

Product Quality and Disposition Department

The vaccines division of sanofi-aventis Group

Diphtheria, tetanus, pertussis (acellular, component),
 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 115/229

CONTROLS ON CELLS:

Observation


Method : Studied through a microscope
 Cells : Vero, 142nd passage
 Number of cells tested : 320*10⁶ cells
 Test on : 15.10.07
 Test off : 29.10.07
 Result : Absence of cytopathic effect


Test for haemadsorbing viruses

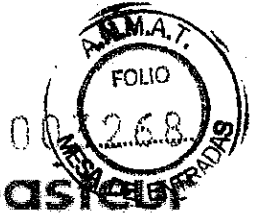
Method : visual inspection
 Number of vials tested : 8
 Type of red blood cells : Guinea-pig
 Incubation : 4 vials, 30 minutes at 5°C ± 3°C
 : 4 vials, 30 minutes at 20-25°C
 Date : 29.10.07
 Result : Absence of hemadsorption

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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Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)

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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

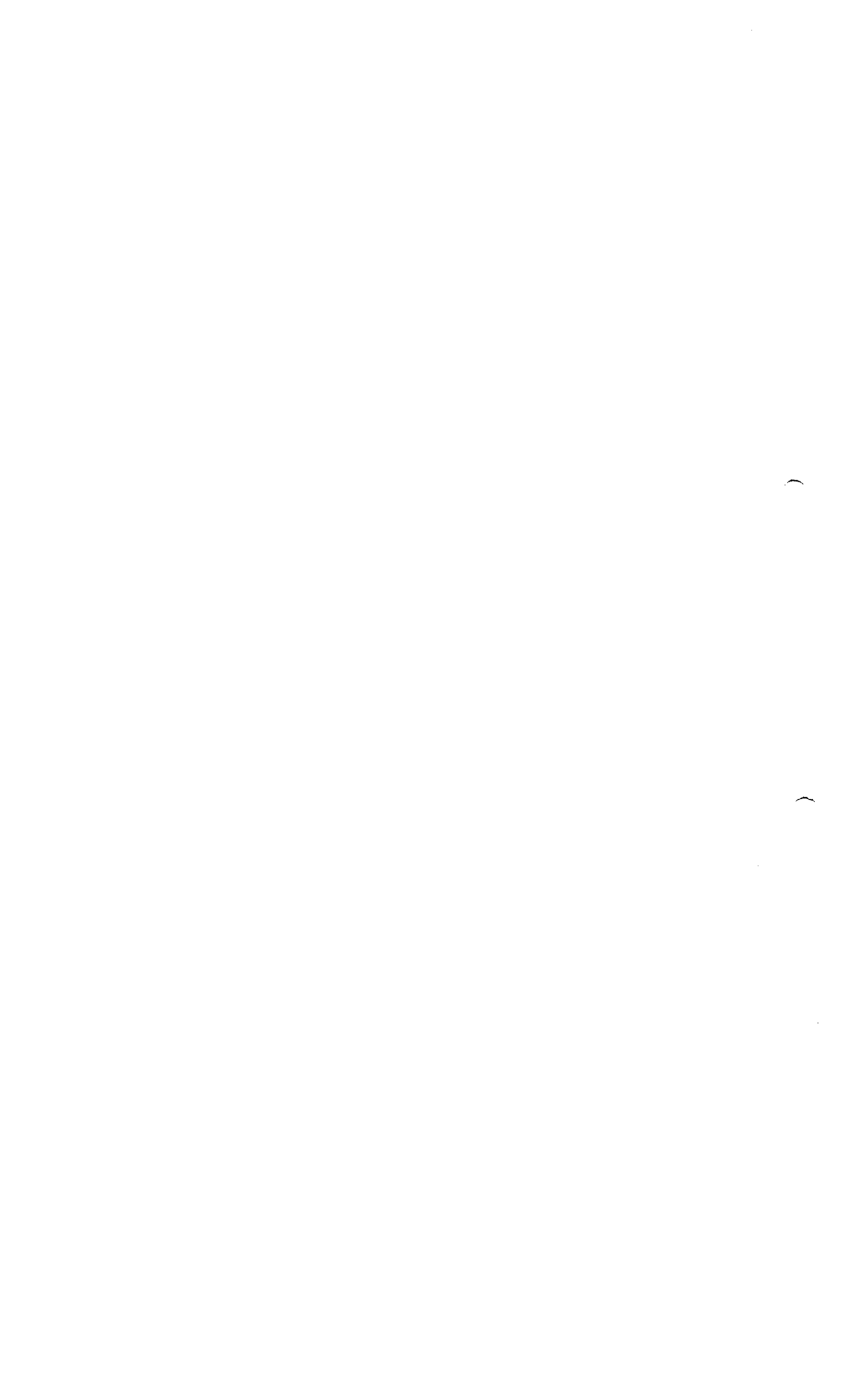
| | |
|---------------------------|--------------------------------|
| Method | : Studied through a microscope |
| Type of cells | : MRC5 |
| Volume tested | : 10 ml |
| Temperature of incubation | : 36 ± 1° C |
| Test on | : 22.01.08 |
| Test off | : 19.02.08 |
| Result | : Absence of cytopathic effect |

