



sanofi pasteur

The vaccines division of sanofi-aventis Group

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)

48/229

HANSENULA POLYMORPHA
Working seed lot n°MWCB 230600BA

Master seed lot : MCB 160600BA
Preparation date : June 23rd, 2000
Release date : June 29th, 2001

CONTROLS

- Purity . **Conforms**
- Identification : **Conforms**
- Full integration of the vector : **Conforms**
- Number of copies of the plasmid in the genome : **Conforms**
- Integrated cDNA gene sequence : **Conforms**
- Sequencing of the regions 3' and 5' : **Conforms**
- Determination of the population of yeast cells containing the cloned gene: **Conforms**

The tests results show that working seed lot has the same characteristics as the master seed lot.

[Signature]
ROXANA MONTEMILONE
 DIRECTORA TÉCNICA
 SANOFI PASTEUR S.A.

[Signature]
CHRISTIAN GUERRERO
 SUPERVISOR
 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° S4312 (clinical batch)

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HEPATITIS B SURFACE ANTIGEN
Lot n° AC002

Strain : K3/8-1
Working seed lot number : MWCB 230600BA
Date of reconstitution of working seed lot vials: October 30th, 2007
Temperature incubation : 28 to 32°C

Harvest

Date of inoculation in last stage of fermentation : November 2nd, 2007
Date of harvest : November 5th, 2007
Volume : 50 liters


CONTROLS


Microbiological purity

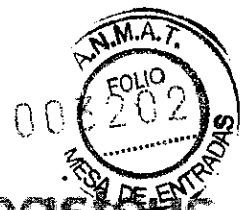
Method : Direct Inoculation
Result : Absence of microbiological contamination

Identification of *Hansenula Polymorpha*

Method : Biochemical and microscopic Tests
Result : Conforms


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REGISTRADO
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Diphtheria, tetanus, pertussis (acellular, component),
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 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)

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HEPATITIS B SURFACE ANTIGEN

TESTS	SPECIFICATIONS
APPEARANCE	Opalescent, slightly cloudy and yellowish solution
pH MEASUREMENT	6.5 - 7.5
PROTEIN CONTENT	1.05 – 1.80 mg/mL
IDENTIFICATION OF HBsAg	Positive
	Main bands of molecular weight around 23 kD, 46 kD and eventually 65 kD
HBsAg CONTENT	≥0.7 mg of HBsAg/mg of total proteins
CARBOHYDRATES CONTENT	≤50 µg of carbohydrates/mg of total proteins
LIPIDS CONTENT	0.5 – 0.9 mg lipids/mg of total proteins
PURITY	≥95%
PERCENTAGE OF HBsAg FREE MONOMER	≤3%
BACTERIAL AND FUNGAL STERILITY TEST	Absence of microbial growth
BACTERIAL ENDOTOXINS	<10 EU/dose (i.e. 10 EU/10µg of proteins)

352_CC5_SPI_AE.dot /19.09.11

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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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HEPATITIS B SURFACE ANTIGEN
Lot number : AC002

Date of manufacture : December 7th, 2007
Storage temperature : + 5°C ± 3°C
Expiry date : November 2010
(shelf life used at the time of the release of the batch)
Quantity: : 3,152 g of proteins

CONTROLS :

Appearance

Method : Visual inspection
Date : January 4th, 2008
Result : **Opalescent, slightly cloudy and yellowish solution**

pH

Method : Glass electrode
Date : January 4th, 2008
Result : **6,9 - Conforms**

Protein content

Method : Lowry
Date : May 1st, 2008
Result : **1,49 mg/ml - Conforms**

Identification of HBsAg

Method : ELISA
Date : May 1st, 2008
Result : **Positive**

Method : SDS - PAGE
Date : June 13th, 2008
Result : **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° S4312 (clinical batch)

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HBsAg Content

Method : ELISA
 Date : May 1st, 2008
 Result : 1,1 mg/mg of total proteins – **Conforms**

Carbohydrates Content

Method : Colorimetric assay
 Date : May 1st, 2008
 Result : 39 µg/mg of total proteins – **Conforms**

Lipids Content

Method : Colorimetric assay
 Date : May 1st, 2008
 Result : 0,8 mg/mg of total proteins – **Conforms**

Purity Content

Method : SDS - PAGE
 Date : June 18th, 2008
 Result : 97 %

Percentage of HBsAg free monomer


Method : SDS - PAGE
 Date : April 30th, 2008
 Result : Less than 3 % - **Conforms**

Bacterial and fungal sterility


Method	:	Membrane filtration
Media	:	Thioglycollate medium Soybean-Casein Digest medium
Temperature	:	30-35° C 20-25° C
Inoculum per Steritest	:	10 ml 10 ml
Volume of medium per Steritest	:	100 ml 100 ml
Test on	:	December 14 th , 2007
Test off	:	January 2 nd , 2008
Result	:	No microbial growth - Conforms

Bacterial Endotoxins

Method : LAL – Gel clot
 Date : January 15th, 2008
 Result : <1 EU/20µg of proteins- **Conforms**



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 CHRISTIAN DOMÍNGUEZ
 CALDERADO
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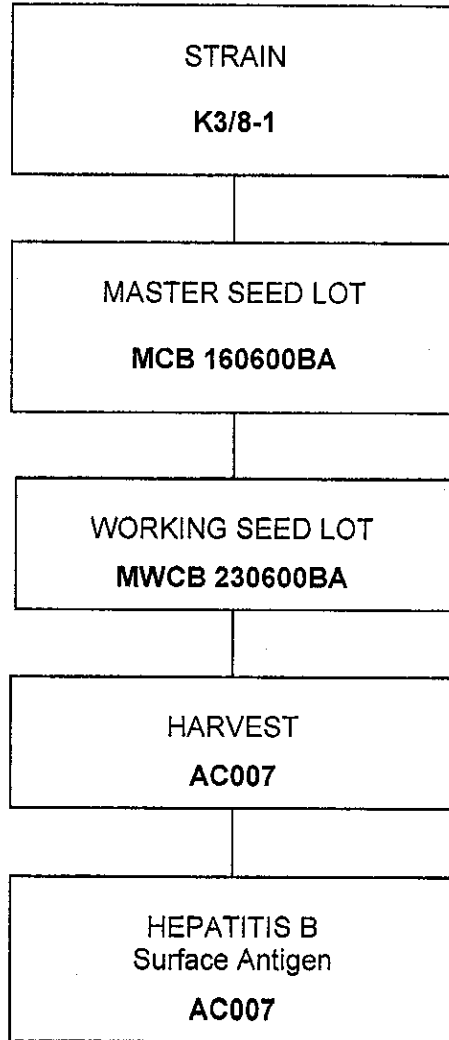


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 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)

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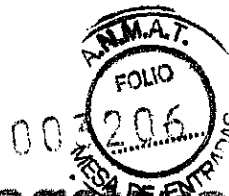


PRODUCTION FLOW SHEET

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Product Quality and Disposition Department

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

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HANSENULA POLYMORPHA
Strain : K3/8-1

STRAIN

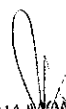
Name : Hansenula Polymorpha RB11
Origin : Rhein Biotech
Received : February 15th, 2000

