

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) 84/211

**

CONTROLS ON SINGLE VIRUS HARVEST:

Polio virus identification

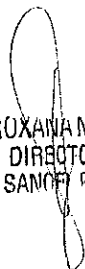

Method	: Cytopathogenic effect neutralization
Cell strain used	: Hep 2
Antiserum	: MAHONEY type 1
Test on	: 01.10.07
Test off	: 08.10.07
Result	: Positive

Polio virus concentration

Method	: Cytopathogenic effect on sensitive cells
Cell strain used	: Hep 2
Test on	: 01.10.07
Test off	: 08.10.07
Virus concentration	: 10 ^{8.87} CCID ₅₀ /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	: 26.09.07
Test off	: 10.10.07
Result	: No microbial growth

 ROXANA MONTEMILONE DIRECTORA TÉCNICA SANOFI PASTEUR S.A.	 CHRISTIAN DOMINGUEZ SUPERVISOR 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° S4314 (clinical batch)**

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**

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	: 28.03.08
Test off	: 11.04.08
<i>Subculture at 3rd day</i>	
Test on	: 31.03.08
Test off	: 14.04.08
<i>Subculture at 7th day</i>	
Test on	: 04.04.08
Test off	: 18.04.08
<i>Subculture at 14th day</i>	
Test on	: 11.04.08
Test off	: 25.04.08
<i>Subculture at 21th day</i>	
Test on	: 18.04.08
Test off	: 25.04.08
Result	: No growth of Mycoplasma

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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)

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CONTROLS ON CONCENTRATED PURIFIED VIRAL SUSPENSION :

Protein content

Method : Spectrophotometry
 Date : 02.10.07
 Result : 124.99 µg/ml

D Antigen content

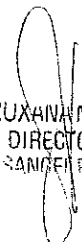
Method : ELISA
 Reference standard : 28.1.99
 Date : 01.10.07
 Result : 11 695 D Antigen U/ml

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	: 01.10.07	
Test off	: 15.10.07	
Result	: No microbial growth	

Purity


Result : 0.011 µg of protein / D Antigen U



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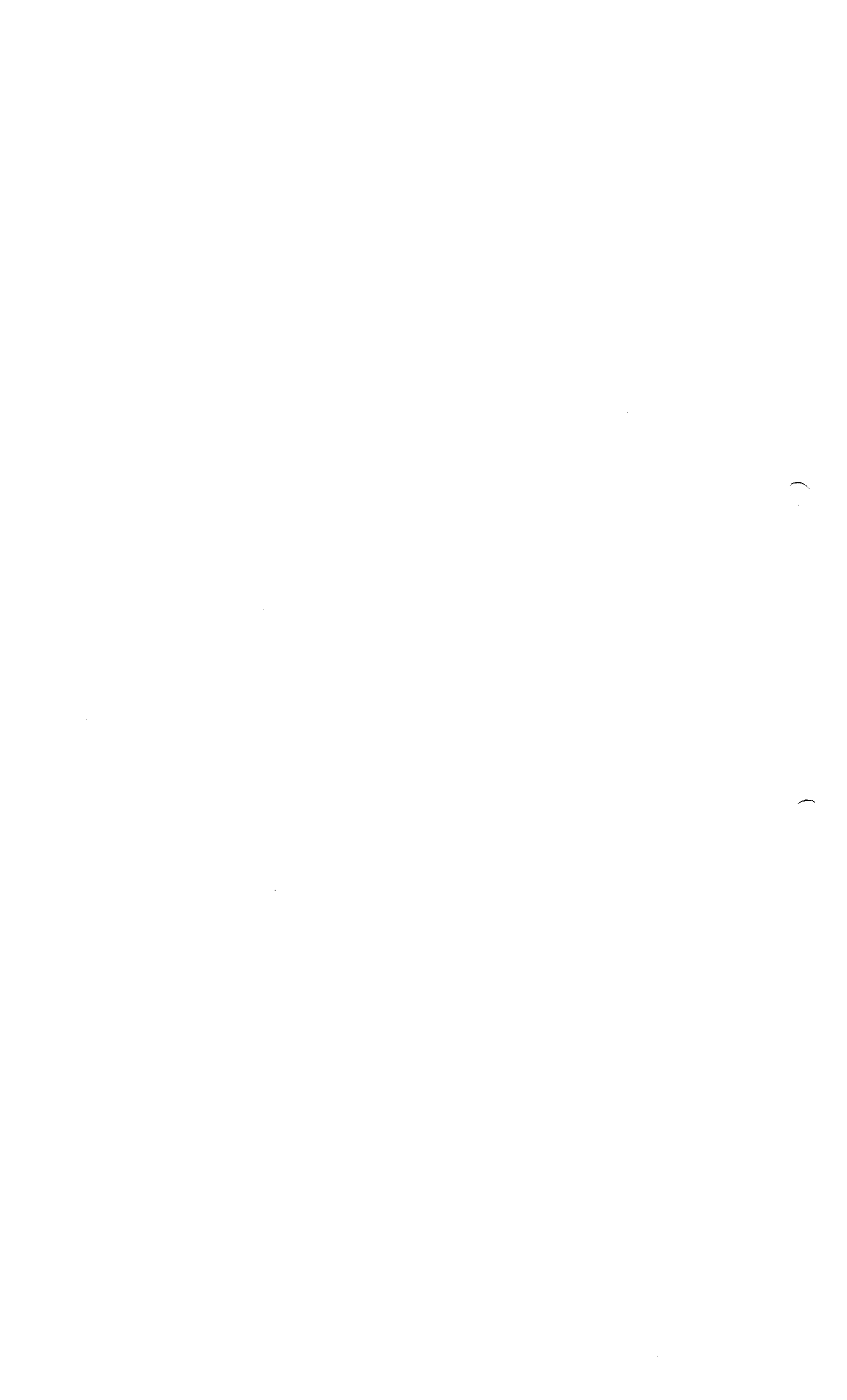
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 CHRISTIAN DOMINGUEZ

