



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° S4313 (clinical batch)

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HAEMOPHILUS AH POLYSACCHARIDE DERIVATIVE

TESTS	SPECIFICATIONS
RESIDUAL CYANIDES CONTENT	≤ 5 µg/ml
POLYSACCHARIDE CONTENT (PHOSPHORUS CONTENT)	For calculation
PERCENTAGE OF POLYSACCHARIDE LINKED ADH	1.8 - 2.9 %
FREE ADH/TOTAL ADH RATIO	≤ 0.1
MOLECULAR SIZE : - Polysaccharide eluted before K _d 0.20 - K _d of polysaccharide	≤ 15 % 0.40 - 0.60
HAEMOPHILUS IDENTIFICATION	Positive


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**HAEMOPHILUS AH
 POLYSACCHARIDE DERIVATIVE**

lot number : FA318451

Date of manufacture : 28.07.08
 Storage temperature : ≤ -35°C
 Expiry date : 28 JULY 2010
 Volume : 2.299 liters

CONTROLS :

Residual cyanides content

Method : Gas Chromatography, cyanide or cyanate ions are transformed
 into cyanogen chloride by chlorination
 Date : 07.08.08
 Result : <0.004 µg/ml – Conforms



Polysaccharide content

Method : Calculated from the theoretical phosphorus
 content of PRP
 Date : 28.08.08
 Result : 10.8 mg/ml

Percentage of polysaccharide linked ADH (Adipic DiHydrazide acid)

Method : Colorimetry
 Date : 11.09.08
 Result : 2.58 % - Conforms

Free ADH/total ADH ratio : 0.022 - Conforms


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Molecular size

Method	: size exclusion Chromatography
Date	: 08.09.08
Result : - Percentage of polysaccharide eluted before K_d 0.20	: 1.94 % - Conforms
- K_d of polysaccharide	: 0.51 - Conforms

Haemophilus identification

Method	: Double diffusion in gel
Date	: 30.07.08
Result	: Positive - Conforms

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HAEMOPHILUS POLYSACCHARIDE CONJUGATE (CONCENTRATED BULK)

TESTS	SPECIFICATIONS
PH	6.5 - 7.5
PHOSPHORUS CONTENT	No specification
POLYSACCHARIDE CONTENT	No specification
SUCROSE CONTENT	No specification
PROTEIN/POLYSACCHARIDE RATIO (after dialysis)	1.8 - 3.0
RESIDUAL EDAC CONTENT	< 10 µmol/l
RESIDUAL PHENOL CONTENT	< 1 µg/ml
FREE POLYSACCHARIDE CONTENT	< 20 %
MOLECULAR SIZE : Percentage of polysaccharide eluted before K _d 0.20	≥ 60 %
FREE TETANUS PROTEIN CONTENT	< 1 %
BACTERIAL AND FUNGAL STERILITY	No microbial growth

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**HAEMOPHILUS POLYSACCHARIDE
CONJUGATE (CONCENTRATED BULK)**
lot number : FA328213

Date of manufacture : 23.10.08
Storage temperature : ≤ -35°C
Expiry date : 23 OCTOBER 2011
Volume : 30.798 liters

CONTROLS :

pH

Method : Glass electrode
Date : 06.11.08
Result : 7.09 - Conforms

Phosphorus content

Method : Chen
Date : 03.11.08
Result : 17.4 µg/ml

Polysaccharide content

Method : Calculated from the theoretical phosphorus
content of PRP
Date : 04.11.08
Result : 207.14 µg/ml

Sucrose content

Method : quantitative analysis of glucose before and after enzymatic
hydrolysis
Date : 05.11.08
Result : 86.31 g/l

Protein/Polysaccharide ratio : 2.2 - Conforms
352_CC5_SPI_AE.dot /19.09.11


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Residual EDAC content (Ethyl-DimethylAminopropyl-Carbodiimide)

Method : Wilcheck
Date : 07.11.08
Result : <10.0 µmol/l - Conforms

Residual phenol content

Method : Colorimetry
Date : 05.11.08
Result : <1.0 µg/ml - Conforms

Free Polysaccharide content


Method : High Performance Anion Exchange
Chromatography with Pulsed Amperometric
Detection method (HPAEC-PAD)
Date : 17.11.08
Result : <4.2 % - Conforms