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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Diphtheria, tetanus, pertussis (acellular, component),
 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 117/229

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 | : 23.05.08 |
| Test off | : 06.06.08 |
| <i>Subculture at 3rd day</i> | |
| Test on | : 26.05.08 |
| Test off | : 09.06.08 |
| <i>Subculture at 7th day</i> | |
| Test on | : 30.05.08 |
| Test off | : 13.06.08 |
| <i>Subculture at 14th day</i> | |
| Test on | : 06.06.08 |
| Test off | : 20.06.08 |
| <i>Subculture at 21th day</i> | |
| Test on | : 13.06.08 |
| Test off | : 20.06.08 |
| 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 | : 22.01.08 |
| Test off | : 29.01.08 |
| Result | : No Mycoplasma detected by epifluorescence in cell culture |

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influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 118/229

CONTROLS ON SINGLE VIRUS HARVEST:

Polio virus identification

Method : Cytopathogenic effect neutralization
Cell strain used : Hep 2
Antiserum : LEPINE type 2
Test on : 29.10.07
Test off : 05.11.07
Result : Positive

Polio virus concentration

Method : Cytopathogenic effect on sensitive cells
Cell strain used : Hep 2
Test on : 29.10.07
Test off : 05.11.07
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 | : 24.10.07 | |
| Test off | : 07.11.07 | |
| Result | : No microbial growth | |


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 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 119/229

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 | : 23.05.08 |
| Test off | : 06.06.08 |
| <i>Subculture at 3rd day</i> | |
| Test on | : 26.05.08 |
| Test off | : 09.06.08 |
| <i>Subculture at 7th day</i> | |
| Test on | : 30.05.08 |
| Test off | : 13.06.08 |
| <i>Subculture at 14th day</i> | |
| Test on | : 06.06.08 |
| Test off | : 20.06.08 |
| <i>Subculture at 21th day</i> | |
| Test on | : 13.06.08 |
| Test off | : 20.06.08 |
| Result | : No growth of Mycoplasma |

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hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
Influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 120/229

CONTROLS ON CONCENTRATED PURIFIED VIRAL SUSPENSION:

Protein content

Method : Spectrophotometry
Date : 08.11.07
Result : 80.00 µg/ml

D Antigen content


Method : ELISA
Reference standard : 28.1.99
Date : 05.11.07
Result : 2 124 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 | : 30.10.07 | |
| Test off | : 13.11.07 | |
| Result | : No microbial growth | |

Purity

Result : 0.0377 µg of protein / D Antigen U


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Diphtheria, tetanus, pertussis (acellular, component),
 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)

121/229

SINGLE HARVEST - Type : 3
 Lot Number : FA292452

CELL:

Working Cell Bank : FA106611
 Date of thawing ampoule of WCB : 08.11.07
 Thawing ampoule amount : One ampoule

VIRUS:

Virus Working Seed lot : FA109086
 Date of inoculation : 03.12.07
 Date of virus harvest : 05.12.07

CRUDE HARVEST:

Storage : from 06.12.07 to 10.12.07
 Volume : 1 535 L
 Storage temperature : +5°C ± 3°C

SINGLE HARVEST:


Date of single harvest : 10.12.07


CONCENTRATION AND PURIFICATION OF THE SINGLE HARVEST

DEAE Spherodex large column : Ion exchange chromatography on 11.12.07
 CL-6-B Sepharose column : Gel filtration on 12.12.07
 DEAE Sphérodex small column : Ion exchange chromatography on 12.12.07

CONCENTRATED PURIFIED VIRAL SUSPENSION :

Manufacture date : 12.12.07
 Volume : 19 600 ml
 Storage temperature : +5°C ± 3°C


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hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 122/229**

CONTROLS ON CELLS:

Observation


Method : Studied through a microscope
Cells : Vero, 142nd passage
Number of cells tested : 320*10⁶ cells
Test on : 03.12.07
Test off : 17.12.07
Result : Absence of cytopathic effect


Test for haemadsorbing viruses

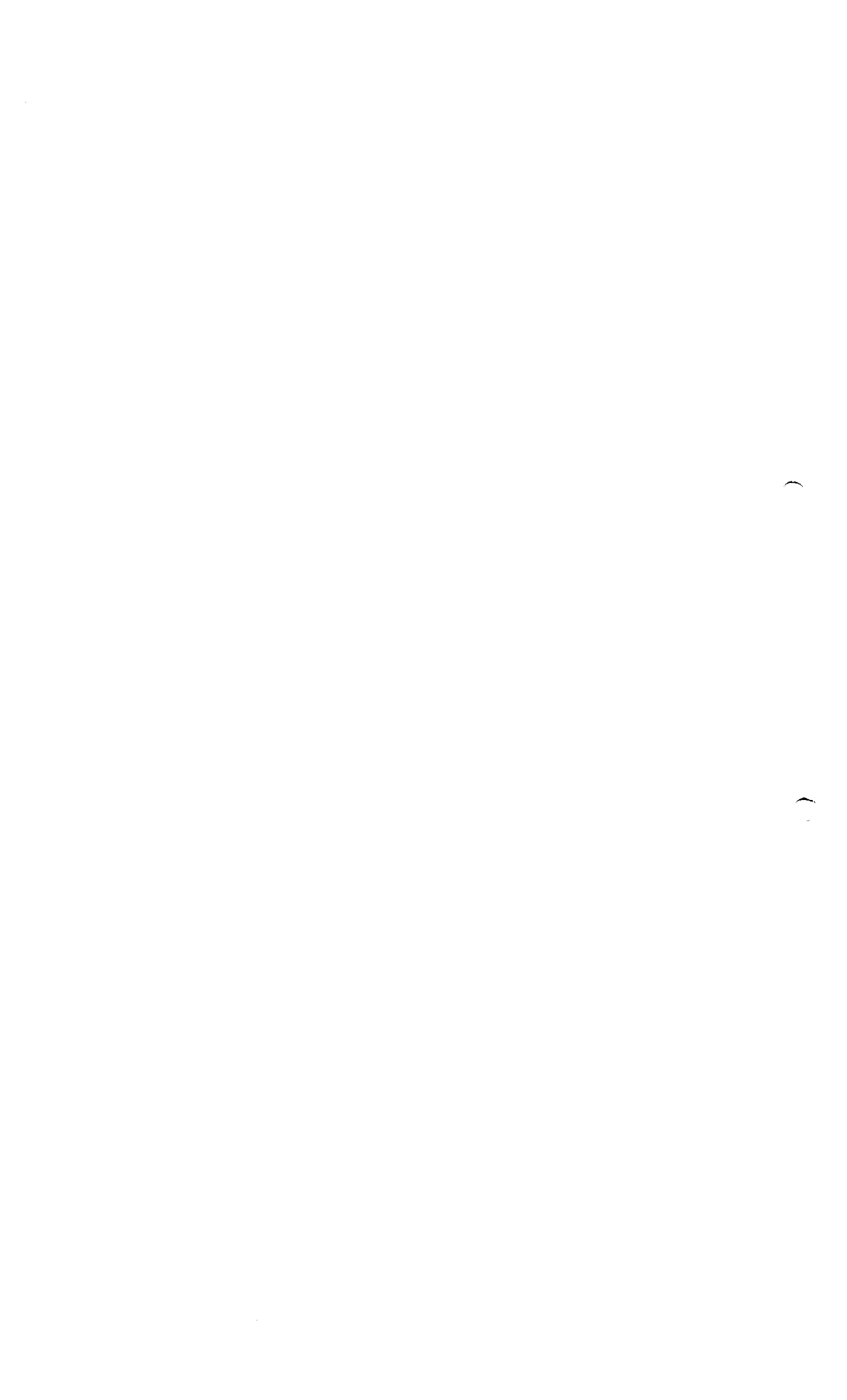
Method : visual inspection
Number of vials tested : 8
Type of red blood cells : Guinea-pig
Incubation : 4 vials, 30 minutes at 5°C ± 3°C
 : 4 vials, 30 minutes at 20-25°C
Date : 17.12.07
Result : Absence of hemadsorption