 AUDERADO

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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)

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**

SINGLE HARVEST - Type : 1
Lot Number : FA296701

CELL:

Working Cell Bank : FA106611
Date of thawing ampoule of WCB : 20.12.07
Thawing ampoule amount : One ampoule

VIRUS:

Virus Working Seed lot : FA159761
Date of inoculation : 14.01.08
Date of virus harvest : 17.01.08

CRUDE HARVEST:

Storage : from 18.01.08 to 21.01.08
Volume : 1 490 L
Storage temperature : +5°C ± 3°C

SINGLE HARVEST:

Date of single harvest : 21.01.08

CONCENTRATION AND PURIFICATION OF THE SINGLE HARVEST

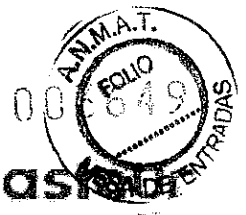
DEAE SpheroDex large column : Ion exchange chromatography on 22.01.08
CL-6-B Sepharose column : Gel filtration on 23.01.08
DEAE SphéroDex small column : Ion exchange chromatography on 23.01.08

CONCENTRATED PURIFIED VIRAL SUSPENSION :

Manufacture date : 23.01.08
Volume : 19 500 ml
Storage temperature : +5°C ± 3°C

352_CC5_SPL_AE.dot /19.09.11

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CHRISTIAN DOMINGUEZ FERRERADO SANOFI PASTEUR S.A.



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influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch)**

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**

CONTROLS ON CELLS:

Observation

Method	: Studied through a microscope
Cells	: Vero, 142 nd passage
Number of cells tested	: 320*10 ⁶ cells
Test on	: 14.01.08
Test off	: 28.01.08
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	: 28.01.08
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	: 03.04.08
Result	: Positive identification

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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)



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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	: 20.10.08
Test off	: 03.11.08
<i>Subculture at 3rd day</i>	
Test on	: 23.10.08
Test off	: 06.11.08
<i>Subculture at 7th day</i>	
Test on	: 27.10.08
Test off	: 12.11.08
<i>Subculture at 14th day</i>	
Test on	: 03.11.08
Test off	: 17.11.08
<i>Subculture at 21th day</i>	
Test on	: 10.11.08
Test off	: 17.11.08
Result	: No growth of Mycoplasma

Test for Mycoplasma by epifluorescence in cell culture

Method	: DNA fluorescence staining
Cell used	: Vero, 146 th passage
Volume tested	: 1 ml
Temperature of incubation	: 36 ± 1° C
Positive control	: <i>M. hyorhinis</i> and <i>M. orale</i>
Test on	: 29.04.08
Test off	: 06.05.08
Result	: No Mycoplasma detected by epifluorescence in cell culture