Molecular size

Method : size exclusion chromatography
Date : 03.12.08
Result : 76.5 % - Conforms

Free tetanus protein content

Method : polyacrylamide gel electrophoresis SDS-PAGE
Date : 02.12.08
Result : <1.0% - Conforms


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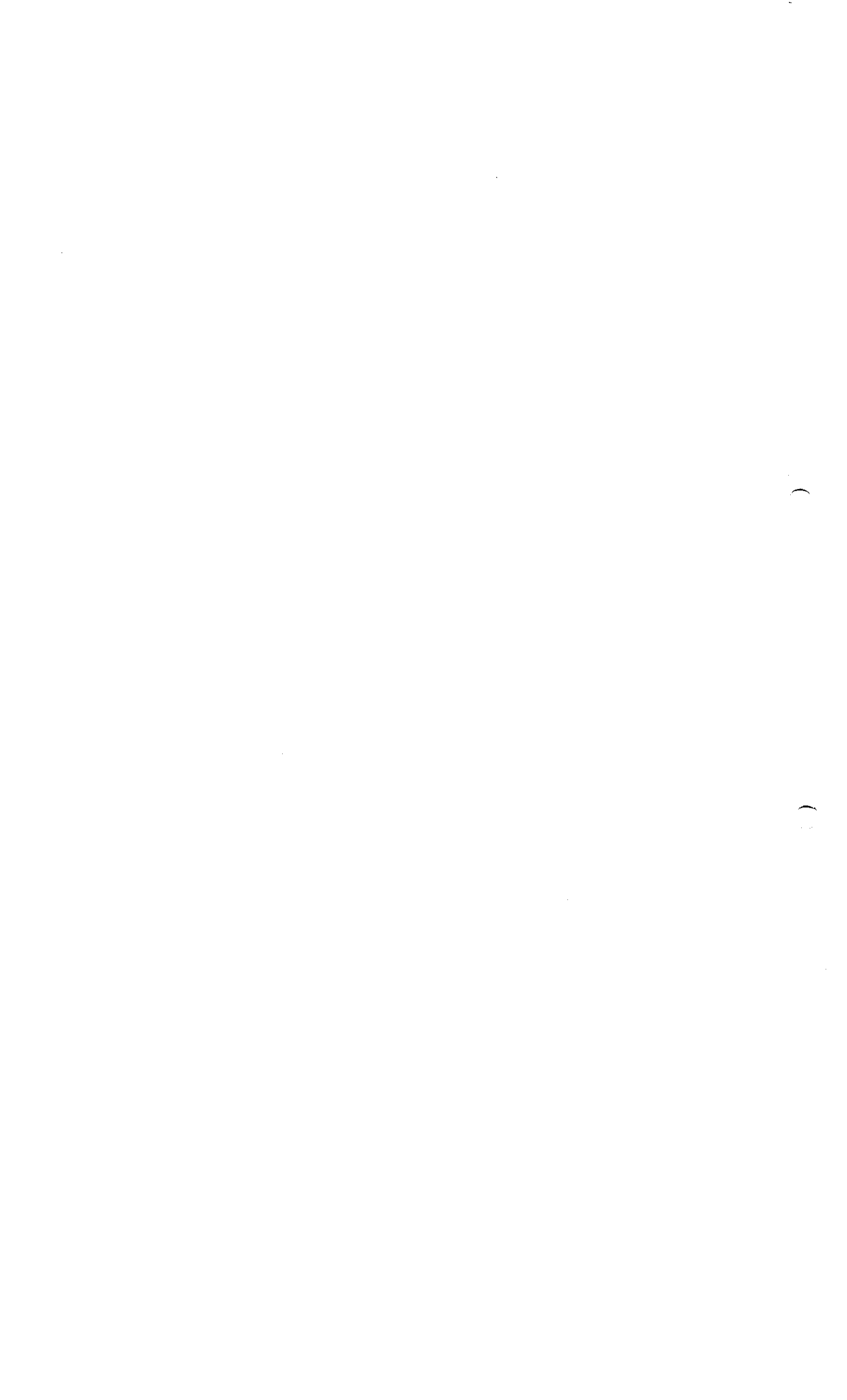
Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed) lot n° S4313 (clinical batch)

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Bacterial and fungal sterility

Method	:	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	:		27.10.08
Test off	:		12.11.08
Result	:	No microbial growth – Conforms	



