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 CHRISTIAN DOMÍNGUEZ  
 REGISTRADO  
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**MONOVALENT BULK - Type : 3  
Lot Number : FA300586**

Single harvest used : **FA290835 – FA292974**  
Date of inactivation : **25.02.08**  
Inactivation method : **0.88% (w/v) Formaldehyde, 37°C, 12 days**  
  
Date of manufacture : **25.02.08**  
Volume : **207 500 ml**  
Storage temperature : **+5°C ± 3°C**  
Monovalent bulk period of validity : **3 years**  
Expiry date : **25 FEBRUARY 2011**

**CONTROLS:**

**Residual formaldehyde content**

Method : **Spectrophotometry**  
Date : **03.03.08**  
Result : **85.93 µg/ml - Conforms**

**Protein content**

Method : **Spectrophotometry**  
Date : **04.03.08**  
Result : **22.67 µg/ml**

**D Antigen content**

Method : **ELISA**  
Reference standard : **28.1.99**  
Date : **28.02.08**  
Result : **1 053 D Antigen U/ml**

**Purity**

Result : **21.527 ng of protein / D Antigen U - Conforms**

*[Signature]*  
**ROXANA MONTEMILONE DIRECTORA TÉCNICA SANOFI PASTEUR S.A.**  
**CHRISTIAN DOMÍNGUEZ GERBERADU SANOFI PASTEUR S.A.**





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The vaccines division of sanofi-aventis Group

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Bacterial and fungal sterility


Method used	:	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	:	27.02.08
Test off	:	12.03.08
Result	:	No microbial growth


Inactivation kinetics

Method	:	viral titration of polio cytopathogenic effect on sensitive cells
Cell strain used	:	Hep 2
Temperature of incubation	:	36 ± 1° C
Test on	:	29.02.08
Test off	:	07.03.08

TIME	D0	D0 + 24H	D0 + 48H	D0 + 72H	D0 + 96H
Titer (CCID <sub>50</sub> /ml)	10 <sup>9.20</sup>	10 <sup>5.30</sup>	≤10 <sup>2.00</sup>	≤10 <sup>1.30</sup>	≤10 <sup>1.30</sup>