	
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 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch)

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 **

CONTROLS ON SINGLE VIRUS HARVEST:

Polio virus identification


Method : Cytopathogenic effect neutralization
 Cell strain used : Hep 2
 Antiserum : MAHONEY type 1
 Test on : 23.07.08
 Test off : 30.07.08
 Result : Positive


Polio virus concentration

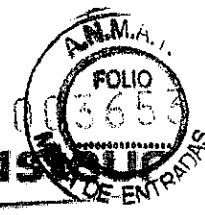
Method : Cytopathogenic effect on sensitive cells
 Cell strain used : Hep 2
 Test on : 23.07.08
 Test off : 30.07.08
 Virus concentration : 10^{8.93} CCID₅₀/ml
 Result : Conforms

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	:	23.01.08	
Test off	:	06.02.08	
Result	:	No microbial growth	


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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>
Primary test	
Test on	: 20.10.08
Test off	: 03.11.08
Subculture at 3 rd day	
Test on	: 23.10.08
Test off	: 06.11.08
Subculture at 7 th day	
Test on	: 27.10.08
Test off	: 12.11.08
Subculture at 14 th day	
Test on	: 03.11.08
Test off	: 17.11.08
Subculture at 21 th day	
Test on	: 10.11.08
Test off	: 17.11.08
Result	: No growth of Mycoplasma



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hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch)

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**

CONTROLS ON CONCENTRATED PURIFIED VIRAL SUSPENSION :

Protein content

Method : Spectrophotometry
Date : **19.02.08**
Result : **119.35 µg/ml**

D Antigen content


Method : ELISA
Reference standard : **28.1.99**
Date : **29.01.08**
Result : **13 282 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	: 28.01.08	
Test off	: 11.02.08	
Result	: No microbial growth	

Purity

Result : **0.009 µg of protein / D Antigen U**


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hepatitis B (rDNA), poliomyelitis (Inactivated) and Haemophilus
influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch)

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**

SINGLE HARVEST - Type : 1
Lot Number : FA297937

CELL:

Working Cell Bank : FA106611
Date of thawing ampoule of WCB : 03.01.08
Thawing ampoule amount : One ampoule

VIRUS:

Virus Working Seed lot : FA159761
Date of inoculation : 28.01.08
Date of virus harvest : 30.01.08

CRUDE HARVEST:

Storage : from 01.02.08 to 04.02.08
Volume : 1 505 L
Storage temperature : +5°C ± 3°C

SINGLE HARVEST:

Date of single harvest : 04.02.08

CONCENTRATION AND PURIFICATION OF THE SINGLE HARVEST

DEAE SpheroDex large column : Ion exchange chromatography on 05.02.08
CL-6-B Sepharose column : Gel filtration on 06.02.08
DEAE SphéroDex small column : Ion exchange chromatography on 06.02.08

CONCENTRATED PURIFIED VIRAL SUSPENSION :

Manufacture date : 06.02.08
Volume : 19 400 ml
Storage temperature : +5°C ± 3°C

[Signature]
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DIRECTORA TÉCNICA
SANOFI PASTEUR S.A.

[Signature]
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° S4314 (clinical batch)

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**

CONTROLS ON CELLS:

Observation

Method : Studied through a microscope
Cells : Vero, 142nd passage
Number of cells tested : 320*10⁶ cells
Test on : 28.01.08
Test off : 11.02.08
Result : Absence of cytopathic effect