HANSENULA POLYMORPHA
Master seed lot n° MCB 160600BA

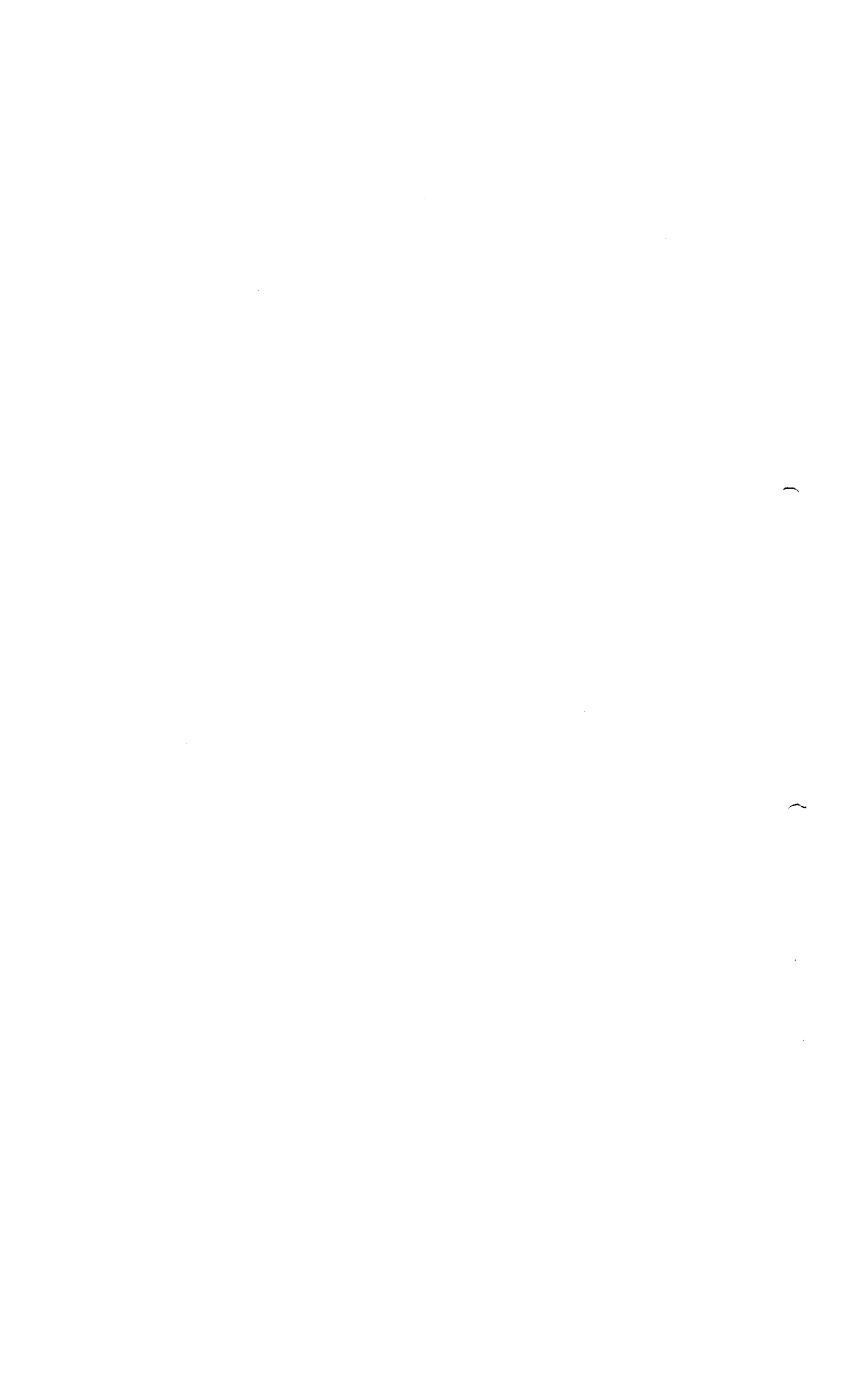
Strain : IM K3/8-1
Preparation date : June 16th, 2000
Release date : June 29th, 2001

CONTROLS

- Purity . **Conforms**
- Identification : **Conforms**
- Full integration of the vector : **Conforms**
- Number of copies of the plasmid in the genome : **Conforms**
- Integrated cDNA gene sequence : **Conforms**
- Sequencing of the regions 3' and 5' : **Conforms**
- Determination of the population of yeast cells containing the cloned gene: **Conforms**


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

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HEPATITIS B SURFACE ANTIGEN
Lot n° AC007

Strain : K3/8-1
Working seed lot number : MWCB 230600BA
Date of reconstitution of working seed lot vials: February 12th, 2008
Temperature incubation : 28 to 32°C

Harvest

Date of inoculation in last stage of fermentation : February 15th, 2008
Date of harvest : February 18th, 2008
Volume : 50 liters

CONTROLS

Microbiological purity

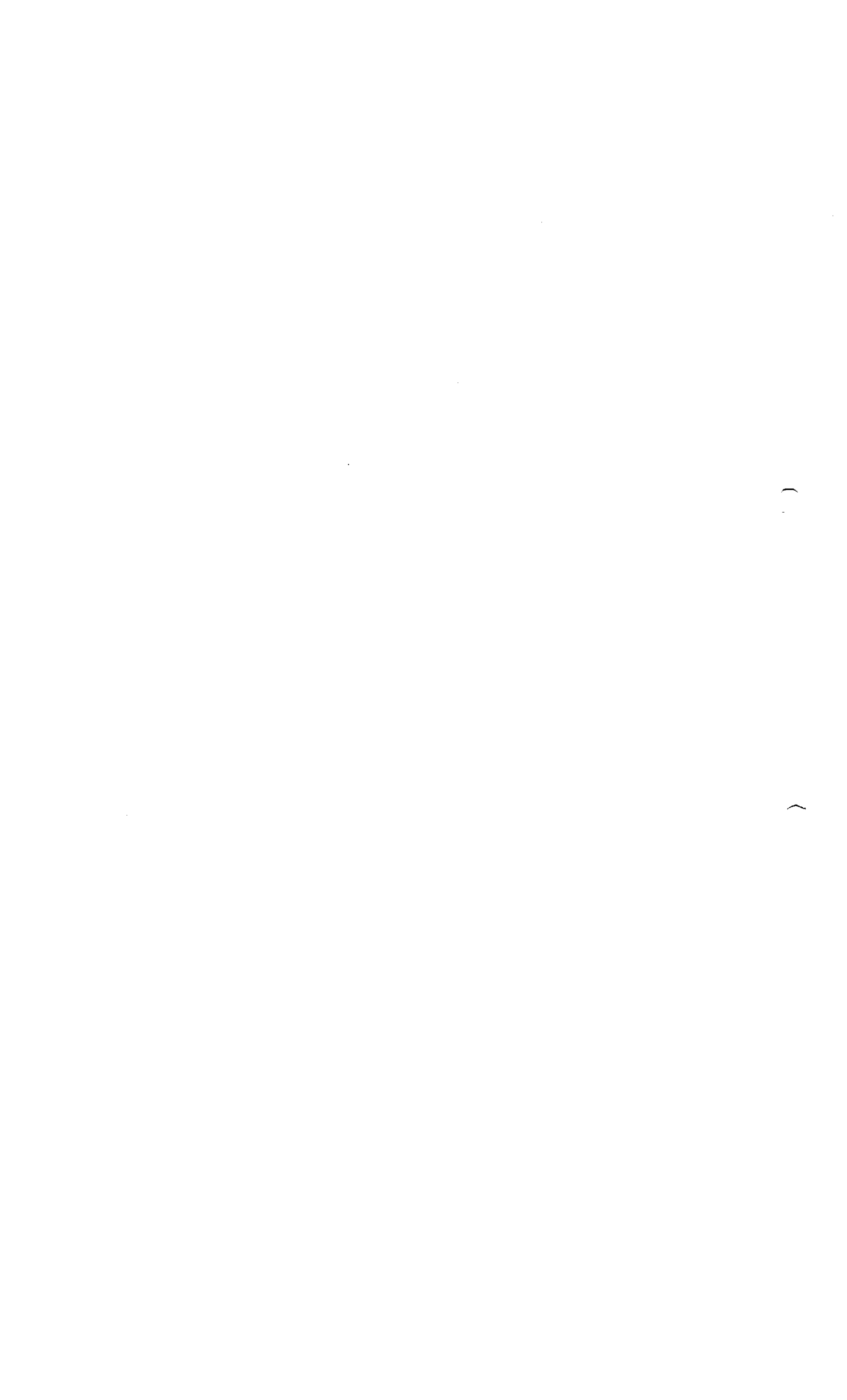
Method : Direct Inoculation
Result : Absence of microbiological contamination

