

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° S4313 (clinical batch)

116/180

CONTROLS ON SUPERNATANTS:

Test for extraneous agents

Vero cells

Method : Studied through a microscope
 Type of cells : Vero
 Volume tested : 10 ml
 Temperature of incubation : 36 ± 1° C
 Test on : 14.01.08
 Test off : 28.01.08
 Result : Absence of cytopathic effect

Human diploid cells

Method : Studied through a microscope
 Type of cells : MRC5
 Volume tested : 10 ml
 Temperature of incubation : 36 ± 1° C
 Test on : 12.02.08
 Test off : 11.03.08
 Result : Absence of cytopathic effect

Primary monkey kidney cells

Method : Studied through a microscope
 Type of cells : Vervet Monkey Cells
 Volume tested : 10 ml
 Temperature of incubation : 36 ± 1° C
 Test on : 15.01.08
 Test off : 29.01.08
 Result : Absence of cytopathic effect

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



Product Quality and Disposition Department

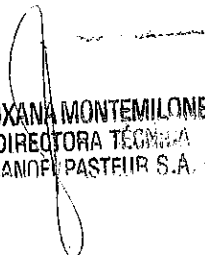

**Diphtheria, tetanus, pertussis (acellular, component),
 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch)** 117/180

Test for Mycoplasma by culture method

Method	: Agar culture
Volume tested	: 34 ml
Media used	: Hayflick solid Hayflick semi-solid B.O.B. solid B.O.B. semi-solid
Temperature of incubation	: 36 ± 1° C
Positive controls	: <i>M. pneumoniae</i> and <i>M. orale</i> and <i>A. laidlawii</i>
<i>Primary test</i>	
Test on	: 28.07.08
Test off	: 11.08.08
<i>Subculture at 3rd day</i>	
Test on	: 31.07.08
Test off	: 14.08.08
<i>Subculture at 7th day</i>	
Test on	: 04.08.08
Test off	: 18.08.08
<i>Subculture at 14th day</i>	
Test on	: 11.08.08
Test off	: 25.08.08
<i>Subculture at 21th day</i>	
Test on	: 18.08.08
Test off	: 25.08.08
Result	: No growth of Mycoplasma

Test for Mycoplasma by epifluorescence in cell culture

Method	: DNA fluorescence staining
Cell used	: Vero, 148 th passage
Volume tested	: 1 ml
Temperature of incubation	: 36 ± 1° C
Positive control	: <i>M. hyorhinae</i> and <i>M. orale</i>
Test on	: 19.02.08
Test off	: 26.02.08
Result	: No Mycoplasma detected by epifluorescence in cell culture

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**Diphtheria, tetanus, pertussis (acellular, component),
 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch) 118/180**

CONTROLS ON SINGLE VIRUS HARVEST :

Polio virus identification

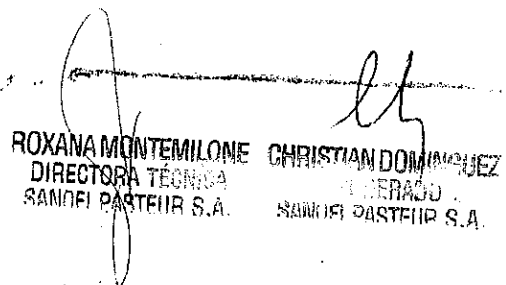
Method : Cytopathogenic effect neutralization
 Cell strain used : Hep 2
 Antiserum : LEPINE type 3
 Test on : 22.02.08
 Test off : 29.02.08
 Result : Positive

Polio virus concentration

Method : Cytopathogenic effect on sensitive cells
 Cell strain used : Hep 2
 Test on : 22.02.08
 Test off : 29.02.08
 Virus concentration : $10^{8.63}$ CCID₅₀/ml
 Result : 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	:	28.11.07	
Test off	:	12.12.07	
Result	:	No microbial growth	



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119/180

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch)