Test for haemadsorbing viruses

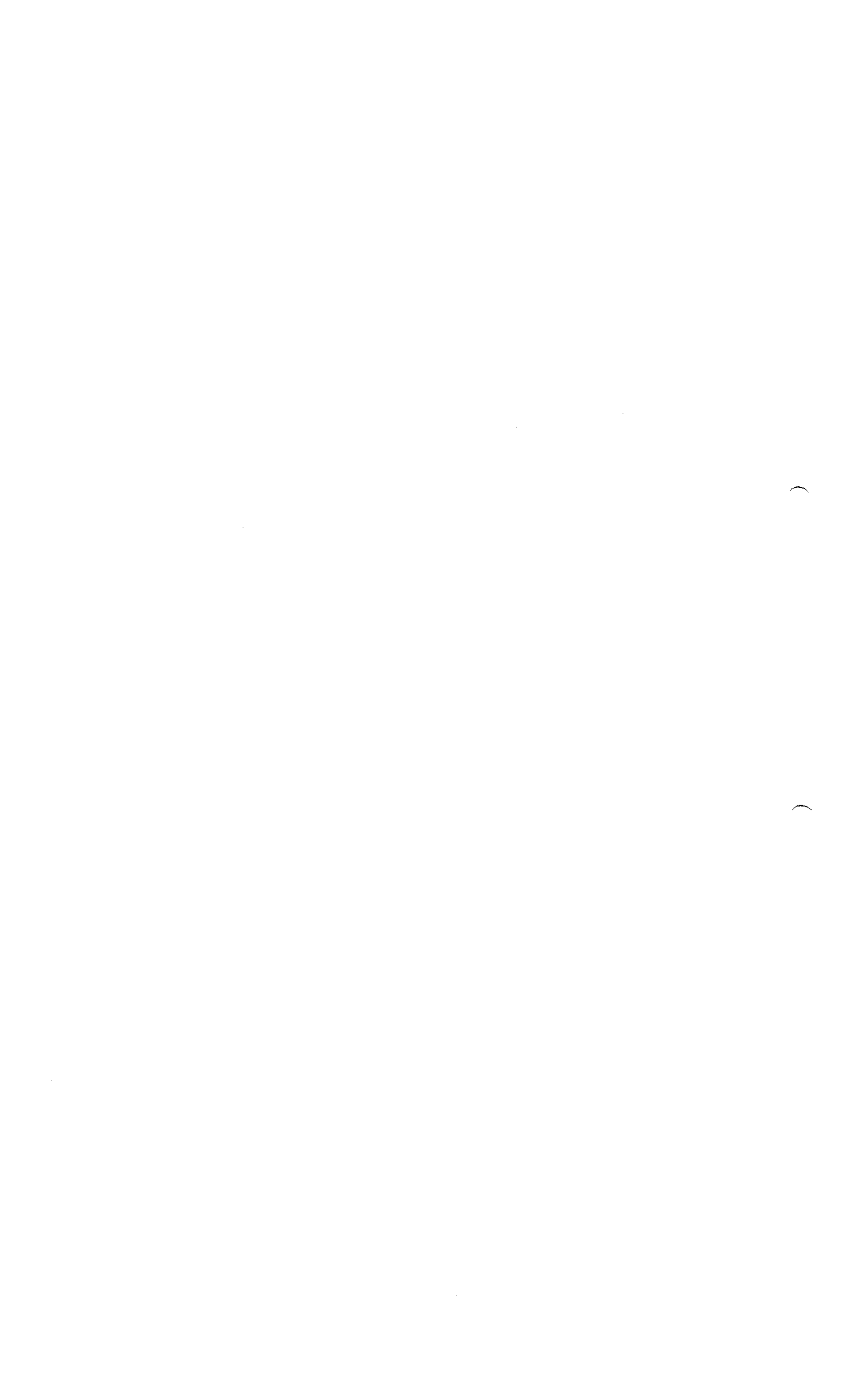
Method : visual inspection
Number of vials tested : 8
Type of red blood cells : Guinea-pig
Incubation : 4 vials, 30 minutes at 5°C ± 3°C
: 4 vials, 30 minutes at 20-25°C
Date : 11.02.08
Result : Absence of hemadsorption

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 : 03.09.08
Result : Positive Identification

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**

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	: 10.03.08
Test off	: 25.03.08
Result	: Absence of cytopathic effect