Identification of *Hansenula Polymorpha*

Method : Biochemical and microscopic Tests
Result : 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° S4312 (clinical batch)

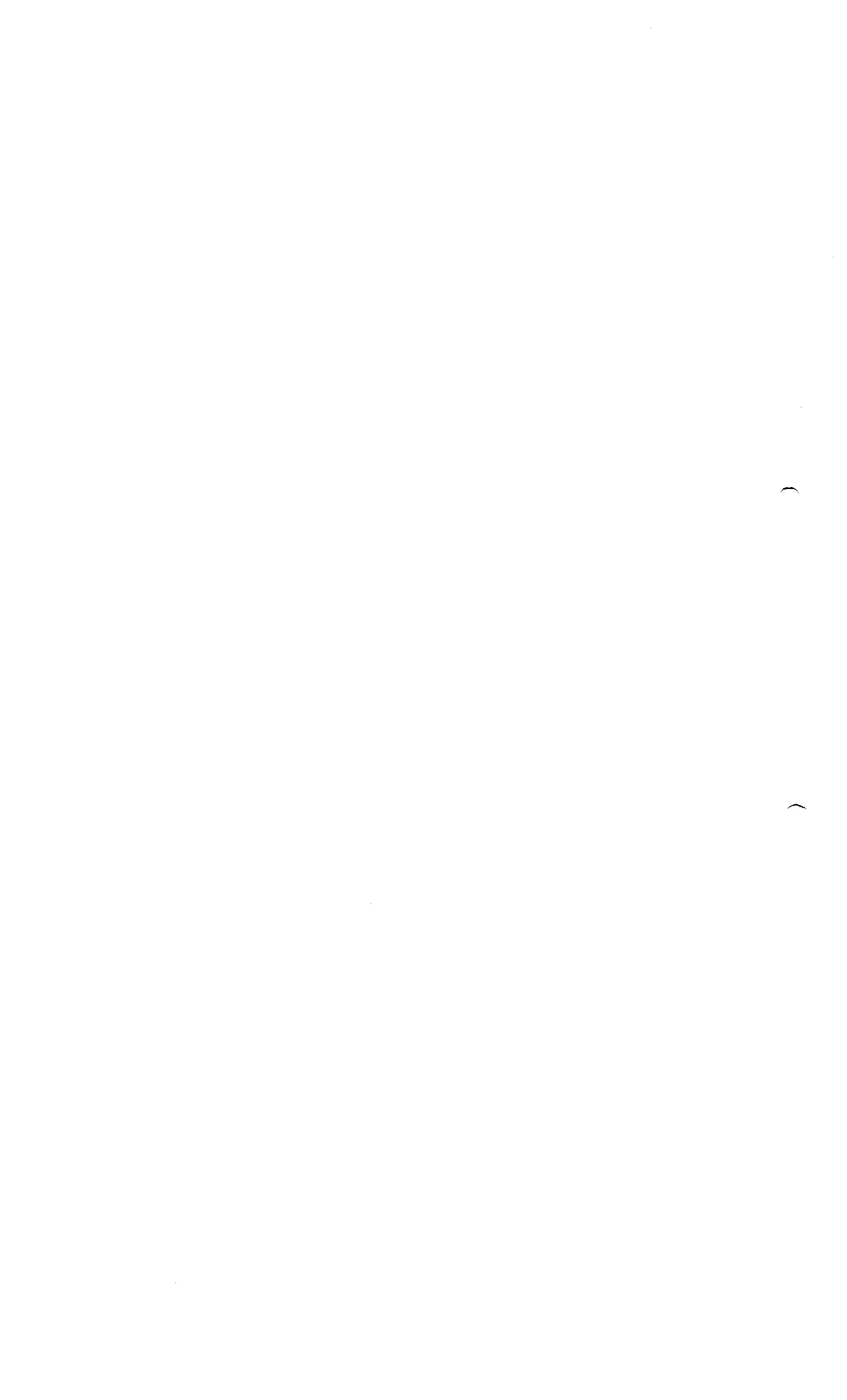
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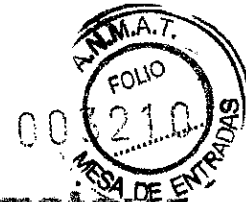
HEPATITIS B SURFACE ANTIGEN

TESTS	SPECIFICATIONS
APPEARANCE	Opalescent, slightly cloudy and yellowish solution
pH MEASUREMENT	6.5 - 7.5
PROTEIN CONTENT	1.05 – 1.80 mg/mL
IDENTIFICATION OF HBsAg	Positive
	Main bands of molecular weight around 23 kD, 46 kD and eventually 65 kD
HBsAg CONTENT	≥0.7 mg of HBsAg/mg of total proteins
CARBOHYDRATES CONTENT	≤50 µg of carbohydrates/mg of total proteins
LIPIDS CONTENT	0.5 – 0.9 mg lipids/mg of total proteins
PURITY	≥95%
PERCENTAGE OF HBsAg FREE MONOMER	≤3%
BACTERIAL AND FUNGAL STERILITY TEST	Absence of microbial growth
BACTERIAL ENDOTOXINS	<10 EU/dose (i.e. 10 EU/10µg of proteins)

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 SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.