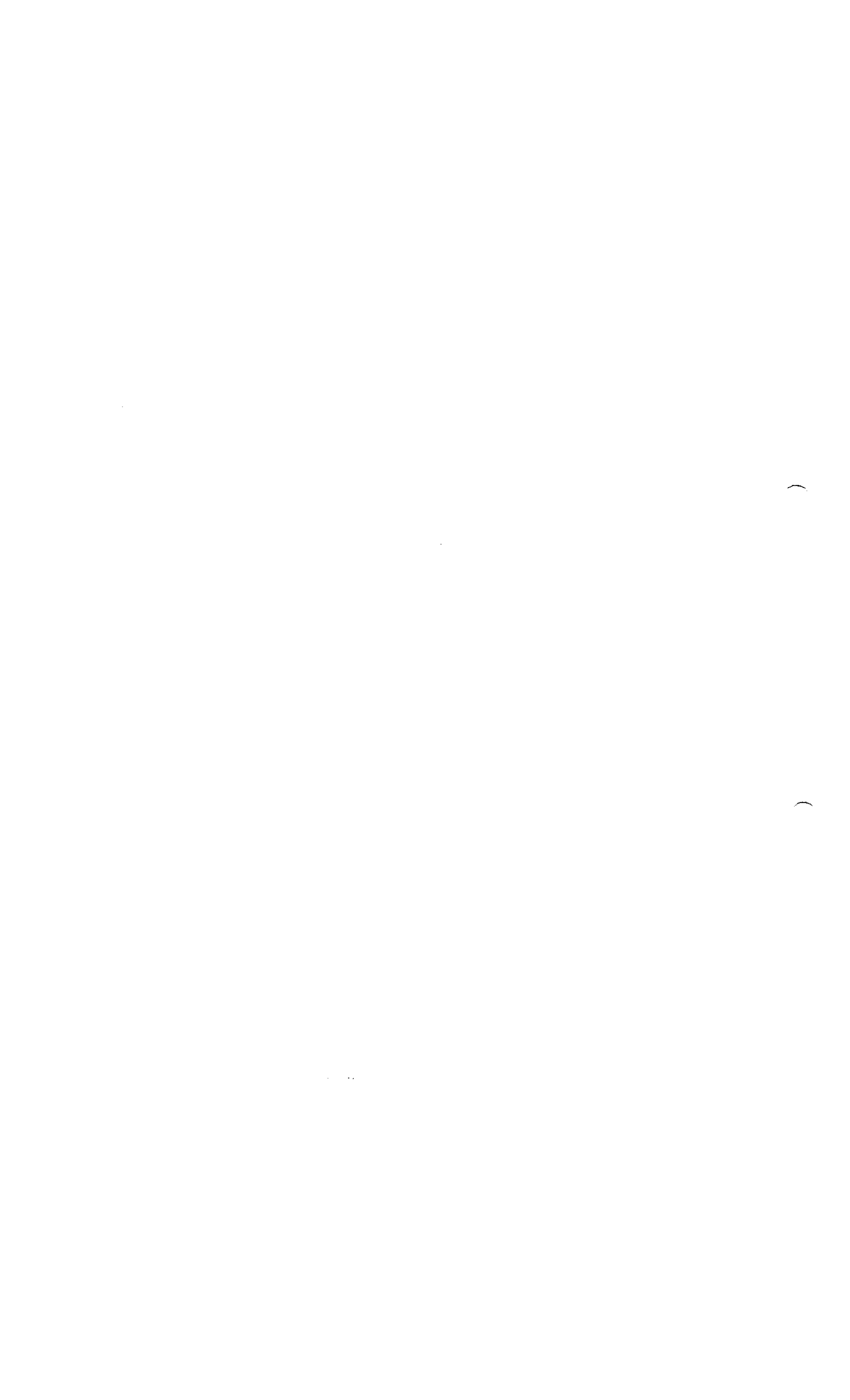
Slope calculation : - 0.1500, Conforms

  
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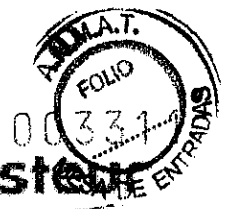
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**CONCENTRATED TRIVALENT BULK**

TESTS	SPECIFICATIONS
pH MEASUREMENT	6.8 - 7.5
RESIDUAL FORMALDEHYDE CONTENT	≤ 100 µg/ml
BOVINE SERUM ALBUMINE CONTENT	≤ 100 ng/ml
BACTERIAL ENDOTOXINS CONTENT	< 50 IU/ml
BACTERIAL AND FUNGAL STERILITY TEST	No microbial growth
D ANTIGEN CONTENT	
Type 1	240 - 560 D antigen units/ml
Type 2	48 - 112 D antigen units/ml
Type 3	192 - 448 D antigen units/ml
TEST FOR EFFECTIVE INACTIVATION	No cytopathic effect


  
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 DIRECTORA TÉCNICA      FUNDADOR  
 SANOFI PASTEUR S.A.      SANOFI PASTEUR S.A.





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CONCENTRATED TRIVALENT BULK
Lot Number : FA327604

Date of manufacture : 29.10.08
Storage temperature : +5°C ± 3°C
Expiry date : 29 OCTOBER 2010

Composition

FORMULA - THEORETICAL COMPOSITION PER ML

Type 1 (MAHONEY) : 400 D units
Type 2 (MEF-1) : 80 D units
Type 3 (SAUKETT) : 320 D units

Table with 3 columns: INGREDIENTS, Lot number, Volume (liter). Rows include Monovalent type 1, 2, 3, 199 Medium, and APPROXIMATE TOTAL VOLUME.

Handwritten signatures and printed names: ROXANA MONTEMILONE, DIRECTORA TÉCNICA, SANOFI PASTEUR S.A. and CHRISTIAN DOMINGUEZ, REPRESENTANTE, SANOFI PASTEUR S.A.



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**CONTROLS :**

**pH measurement**

Method : Glass electrode  
 Date : 03.11.08  
 Result : 7.12 - Conforms

**Residual formaldehyde content**

Method : Spectrophotometry  
 Date : 04.11.08  
 Result : 57.42 µg/ml - Conforms

**Bovine serum albumin content**



Method : ELISA  
 Date : 05.11.08  
 Result : <3.9 ng/ml - Conforms

**Bacterial endotoxins content**

Method : LAL  
 Date : 03.11.08  
 Result : <0.50 IU/ml - Conforms

**Bacterial and fungal sterility**

Method used	:	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	:	31.10.08	
Test off	:	14.11.08	
Result	:	Conforms	

  
 ROXANA MONTEMILONE  
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 CHRISTIAN DOMÍNGUEZ  
 SUPERVISOR  
 SANOFI PASTEUR S.A.





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**D Antigen content**

Method : ELISA  
 Reference standard : 11/07/07  
 Date : 03.11.08

	D Antigen unit/ml		
	Type 1	Type 2	Type 3
Product tested	477	83	325

Result : **Conforms**



**Test for effective inactivation**

*First test*

Method : Cytopathogenic effect on sensitive cells  
 Cell strain : Vervet  
 Volume tested : 3000 theoretical human doses  
 Virulence challenge : viral suspension (type 1, 2, 3)  
 about 100-300 CCID<sub>50</sub>/ml  
 Temperature of incubation : 37 ± 1°C  
 Test on : 19.11.08  
 Test off : 10.12.08

	Inoculation date	Reading date			Result
		At 7 <sup>th</sup> day	At 14 <sup>th</sup> day	At 21 <sup>st</sup> day	
primary test Vervet - V1084	19.11.08	26.11.08	03.12.08	10.12.08	no CPE
subculture at 7 <sup>th</sup> day Vervet - V1083	26.11.08		10.12.08		no CPE
subculture at 14 <sup>th</sup> day Vervet - V1085	10.12.08		24.12.08		no CPE
subculture at 21 <sup>st</sup> day Vervet - V1085	10.12.08		24.12.08		no CPE
virulence challenge Vervet - V1084	11.12.08	18.12.08			CPE

Result : **No cytopathic effect (CPE)**

  
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 CHRISTIAN DOMINGUEZ  
 ENCARGADO  
 SANOFI PASTEUR S.A.