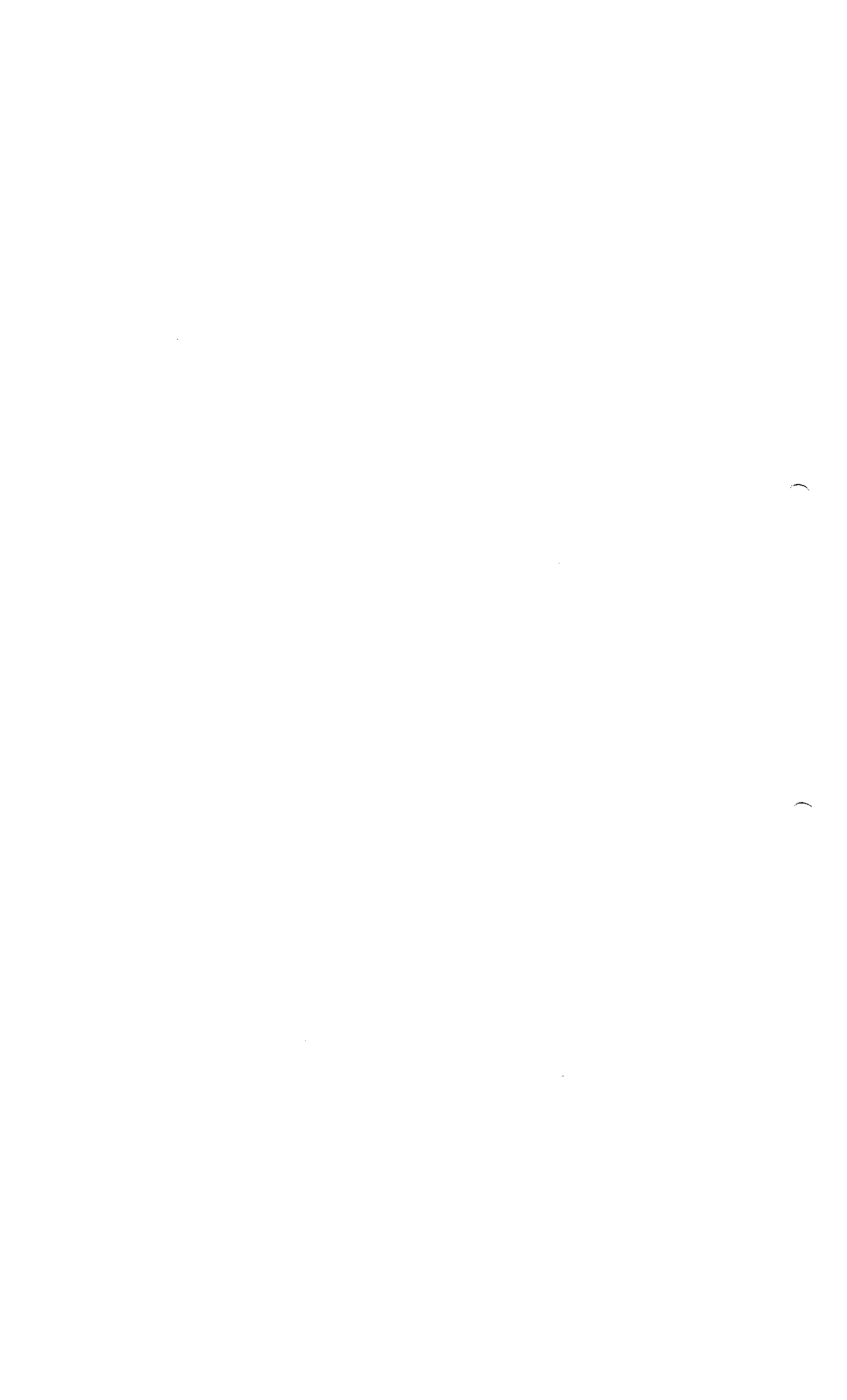
Human diploid cells

Method	: Studied through a microscope
Type of cells	: MRC5
Volume tested	: 10 ml
Temperature of incubation	: 36 ± 1° C
Test on	: 11.03.08
Test off	: 08.04.08
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	: 12.02.08
Test off	: 26.02.08
Result	: Absence of cytopathic effect

	
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Influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch)

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**

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	: 20.10.08
Test off	: 03.11.08
<i>Subculture at 3rd day</i>	
Test on	: 23.10.08
Test off	: 06.11.08
<i>Subculture at 7th day</i>	
Test on	: 27.10.08
Test off	: 12.11.08
<i>Subculture at 14th day</i>	
Test on	: 03.11.08
Test off	: 17.11.08
<i>Subculture at 21th day</i>	
Test on	: 10.11.08
Test off	: 17.11.08
Result	: No growth of Mycoplasma

Test for Mycoplasma by epifluorescence in cell culture

Method	: DNA fluorescence staining
Cell used	: Vero, 152 nd passage
Volume tested	: 1 ml
Temperature of incubation	: 36 ± 1° C
Positive control	: <i>M. hyorhinis</i> and <i>M. orale</i>
Test on	: 20.05.08
Test off	: 27.05.08
Result	: No Mycoplasma detected by epifluorescence in cell culture

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**

CONTROLS ON SINGLE VIRUS HARVEST:

Polio virus identification

Method : Cytopathogenic effect neutralization
Cell strain used : Hep 2
Antiserum : MAHONEY type 1
Test on : 10.09.08
Test off : 17.09.08
Result : Positive

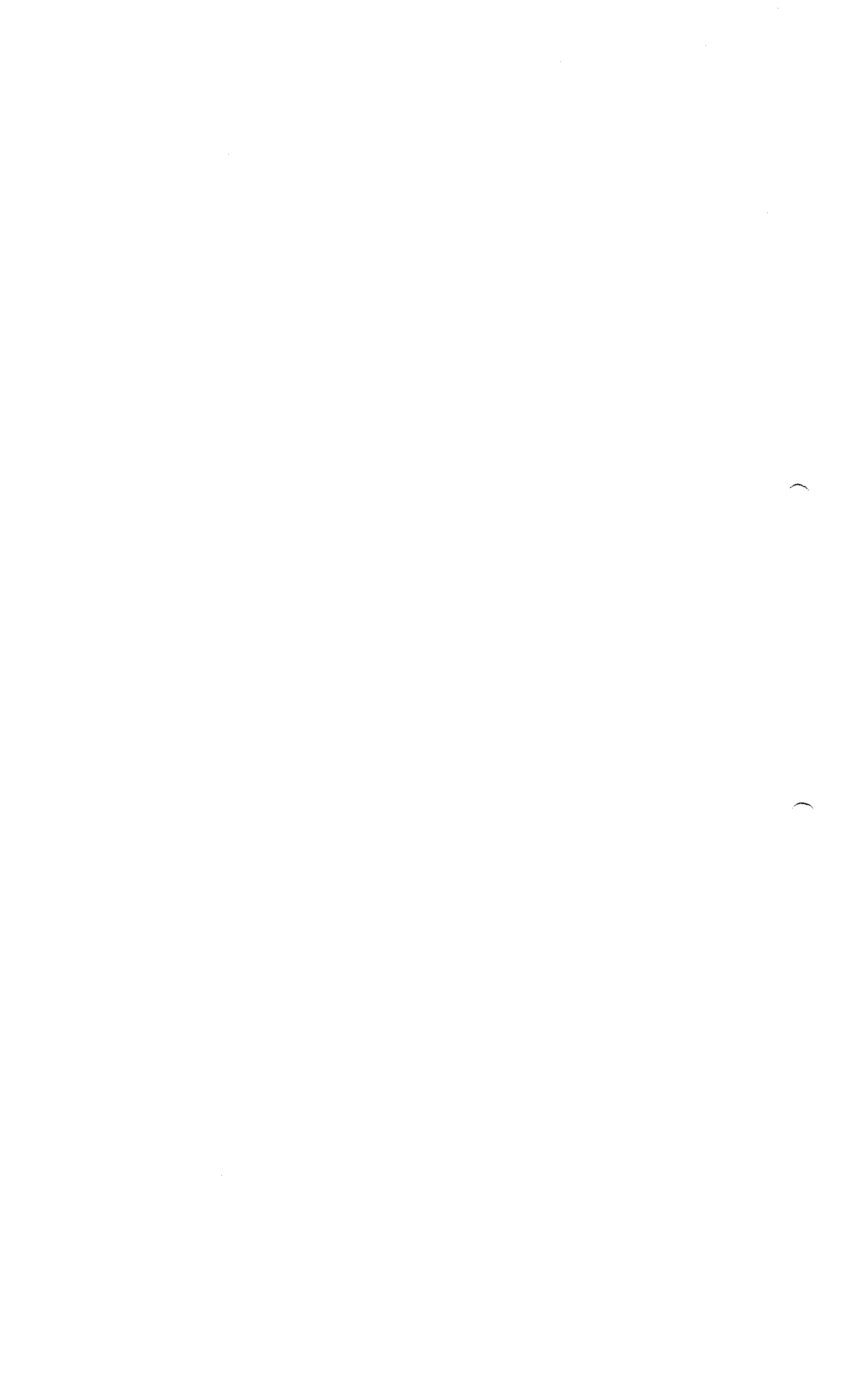
Polio virus concentration

Method : Cytopathogenic effect on sensitive cells
Cell strain used : Hep 2
Test on : 10.09.08
Test off : 17.09.08
Virus concentration : 10^{8.47} 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 : 05.02.08
Test off : 19.02.08
Result : No microbial growth