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hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 58/229

HEPATITIS B SURFACE ANTIGEN
Lot number : AC007

Date of manufacture : March 22nd, 2008
Storage temperature : + 5°C ± 3°C
Expiry date : February 2011
(shelf life used at the time of the release of the batch)
Quantity: : 3,1336 g of proteins

CONTROLS :

Appearance

Method : Visual inspection
Date : April 10th, 2008
Result : Opalescent, slightly cloudy and yellowish solution

pH

Method : Glass electrode
Date : April 10th, 2008
Result : 6,9 - Conforms

Protein content

Method : Lowry
Date : April 21st, 2008
Result : 1,45 mg/ml - Conforms

Identification of HBsAg

Method : ELISA
Date : April 21st, 2008
Result : Positive

Method : SDS - PAGE
Date : August 22th, 2008
Result : 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° S4312 (clinical batch)

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HBsAg Content

Method : ELISA
Date : April 21st,2008
Result : 1,2 mg/mg of total proteins – **Conforms**

Carbohydrates Content

Method : Colorimetric assay
Date : April 21st,2008
Result : 32 µg/mg of total proteins – **Conforms**

Lipids Content

Method : Colorimetric assay
Date : April 21st,2008
Result : 0,8 mg/mg of total proteins – **Conforms**

Purity Content

Method : SDS - PAGE
Date : August 22th,2008
Result : 97 %

Percentage of HBsAg free monomer


Method : SDS - PAGE
Date : April 22th,2008
Result : Less than 3 % - **Conforms**

Bacterial and fungal sterility

Method	:	Membrane filtration
Media	:	Thioglycollate medium Soybean-Casein Digest medium
Temperature	:	30-35° C 20-25° C
Inoculum per Steritest	:	10 ml 10 ml
Volume of medium per Steritest	:	100 ml 100 ml
Test on	:	March 25 th , 2008
Test off	:	April 8 th , 2008
Result	:	No microbial growth - Conforms

Bacterial Endotoxins

Method : LAL – Gel clot
Date : April 9th, 2008
Result : ≤1 EU/20µg of proteins- **Conforms**



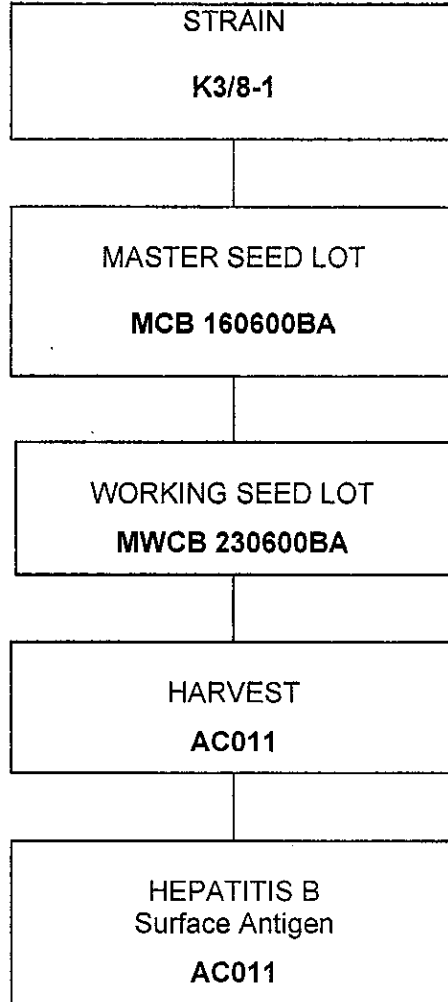
 ROMANA MONTEMILONE CHRISTIAN DOMINGUEZ
 DIRECTORA TÉCNICA ASESORADO
 SANOFI PASTEUR S.A. SANOFI PASTEUR S.A.





Product Quality and Disposition Department

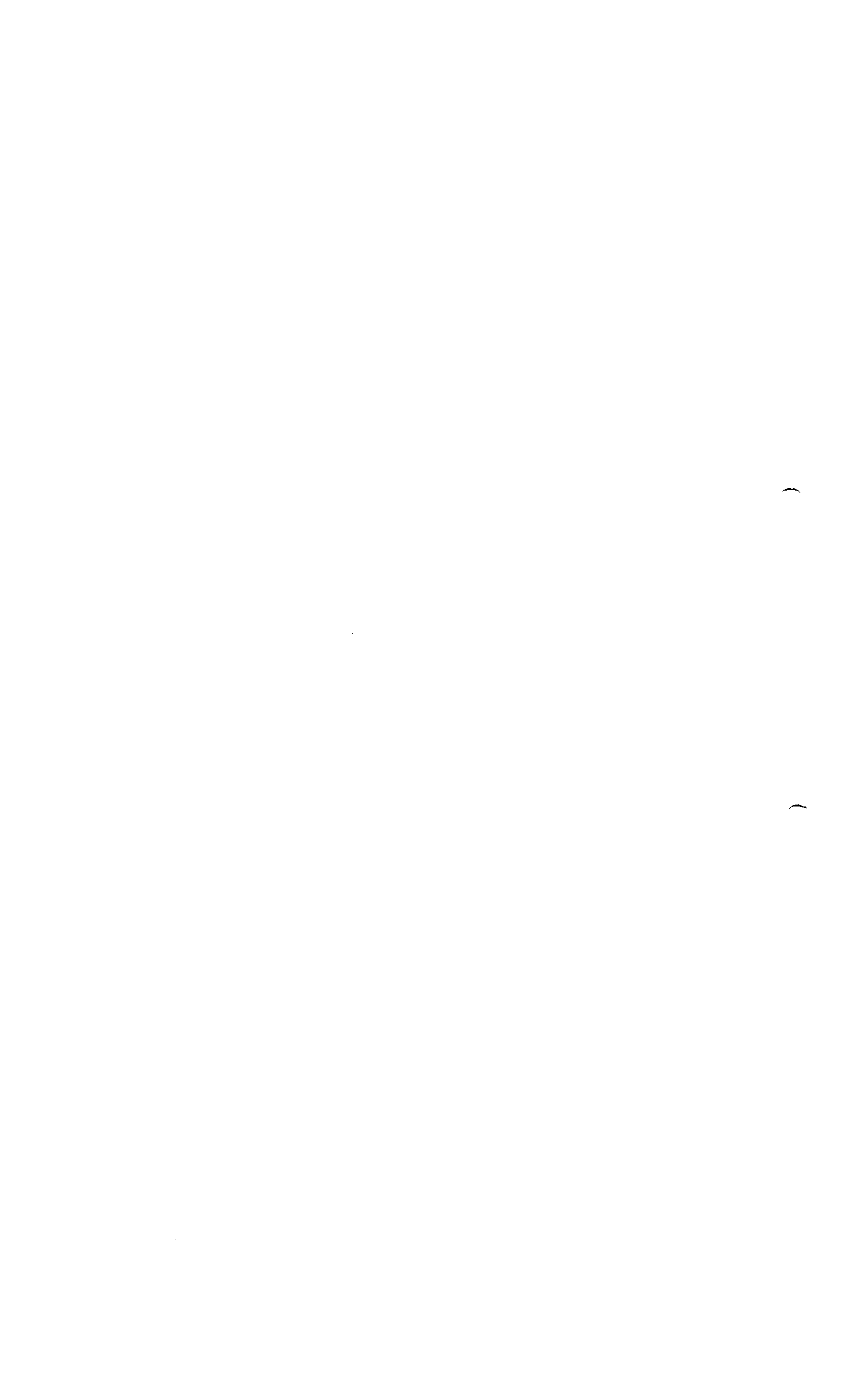
Diphtheria, tetanus, pertussis (acellular, component),
 hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus
 influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)