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**- F - HAEMOPHILUS type b CONJUGATE**

  
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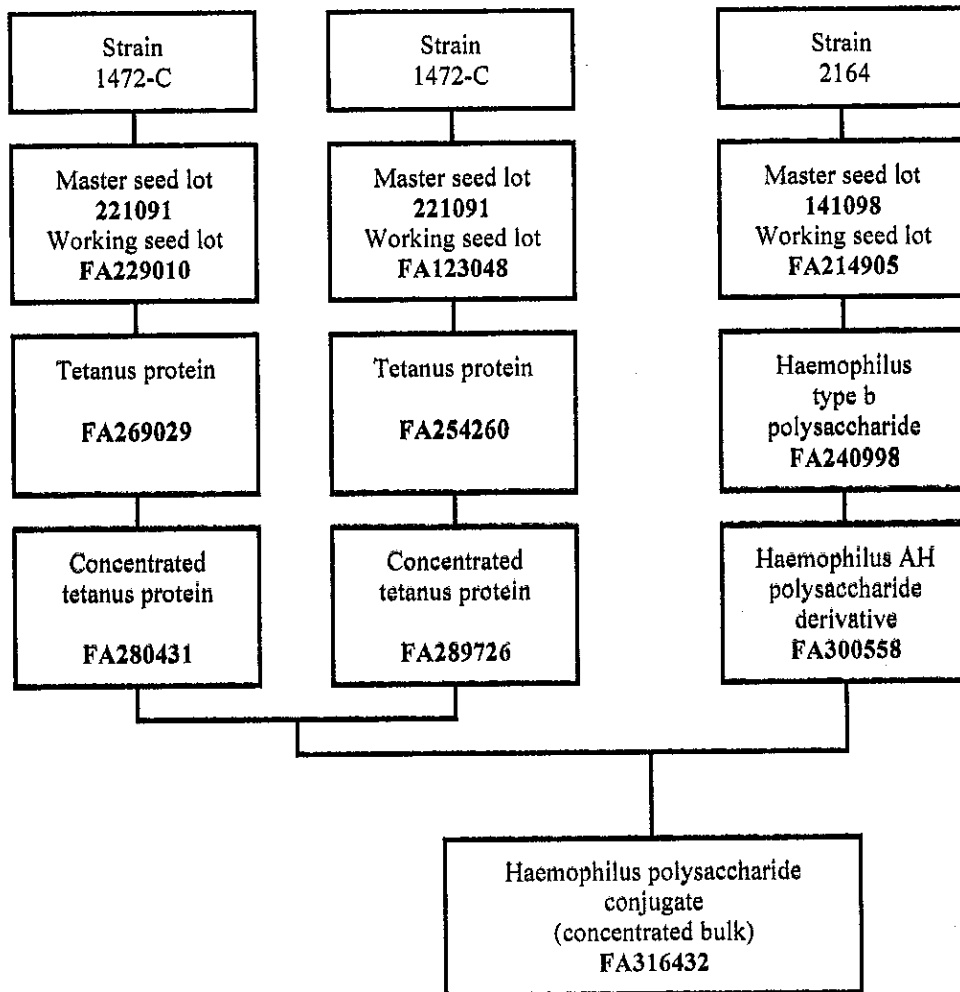



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**PRODUCTION FLOW SHEET**




  
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**HAEMOPHILUS INFLUENZAE**  
 Strain : Haemophilus Influenzae 2164

**STRAIN**



Name : Haemophilus influenzae type b – strain 1482  
 Origin : Dr John ROBBINS (FDA)  
           Bethesda – Maryland 20014  
 Received : 12.12.75  
 Institut Mérieux number : IM 2164

**HAEMOPHILUS INFLUENZAE**  
 Master seed lot n° 141098

Strain number : IM 2164  
 Preparation date : 14.10.98  
 Release date : 11.09.01

**CONTROLS**

- Purity  
 Identification
- Morphology
  - Growth characteristics
  - Biochemical characteristics
  - Antigenic characteristics

 ROXANA MONTEMILONE DIRECTORA TÉCNICA SANOFI PASTEUR S.A.	 CHRISTIAN DOMÍNGUEZ COORDINADOR SANOFI PASTEUR S.A.
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