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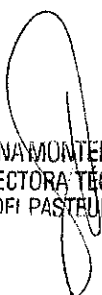
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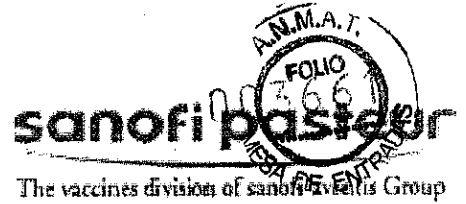
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Test for Mycoplasma by culture method

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	: 20.10.08
Test off	: 03.11.08
<i>Subculture at 3rd day</i>	
Test on	: 23.10.08
Test off	: 06.11.08
<i>Subculture at 7th day</i>	
Test on	: 27.10.08
Test off	: 12.11.08
<i>Subculture at 14th day</i>	
Test on	: 03.11.08
Test off	: 17.11.08
<i>Subculture at 21th day</i>	
Test on	: 10.11.08
Test off	: 17.11.08
Result	: No growth of Mycoplasma


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 ANGELO RAO
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Product Quality and Disposition Department

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 hepatitis B (rdNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4314 (clinical batch) 100/211

**

CONTROLS ON CONCENTRATED PURIFIED VIRAL SUSPENSION :

Protein content

Method : Spectrophotometry
 Date : 18.02.08
 Result : 94.47 µg/ml

D Antigen content

Method : ELISA
 Reference standard : 28.1.99
 Date : 06.03.08
 Result : 8 818 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	:	11.02.08
Test off	:	25.02.08
Result	:	No microbial growth

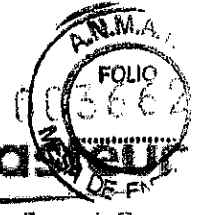
Purity

Result : 0.011 µg of protein / D Antigen U



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**

SINGLE HARVEST - Type : 2
Lot Number : FA286930

CELL:

Working Cell Bank : FA106611
Date of thawing ampoule of WCB : 13.09.07
Thawing ampoule amount : One ampoule

VIRUS:

Virus Working Seed lot : FA091251
Date of inoculation : 08.10.07
Date of virus harvest : 11.10.07

CRUDE HARVEST:

Storage : from 12.10.07 to 15.10.07
Volume : 1 506 L
Storage temperature : +5°C ± 3°C

SINGLE HARVEST:

Date of single harvest : 15.10.07

CONCENTRATION AND PURIFICATION OF THE SINGLE HARVEST

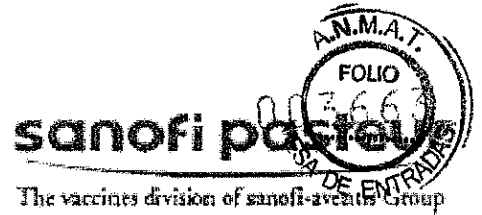
DEAE SpheroDex large column : Ion exchange chromatography on 16.10.07
CL-6-B Sepharose column : Gel filtration on 17.10.07
DEAE SphéroDex small column : Ion exchange chromatography on 17.10.07

CONCENTRATED PURIFIED VIRAL SUSPENSION :

Manufacture date : 17.10.07
Volume : 19 800 ml
Storage temperature : +5°C ± 3°C

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CHRISTIAN DOMINGUEZ GERENTE 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° S4314 (clinical batch) 102/211

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CONTROLS ON CELLS:

Observation

Method : Studied through a microscope
 Cells : Vero, 142nd passage
 Number of cells tested : 320*10⁶ cells
 Test on : 08.10.07
 Test off : 22.10.07
 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 : 22.10.07
 Result : Absence of hemadsorption

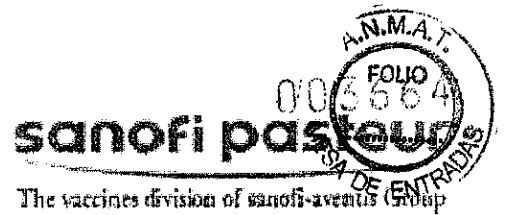
Simian cells identification

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 : 29.01.08
 Result : Positive identification

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 DIRECTORA TÉCNICA
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 ARZOBISPO
 SANOFI PASTEUR S.A.





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103/211

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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	: 12.11.07
Test off	: 26.11.07
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	: 22.01.08
Test off	: 19.02.08
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	: 30.10.07
Test off	: 13.11.07
Result	: Absence of cytopathic effect

	
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