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 : 10.06.08
Result : Positive identification


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influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)

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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 | : 14.01.08 |
| Test off | : 28.01.08 |
| Result | : Absence of cytopathic effect |

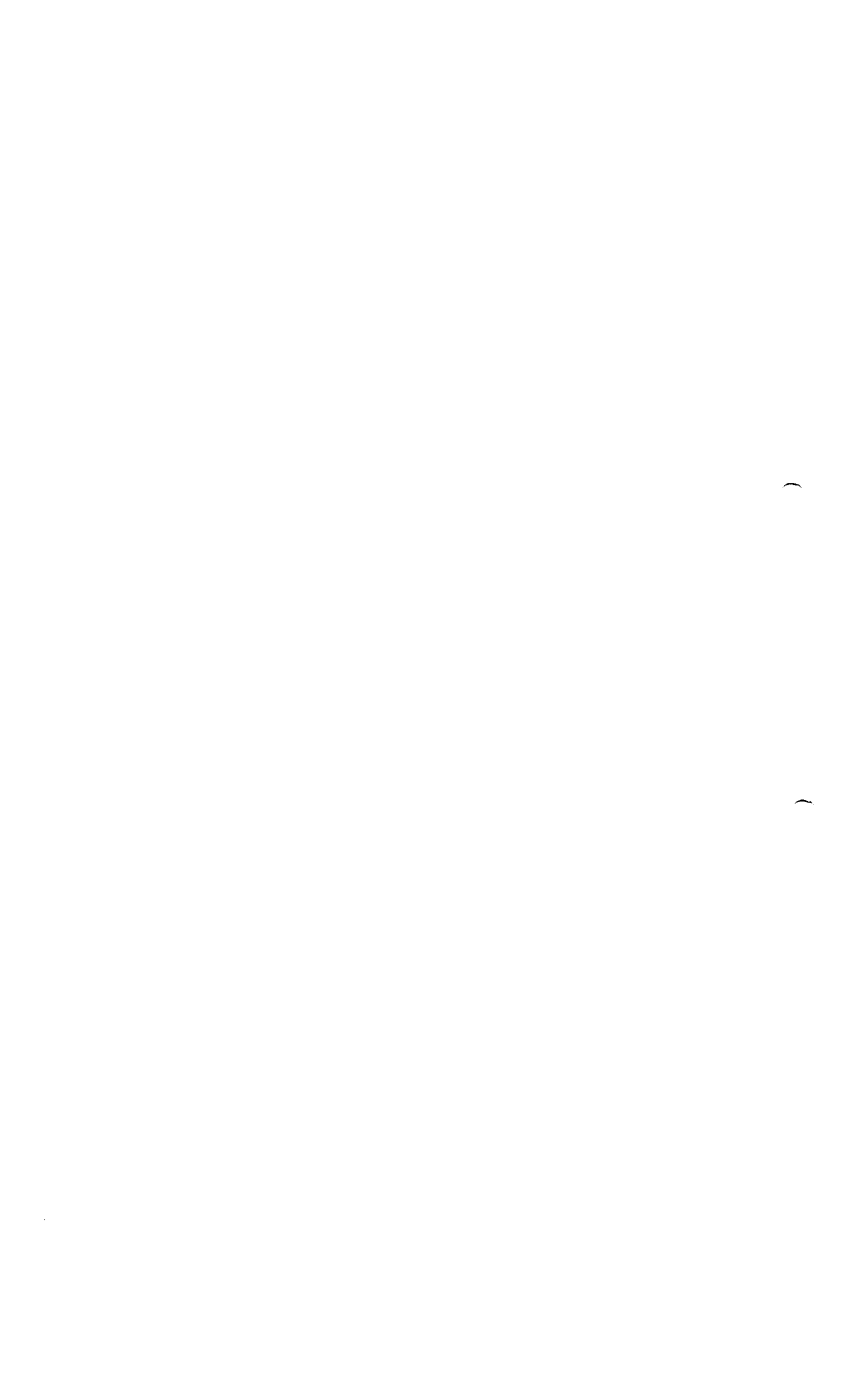
Human diploid cells

| | |
|---------------------------|---------------------------------------|
| 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 |

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 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)



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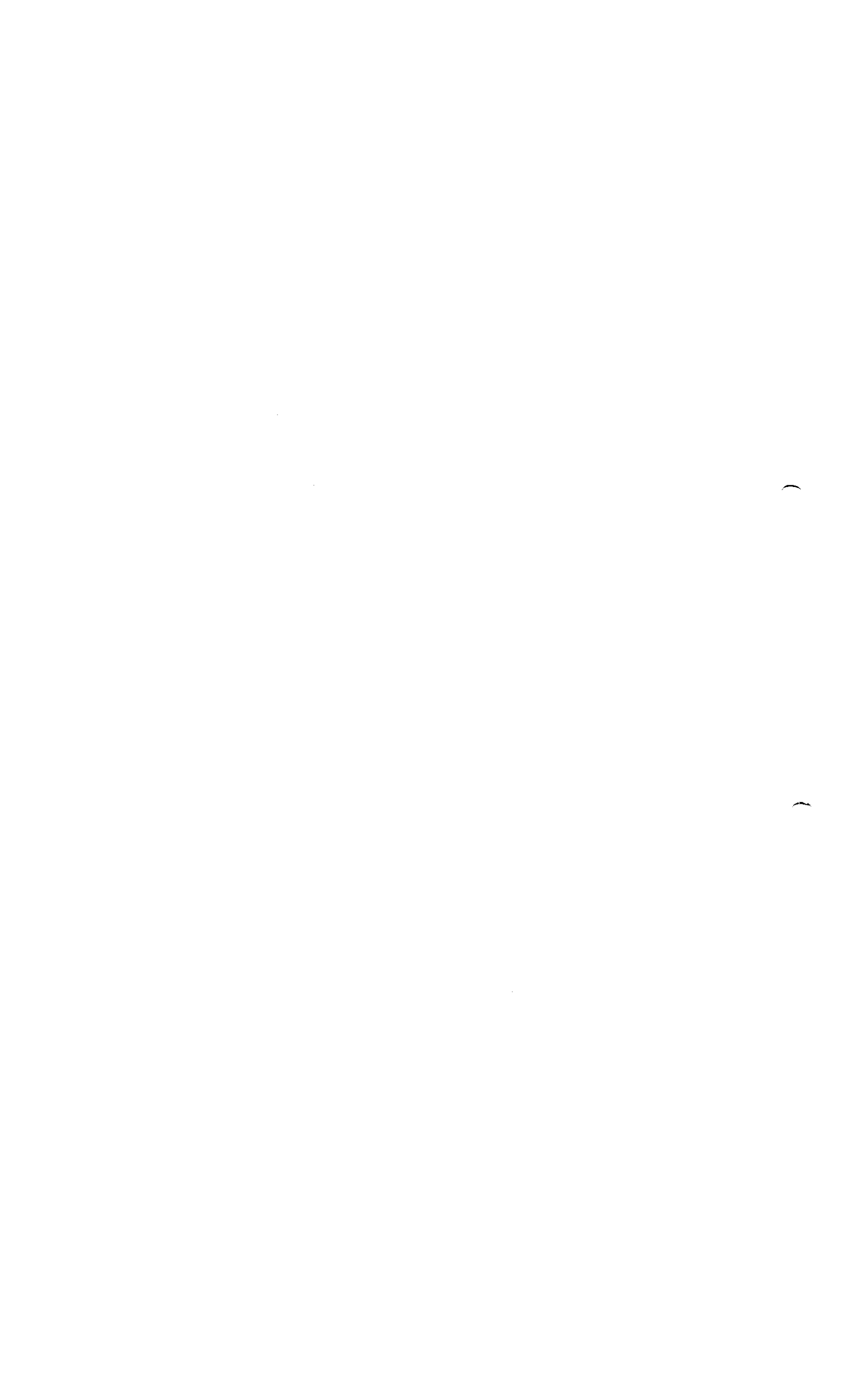
Test for Mycoplasma by culture method