Test for Mycoplasma by culture method

Method	: Agar culture
Volume tested	: 34 ml
Media used	: Hayflick solid Hayflick semi-solid B.O.B. solid B.O.B. semi-solid
Temperature of incubation	: 36 ± 1° C
Positive controls	: <i>M. pneumoniae</i> and <i>M. orale</i> and <i>A. laidlawii</i>
<i>Primary test</i>	
Test on	: 28.07.08
Test off	: 11.08.08
<i>Subculture at 3rd day</i>	
Test on	: 31.07.08
Test off	: 14.08.08
<i>Subculture at 7th day</i>	
Test on	: 04.08.08
Test off	: 18.08.08
<i>Subculture at 14th day</i>	
Test on	: 11.08.08
Test off	: 25.08.08
<i>Subculture at 21th day</i>	
Test on	: 18.08.08
Test off	: 25.08.08
Result	: No growth of Mycoplasma

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch) 120/180

CONTROLS ON CONCENTRATED PURIFIED VIRAL SUSPENSION:

Protein content

Method : Spectrophotometry
Date : 04.12.07
Result : 91.88 µg/ml

D Antigen content

Method : ELISA
Reference standard : 28.1.99
Date : 05.12.07
Result : 6 443 D Antigen U/ml

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
Volume of medium per Steritest : 100 ml
Test on : 04.12.07
Test off : 18.12.07
Result : No microbial growth

Purity

Result : 0.014 µg of protein / D Antigen U

Handwritten signatures and stamps for Roxana Montemilone and Christian Domínguez, Directors at Sanofi Pasteur S.A.





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Diphtheria, tetanus, pertussis (acellular, component),
hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch)

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SINGLE HARVEST - Type : 3
Lot Number : FA292974

CELL:

Working Cell Bank : FA106611
Date of thawing ampoule of WCB : 15.11.07
Thawing ampoule amount : One ampoule

VIRUS:

Virus Working Seed lot : FA109086
Date of inoculation : 10.12.07
Date of virus harvest : 13.12.07

CRUDE HARVEST:

Storage : from 14.12.07 to 17.12.07
Volume : 1 489 L
Storage temperature : +5°C ± 3°C

SINGLE HARVEST:

Date of single harvest : 17.12.07

CONCENTRATION AND PURIFICATION OF THE SINGLE HARVEST

DEAE Spherodex large column : Ion exchange chromatography on 18.12.07
CL-6-B Sepharose column : Gel filtration on 19.12.07
DEAE Sphérodex small column : Ion exchange chromatography on 19.12.07

CONCENTRATED PURIFIED VIRAL SUSPENSION :

Manufacture date : 19.12.07
Volume : 19 600 ml
Storage temperature : +5°C ± 3°C

352_CC5_SPL_AE.dot /19.09.11

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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch) 122/180

CONTROLS ON CELLS:

Observation


Method : Studied through a microscope
Cells : Vero, 142nd passage
Number of cells tested : 320*10⁶ cells
Test on : 10.12.07
Test off : 24.12.07
Result : Absence of cytopathic effect


Test for haemadsorbing viruses

Method : visual inspection
Number of vials tested : 8
Type of red blood cells : Guinea-pig
Incubation : 4 vials, 30 minutes at 5°C ± 3°C
: 4 vials, 30 minutes at 20-25°C
Date : 24.12.07
Result : Absence of hemadsorption

Simian cells Identification

Method : Isoenzymes analysis by IsoElectric Focusing
Iso-enzymes analysed : Lactate DeHydrogenase
Phospho Gluconate Dehydrogenase
Glucose Phosphate Isomerase
Reference cells : Vero, MRC5, WI38, Hep 2
Date : 14.02.08
Result : Positive identification


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 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch) 123/180

CONTROLS ON SUPERNATANTS:

Test for extraneous agents

Vero cells


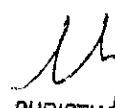
Method	: Studied through a microscope
Type of cells	: Vero
Volume tested	: 10 ml
Temperature of incubation	: 36 ± 1° C
Test on	: 14.01.08
Test off	: 28.01.08
Result	: Absence of cytopathic effect

Human diploid cells

Method	: Studied through a microscope
Type of cells	: MRC5
Volume tested	: 10 ml
Temperature of incubation	: 36 ± 1° C
Test on	: 20.02.08
Test off	: 19.03.08
Result	: Absence of cytopathic effect