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PRODUCTION FLOW SHEET



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 SANOFI PASTEUR S.A. 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° S4312 (clinical batch)

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HANSENULA POLYMORPHA
Strain : K3/8-1

STRAIN

Name : Hansenula Polymorpha RB11
Origin : Rhein Biotech
Received : February 15th, 2000

HANSENULA POLYMORPHA
Master seed lot n° MCB 160600BA

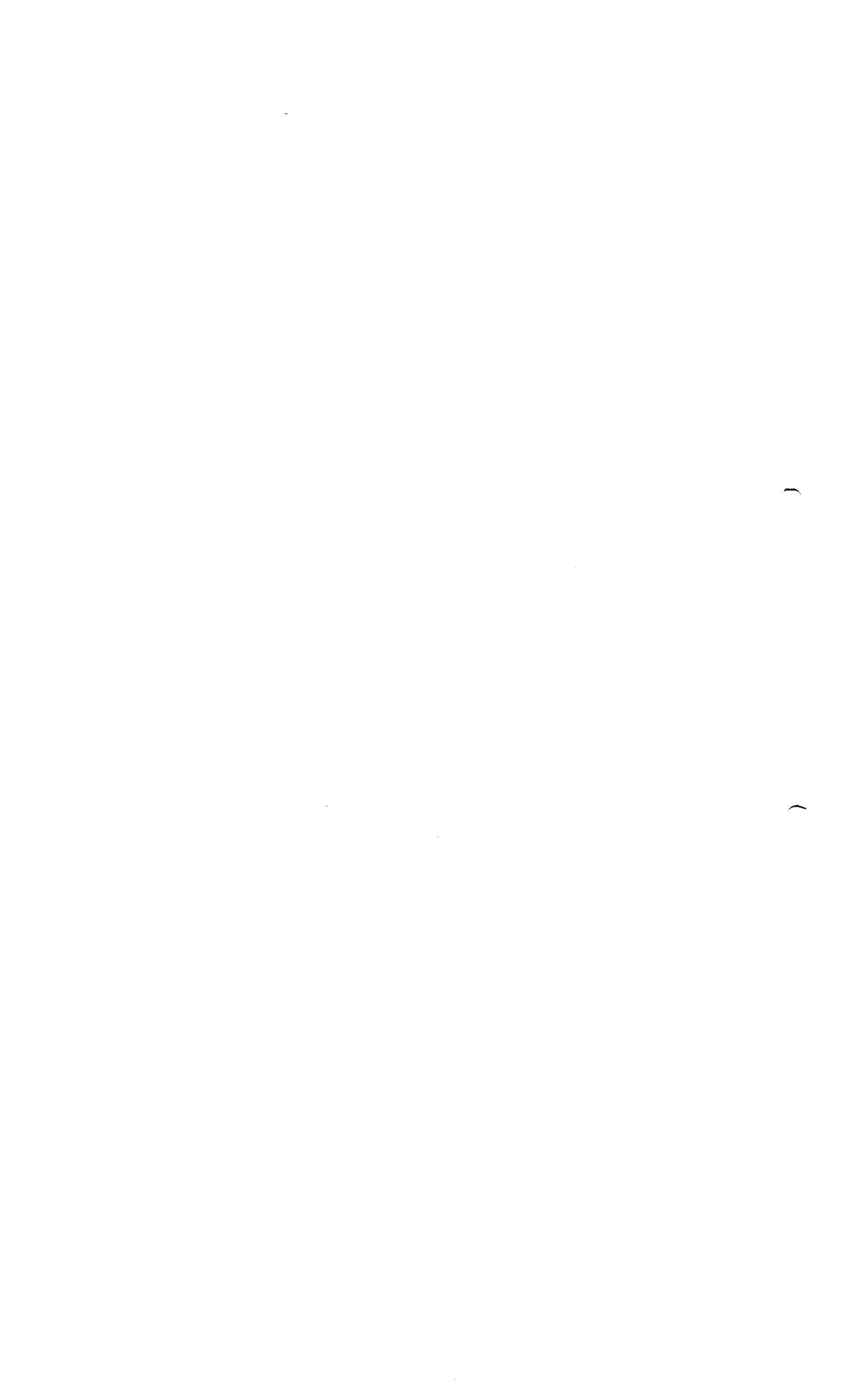
Strain : IM K3/8-1
Preparation date : June 16th, 2000
Release date : June 29th, 2001

CONTROLS

- Purity : **Conforms**
- Identification : **Conforms**
- Full integration of the vector : **Conforms**
- Number of copies of the plasmid in the genome : **Conforms**
- Integrated cDNA gene sequence : **Conforms**
- Sequencing of the regions 3' and 5' : **Conforms**
- Determination of the population of yeast cells containing the cloned gene: **Conforms**

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

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HANSENULA POLYMORPHA
Working seed lot n°MWCB 230600BA


Master seed lot : MCB 160600BA
Preparation date : June 23rd, 2000
Release date : June 29th, 2001