| | |
|------------------------------------------|------------------------------------------------------------------------------|
| 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 | : 29.08.08 |
| Test off | : 12.09.08 |
| <i>Subculture at 3rd day</i> | |
| Test on | : 01.09.08 |
| Test off | : 15.09.08 |
| <i>Subculture at 7th day</i> | |
| Test on | : 05.09.08 |
| Test off | : 19.09.08 |
| <i>Subculture at 14th day</i> | |
| Test on | : 12.09.08 |
| Test off | : 26.09.08 |
| <i>Subculture at 21th day</i> | |
| Test on | : 19.09.08 |
| Test off | : 26.09.08 |
| Result | : No growth of Mycoplasma |

Test for Mycoplasma by epifluorescence in cell culture

| | |
|---------------------------|----------------------------------------------------------------|
| Method | : DNA fluorescence staining |
| Cell used | : Vero, 154 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 | : 11.03.08 |
| Test off | : 18.03.08 |
| Result | : No Mycoplasma detected by epifluorescence in cell culture |

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 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 125/229

CONTROLS ON SINGLE VIRUS HARVEST :

Polio virus identification



Method : Cytopathogenic effect neutralization
 Cell strain used : Hep 2
 Antiserum : LEPINE type 3
 Test on : 08.04.08
 Test off : 15.04.08
 Result : Positive