Primary monkey kidney cells

Method	: Studied through a microscope
Type of cells	: Vervet Monkey Cells
Volume tested	: 10 ml
Temperature of incubation	: 36 ± 1° C
Test on	: 15.01.08
Test off	: 29.01.08
Result	: Absence of cytopathic effect

 ROXANA MONTEMILONE DIRECTORA TÉCNICA SANOFI PASTEUR S.A.	 CHRISTIAN DOMÍNGUEZ SUPERVISOR SANOFI PASTEUR S.A.
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Diphtheria, tetanus, pertussis (acellular, component),
hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
Influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch)

124/180

Test for Mycoplasma by culture method

Method : Agar culture
 Volume tested : 34 ml
 Media used : Hayflick solid
 Hayflick semi-solid
 B.O.B. solid
 B.O.B. semi-solid
 Temperature of incubation : 36 ± 1° C
 Positive controls : *M. pneumoniae* and *M. orale* and *A. laidlawii*

Primary test
 Test on : 24.11.08
 Test off : 08.12.08

Subculture at 3rd day
 Test on : 27.11.08
 Test off : 11.12.08


Subculture at 7th day
 Test on : 01.12.08
 Test off : 15.12.08


Subculture at 14th day
 Test on : 08.12.08
 Test off : 22.12.08

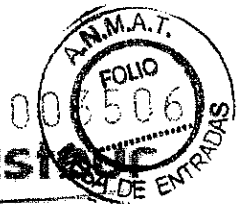
Subculture at 21th day
 Test on : 15.12.08
 Test off : 22.12.08
 Result : No growth of Mycoplasma

Test for Mycoplasma by epifluorescence in cell culture

Method : DNA fluorescence staining
 Cell used : Vero, 146th passage
 Volume tested : 1 ml
 Temperature of incubation : 36 ± 1° C
 Positive control : *M. hyorhinis* and *M. orale*
 Test on : 20.03.08
 Test off : 27.03.08
 Result : No Mycoplasma detected by epifluorescence
 in cell culture


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Diphtheria, tetanus, pertussis (acellular, component),
hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch) 125/180

CONTROLS ON SINGLE VIRUS HARVEST :

Polio virus identification



Method : Cytopathogenic effect neutralization
Cell strain used : Hep 2
Antiserum : LEPINE type 3
Test on : 21.07.08
Test off : 29.07.08
Result : Positive

Polio virus concentration

Method : Cytopathogenic effect on sensitive cells
Cell strain used : Hep 2
Test on : 21.07.08
Test off : 29.07.08
Virus concentration : $10^{8.40}$ CCID₅₀/ml
Result : 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	:	19.12.07
Test off	:	03.01.08
Result	:	No microbial growth