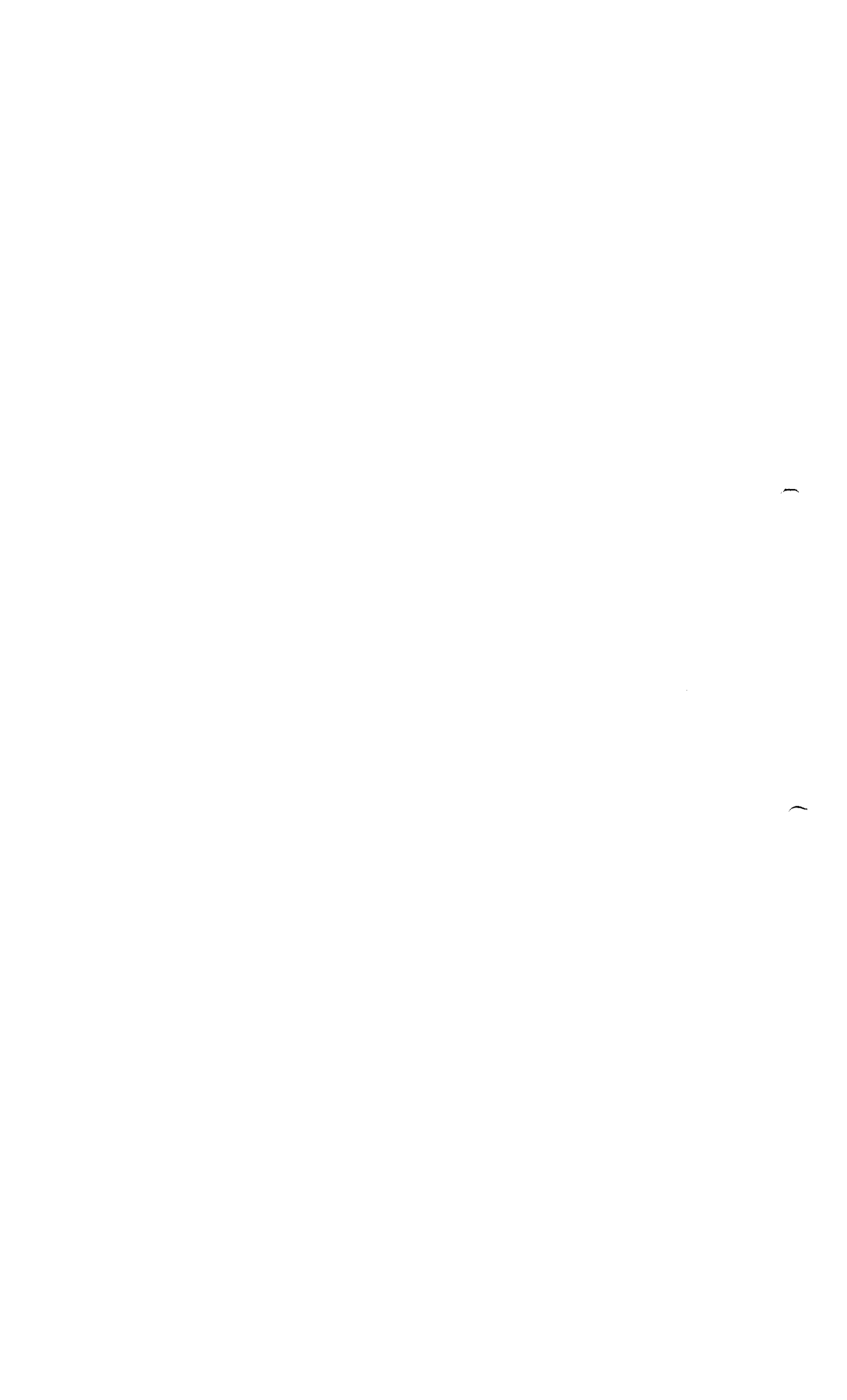
CONTROLS

- Purity : **Conforms**
- Identification : **Conforms**
- Full integration of the vector : **Conforms**
- Number of copies of the plasmid in the genome : **Conforms**
- Integrated cDNA gene sequence : **Conforms**
- Sequencing of the regions 3' and 5' : **Conforms**
- Determination of the population of yeast cells containing the cloned gene: **Conforms**

The tests results show that working seed lot has the same characteristics as the master seed lot.


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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° S4312 (clinical batch)

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HEPATITIS B SURFACE ANTIGEN
Lot n° AC011

Strain : K3/8-1
Working seed lot number : MWCB 230600BA
Date of reconstitution of working seed lot vials: March 18th, 2008
Temperature incubation : 28 to 32°C

Harvest

Date of inoculation in last stage of fermentation : March 21st, 2008
Date of harvest : March 24th, 2008
Volume : 50 liters

CONTROLS

Microbiological purity

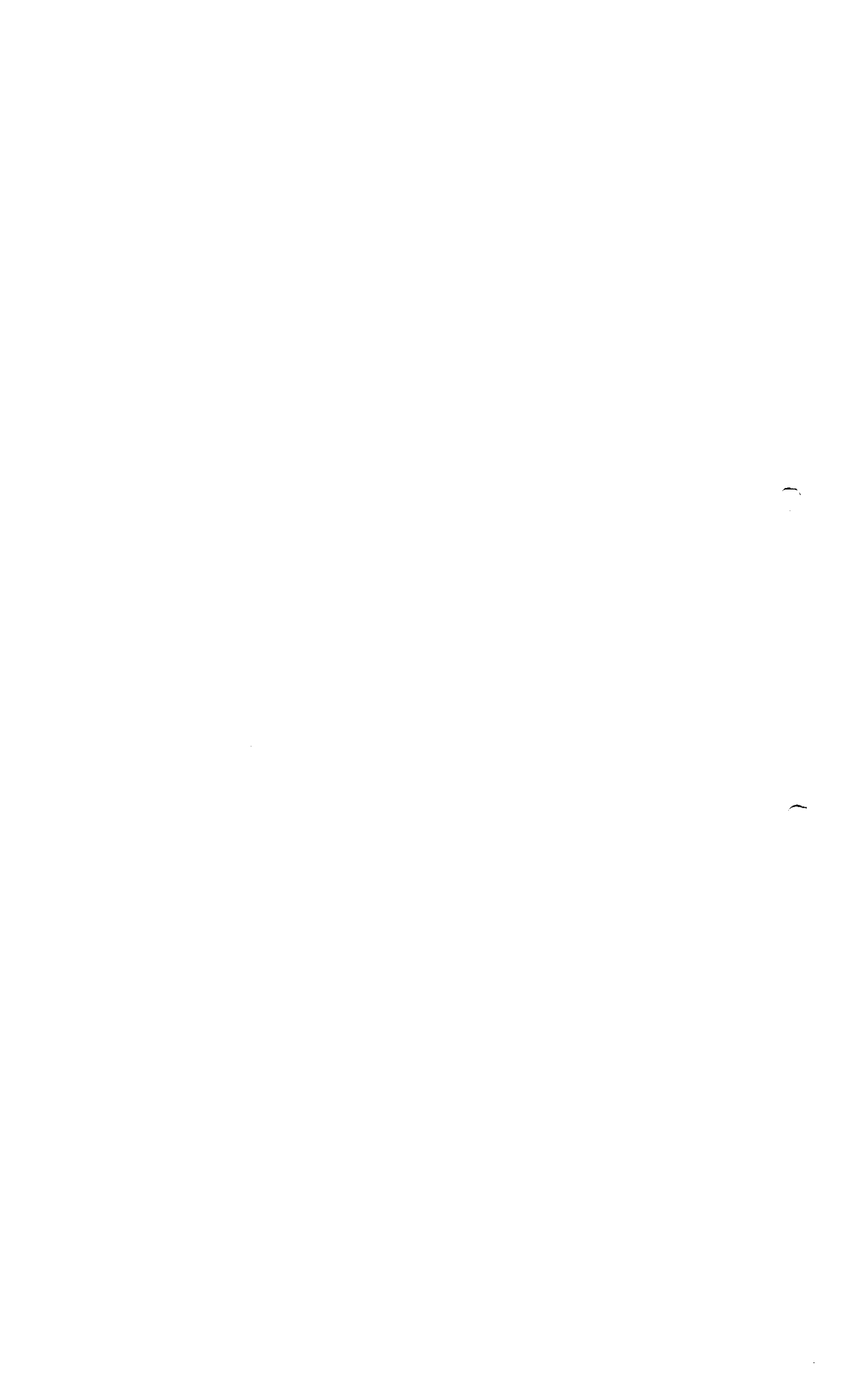
Method : Direct Inoculation
Result : Absence of microbiological contamination