Polio virus concentration

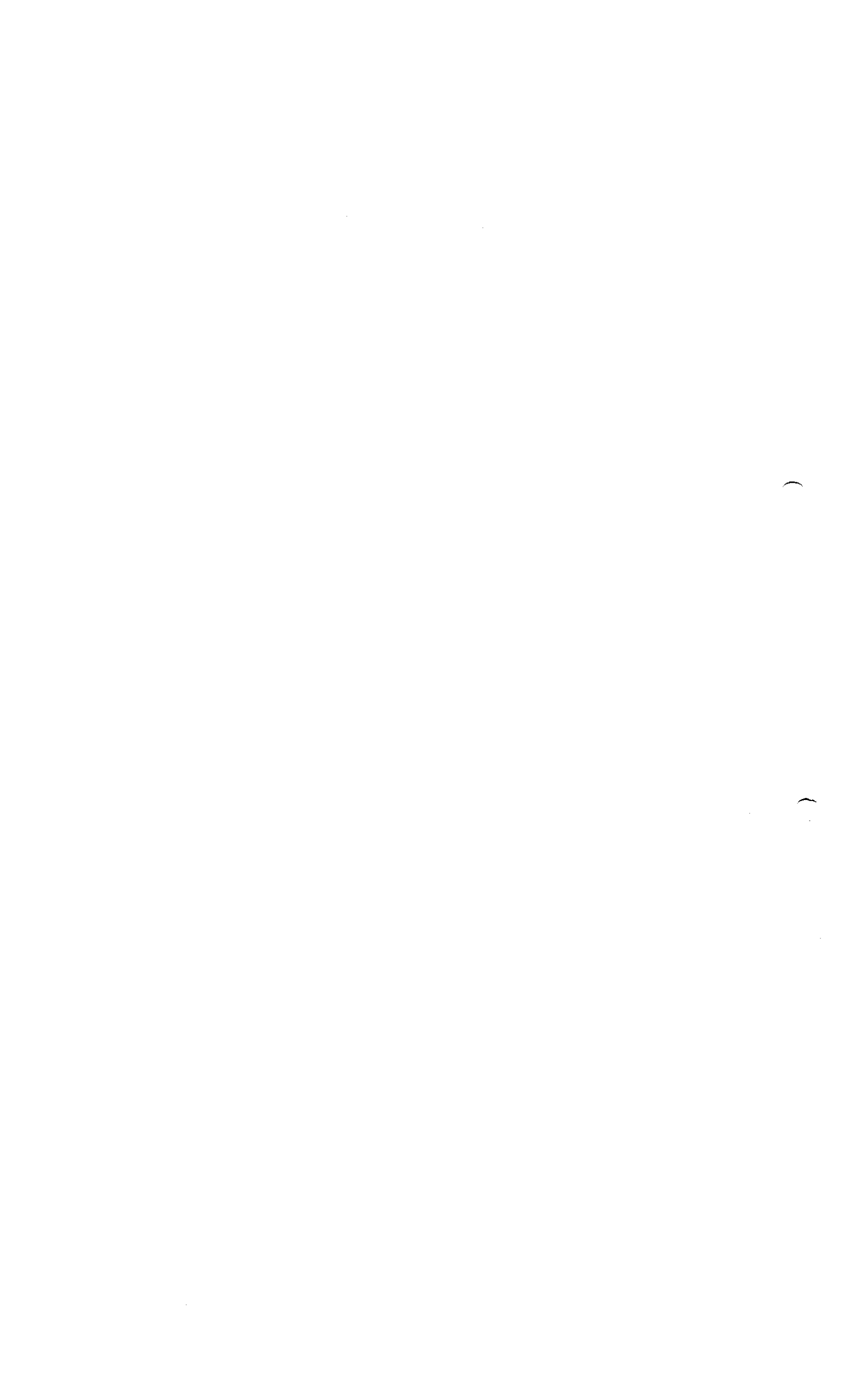
Method : Cytopathogenic effect on sensitive cells
 Cell strain used : Hep 2
 Test on : 08.04.08
 Test off : 15.04.08
 Virus concentration : $10^{8.57}$ CCID₅₀/ml
 Result : Conforms

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 | : | 13.12.07 | |
| Test off | : | 27.12.07 | |
| Result | : | No microbial growth | |

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 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)