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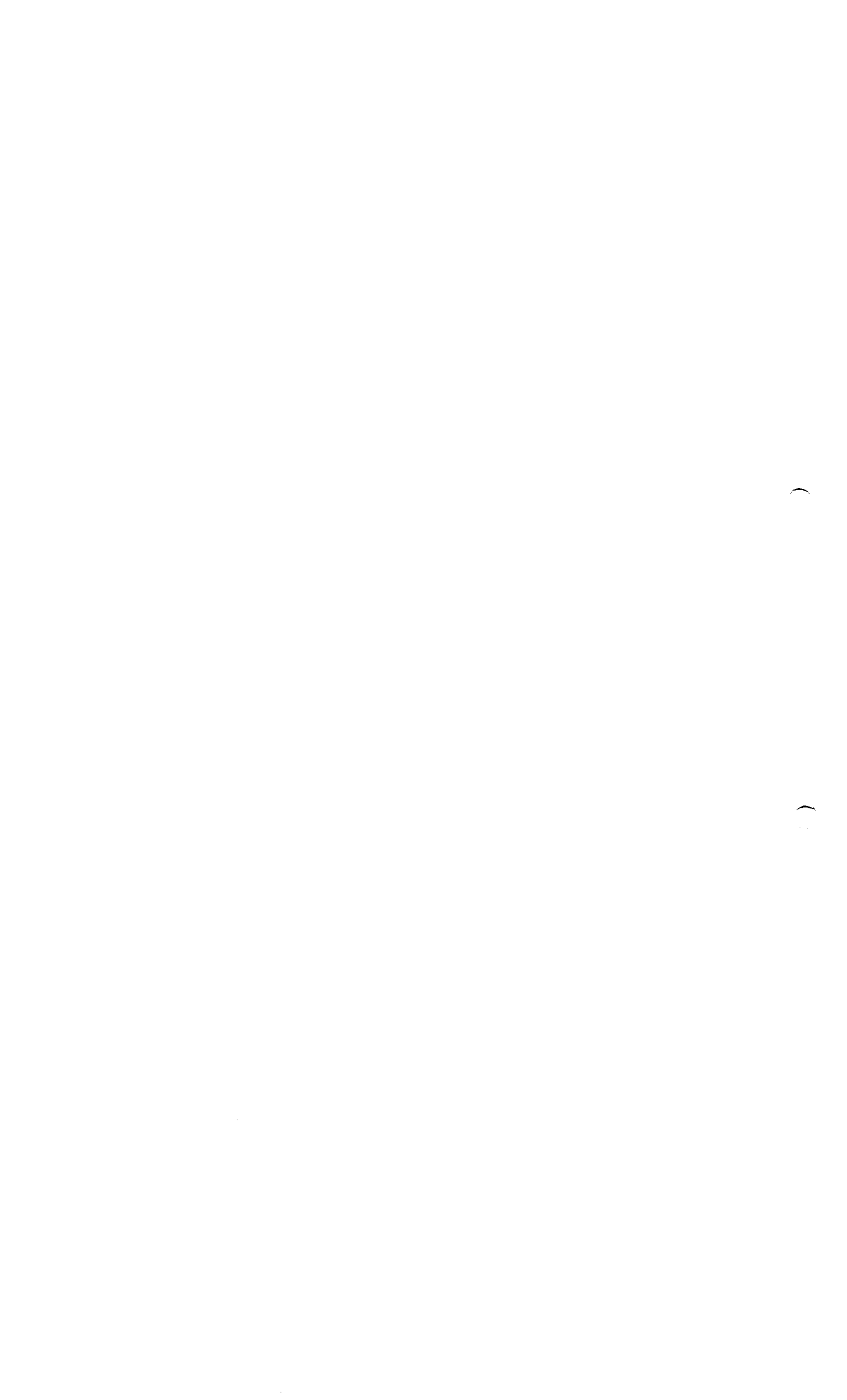
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PART 2
FINAL BULK PRODUCT