Identification of *Hansenula Polymorpha*

Method : Biochemical and microscopic Tests
Result : Conforms


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

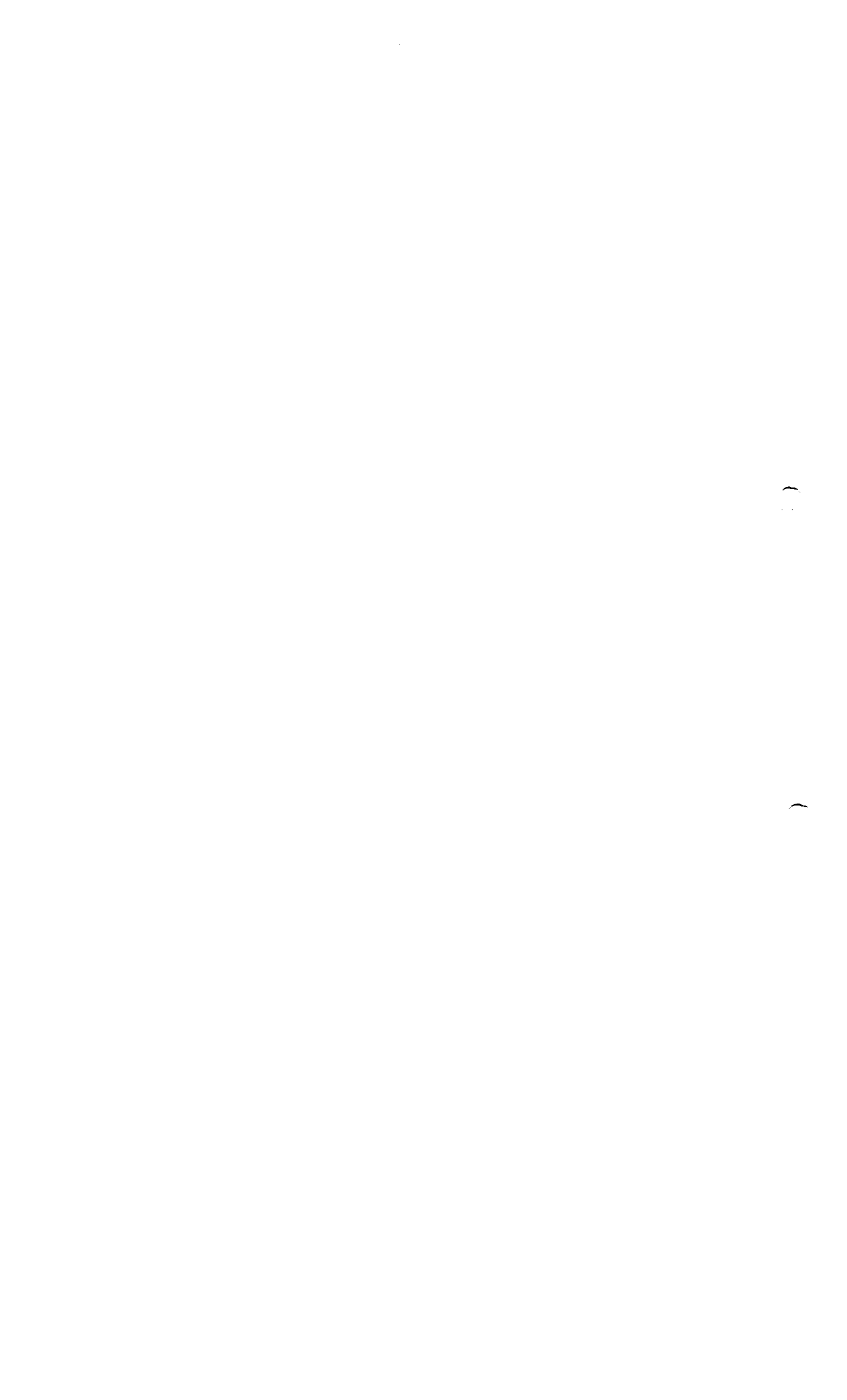
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HEPATITIS B SURFACE ANTIGEN

TESTS	SPECIFICATIONS
APPEARANCE	Opalescent, slightly cloudy and yellowish solution
pH MEASUREMENT	6.5 - 7.5
PROTEIN CONTENT	1.05 – 1.80 mg/mL
IDENTIFICATION OF HBsAg	Positive
	Main bands of molecular weight around 23 kD, 46 kD and eventually 65 kD
HBsAg CONTENT	≥0.7 mg of HBsAg/mg of total proteins
CARBOHYDRATES CONTENT	≤50 µg of carbohydrates/mg of total proteins
LIPIDS CONTENT	0.5 – 0.9 mg lipids/mg of total proteins
PURITY	≥95%
PERCENTAGE OF HBsAg FREE MONOMER	≤3%
BACTERIAL AND FUNGAL STERILITY TEST	Absence of microbial growth
BACTERIAL ENDOTOXINS	<10 EU/dose (i.e. 10 EU/10µg of proteins)


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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° S4312 (clinical batch)

65/229

HEPATITIS B SURFACE ANTIGEN

Lot number : AC011

Date of manufacture : April 25th, 2008
 Storage temperature : + 5°C ± 3°C
 Expiry date : March 2011
 (shelf life used at the time of the release of the batch)
 Quantity: : 3,13962 g of proteins

CONTROLS :

Appearance

Method : Visual inspection
 Date : May 8th, 2008
 Result : Opalescent, slightly cloudy and yellowish solution