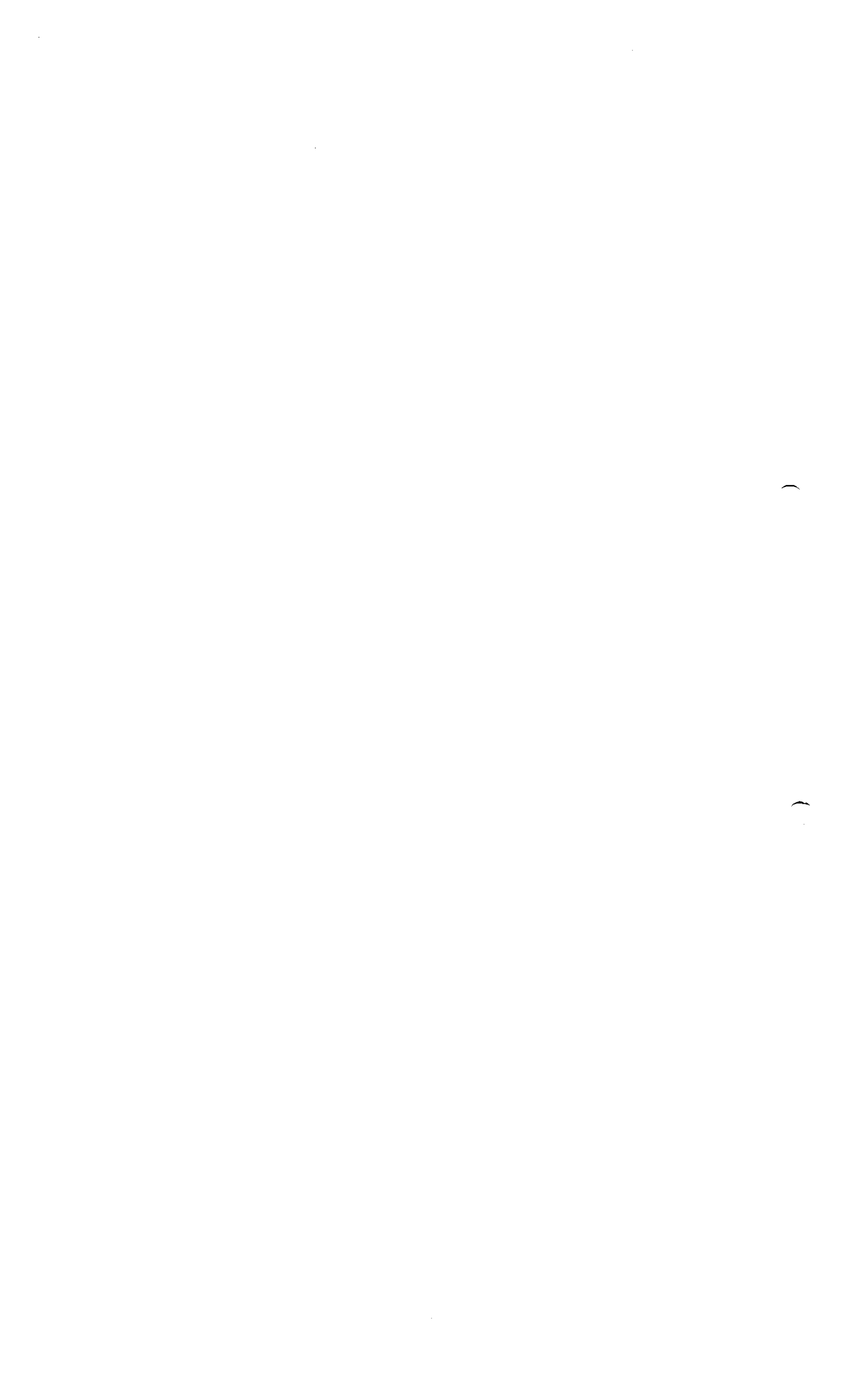
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Test for Mycoplasma by culture method

| | |
|------------------------------------------|------------------------------------------------------------------------------|
| 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 | : 29.08.08 |
| Test off | : 12.09.08 |
| <i>Subculture at 3rd day</i> | |
| Test on | : 01.09.08 |
| Test off | : 15.09.08 |
| <i>Subculture at 7th day</i> | |
| Test on | : 05.09.08 |
| Test off | : 19.09.08 |
| <i>Subculture at 14th day</i> | |
| Test on | : 12.09.08 |
| Test off | : 26.09.08 |
| <i>Subculture at 21th day</i> | |
| Test on | : 19.09.08 |
| Test off | : 26.09.08 |
| Result | : No growth of Mycoplasma |


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 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 127/229**

CONTROLS ON CONCENTRATED PURIFIED VIRAL SUSPENSION:

Protein content

Method : Spectrophotometry
 Date : 19.12.07
 Result : 85.41 µg/ml

D Antigen content


Method : ELISA
 Reference standard : 28.1.99
 Date : 27.12.07
 Result : 6 530 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 | : 17.12.07 | |
| Test off | : 31.12.07 | |
| Result | : No microbial growth | |

Purity

Result : 0.013 µg of protein / D Antigen U


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