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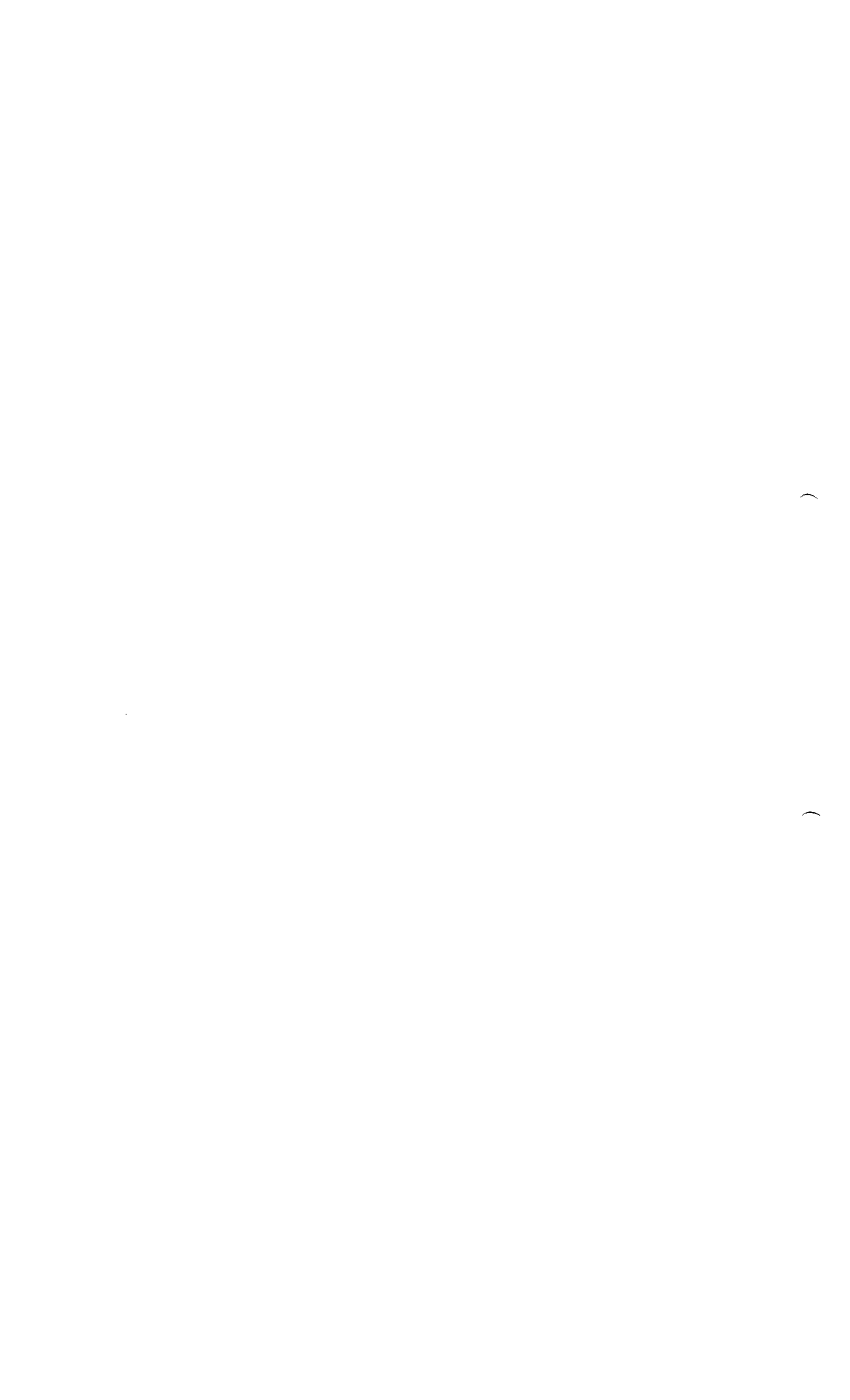
Product Quality and Disposition Department

Diphtheria, tetanus, pertussis (acellular, component),
 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch) 126/180

Test for Mycoplasma by culture method

Method	: Agar culture
Volume tested	: 34 ml
Media used	: Hayflick solid Hayflick semi-solid B.O.B. solid B.O.B. semi-solid
Temperature of incubation	: 36 ± 1° C
Positive controls	: <i>M. pneumoniae</i> and <i>M. orale</i> and <i>A. laidlawii</i>
<i>Primary test</i>	
Test on	: 24.11.08
Test off	: 08.12.08
<i>Subculture at 3rd day</i>	
Test on	: 27.11.08
Test off	: 11.12.08
<i>Subculture at 7th day</i>	
Test on	: 01.12.08
Test off	: 15.12.08
<i>Subculture at 14th day</i>	
Test on	: 08.12.08
Test off	: 22.12.08
<i>Subculture at 21th day</i>	
Test on	: 15.12.08
Test off	: 22.12.08
Result	: No growth of Mycoplasma

 ROXANA MONTEMILONE DIRECTORA TÉCNICA SANOFI PASTEUR S.A.	 CHRISTIAN DOMÍNGUEZ COORDINADOR SANOFI PASTEUR S.A.
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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° S4313 (clinical batch) 127/180

CONTROLS ON CONCENTRATED PURIFIED VIRAL SUSPENSION:

Protein content

Method : Spectrophotometry
 Date : 27.12.07
 Result : 88.90 µg/ml

D Antigen content


Method : ELISA
 Reference standard : 28.1.99
 Date : 14.01.08
 Result : 7 403 D Antigen U/ml