pH

Method : Glass electrode
 Date : May 8th, 2008
 Result : 6,9 - Conforms

Protein content

Method : Lowry
 Date : June 18th, 2008
 Result : 1,50 mg/ml - Conforms

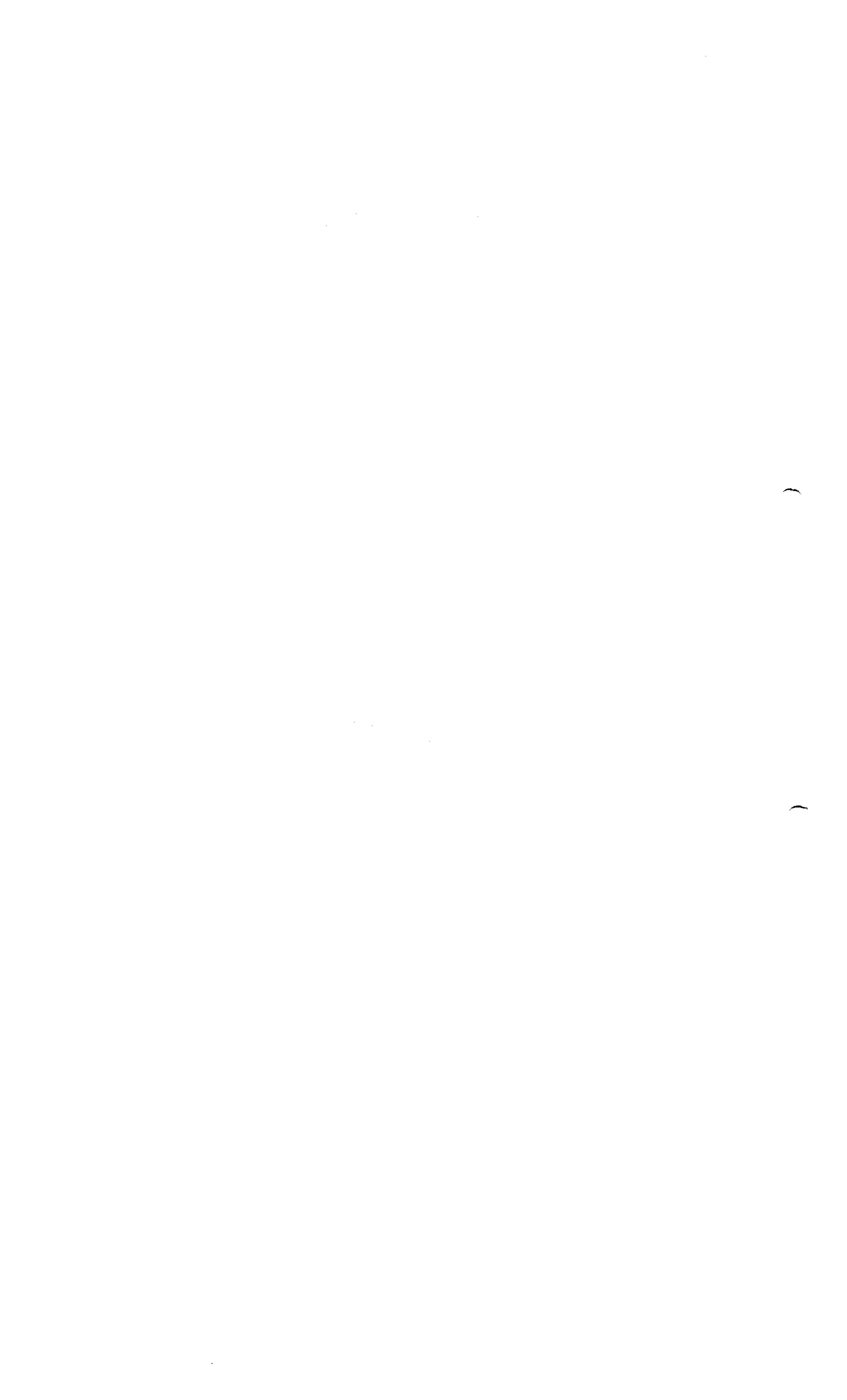
Identification of HBsAg

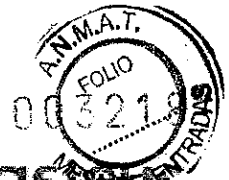
Method : ELISA
 Date : June 19th, 2008
 Result : Positive

Method : SDS - PAGE
 Date : June 19th, 2008
 Result : Conforms



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Diphtheria, tetanus, pertussis (acellular, component),
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influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch)

66/229

HBsAg Content

Method : ELISA
Date : June 19th, 2008
Result : 1,1 mg/mg of total proteins – **Conforms**

Carbohydrates Content

Method : Colorimetric assay
Date : June 19th, 2008
Result : 38 µg/mg of total proteins – **Conforms**

Lipids Content

Method : Colorimetric assay
Date : June 19th, 2008
Result : 0,8 mg/mg of total proteins – **Conforms**

Purity Content

Method : SDS - PAGE
Date : June 19th, 2008
Result : 97 %

Percentage of HBsAg free monomer

Method : SDS - PAGE
Date : June 19th, 2008
Result : Less than 3 % - **Conforms**

Bacterial and fungal sterility

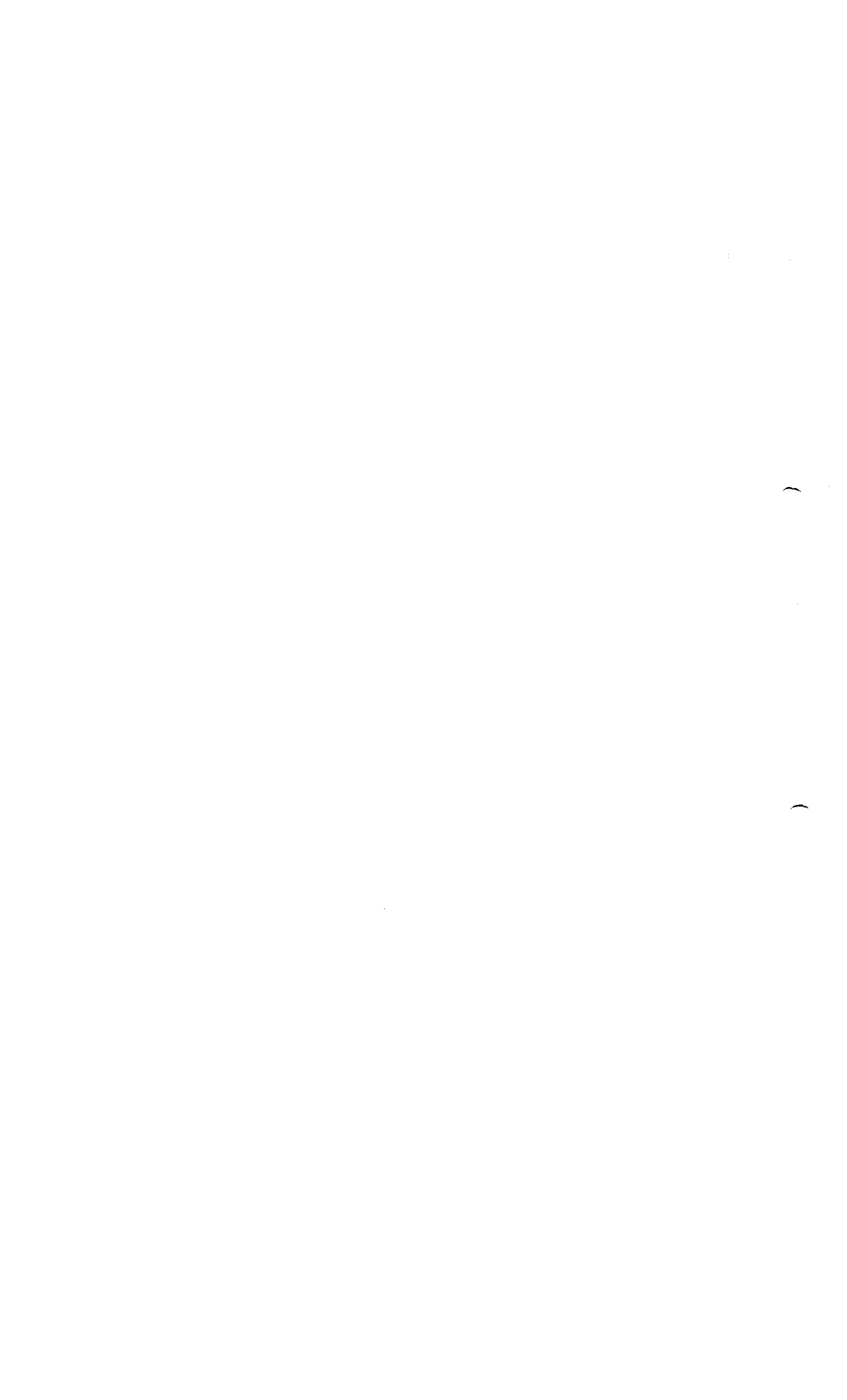
Method	:	Membrane filtration
Media	:	Thioglycollate medium Soybean-Casein Digest medium
Temperature	:	30-35° C 20-25° C
Inoculum per Steritest	:	10 ml 10 ml
Volume of medium per Steritest	:	100 ml 100 ml
Test on	:	May 6 th , 2008
Test off	:	May 20 th , 2008
Result	:	No microbial growth - Conforms

Bacterial Endotoxins

Method : LAL – Gel clot
Date : May 7th, 2008
Result : ≤1 EU/20µg of proteins- **Conforms**


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 CHRISTIAN DOMINGUEZ
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MESA DE ENTRADAS

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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)

67/229

- E - INACTIVATED POLIOMYELITIS TRIVALENT

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