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	: 24.12.07	
Test off	: 07.01.08	
Result	: No microbial growth	

Purity

Result : 0.012 µg of protein / D Antigen U



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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° S4313 (clinical batch)

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MONOVALENT BULK (TYPE 1, 2 AND 3)

TESTS	ACCEPTANCE CRITERIA
RESIDUAL FORMALDEHYDE CONTENT	80 ± 30 µg/ml
PROTEIN CONTENT	For purity calculation
D ANTIGEN CONTENT	For purity calculation
PURITY	≤ 50 ng of protein/D antigen unit
BACTERIAL AND FUNGAL STERILITY TEST	No microbial growth
KINETICS OF INACTIVATION DAY 0 DAY 24H DAY 48H DAY 72H DAY 96H SLOPE CALCULATION (D0, D0+24H, D0+48H)	The infectious titer drops in linear mode Type 1 : within -0.1187 and -0.1758 Type 2 : within -0.0955 and -0.1890 Type 3 : within -0.1090 and -0.1933
TEST FOR EFFECTIVE INACTIVATION : DAY 9 DAY 12	No cytopathic effect during amplification process No cytopathic effect during amplification process


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influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch) 129/180

MONOVALENT BULK - Type : 1
Lot Number : FA303359

Single harvest used : FA295889 – FA297421
Date of inactivation : 17.03.08
Inactivation method : 0.88% (w/v) Formaldehyde, 37°C, 12 days

Date of manufacture : 17.03.08
Volume : 260 550 ml
Storage temperature : +5°C ± 3°C
Monovalent bulk period of validity : 3 years
Expiry date : 17 MARCH 2011

CONTROLS:

Residual formaldehyde content

Method : Spectrophotometry
Date : 25.03.08
Result : 84.62 µg/ml - Conforms

Protein content

Method : Spectrophotometry
Date : 26.03.08
Result : 21.83 µg/ml

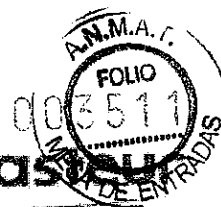
D Antigen content

Method : ELISA
Reference standard : 28.1.99
Date : 25.03.08
Result : 1 218 D Antigen U/ml

Purity

Result : 17.922 ng of protein / D Antigen U - Conforms

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DIRECTORA TÉCNICA REPRESENTANTE
SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.



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° S4313 (clinical batch) 130/180

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	:	19.03.08
Test off	:	02.04.08
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 ₅₀ /ml)	10 ^{9.60}	10 ^{5.50}	≤10 ^{2.30}	≤10 ^{1.30}	≤10 ^{1.30}

Slope calculation : - 0.1521, Conforms


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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° S4313 (clinical batch) 132/180

MONOVALENT BULK - Type : 1
Lot Number : FA304026

Single harvest used : FA296701 – FA297937
Date of inactivation : 31.03.08
Inactivation method : 0.88% (w/v) Formaldehyde, 37°C, 12 days

Date of manufacture : 31.03.08
Volume : 254 200 ml
Storage temperature : +5°C ± 3°C
Monovalent bulk period of validity : 3 years
Expiry date : 31 MARCH 2011

CONTROLS:

Residual formaldehyde content

Method : Spectrophotometry
Date : 10.04.08
Result : 88.18 µg/ml - **Conforms**

Protein content

Method : Spectrophotometry
Date : 15.04.08
Result : 21.00 µg/ml

D Antigen content

Method : ELISA
Reference standard : 28.1.99
Date : 03.04.08
Result : 1 364 D Antigen U/ml

Purity

Result : 15.396 ng of protein / D Antigen U - **Conforms**

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influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch) 133/180

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	:	04.04.08	
Test off	:	18.04.08	
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	:	04.04.08
Test off	:	11.04.08

TIME	D0	D0 + 24H	D0 + 48H	D0 + 72H	D0 + 96H
Titer (CCID ₅₀ /ml)	10 ^{9.30}	10 ^{5.00}	≤10 ^{2.20}	≤10 ^{1.30}	≤10 ^{1.30}

Slope calculation : - 0.1479, Conforms


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