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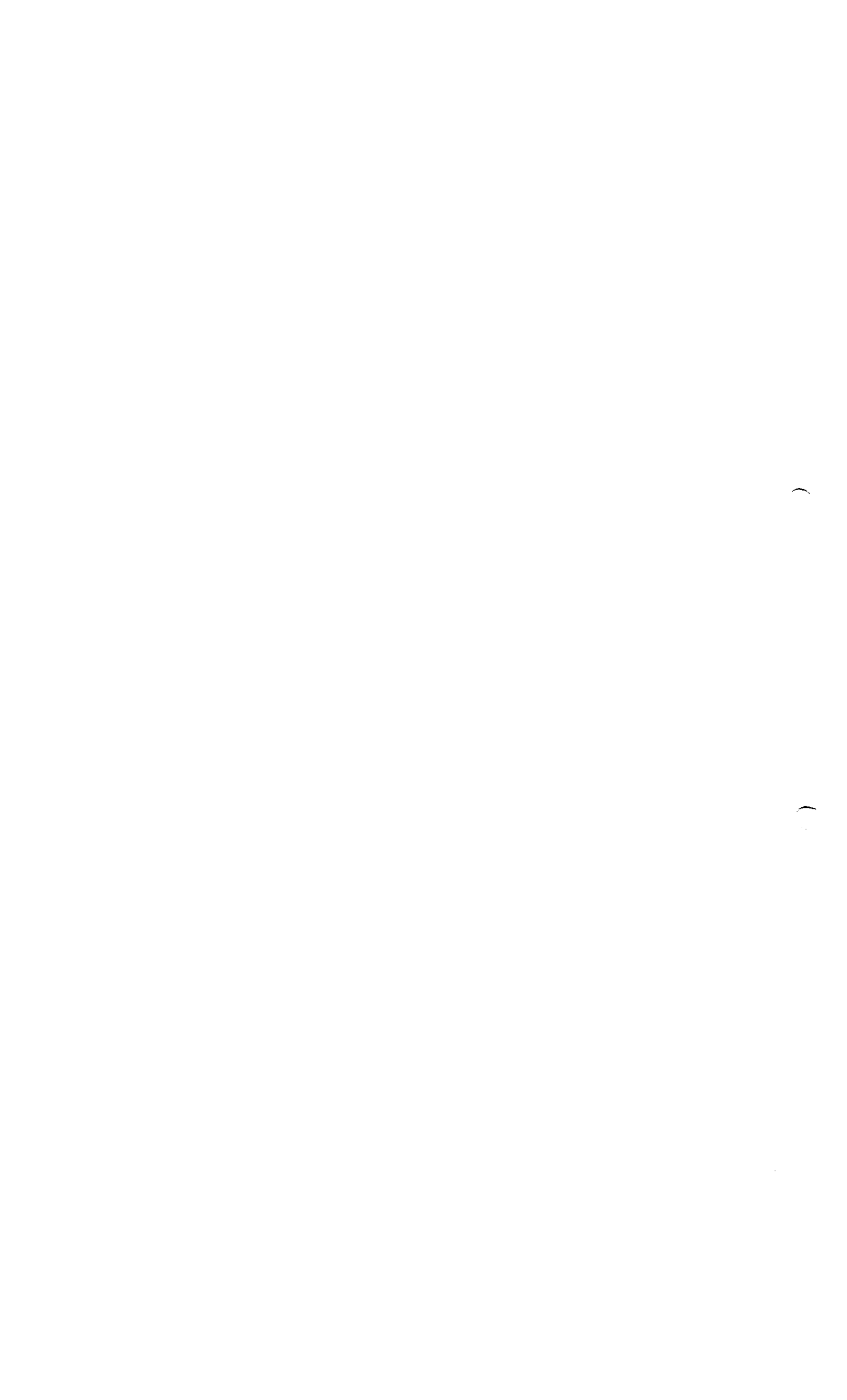
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FINAL BULK

TESTS	SPECIFICATIONS
OSMOLALITY	300 - 400 mosmol/kg
FREE FORMALDEHYDE CONTENT	≤30 µg/mL
BACTERIAL AND FUNGAL STERILITY	No microbial growth
HISTAMINE-SENSITIZING ACTIVITY	≥95% survival
NON ADSORBED POLYRIBOSYL RIBITOL PHOSPHATE (PRP)	≥8.0 µg/dose
DEPOLYMERIZED PRP	<20.0%
PERCENT ADSORPTION – DIPHTHERIA TOXOID	≥23% At time of release, this acceptance criterion was not defined
PERCENT ADSORPTION – HEPATITIS B	≥64% At time of release, this acceptance criterion was not defined
DIPHTHERIA POTENCY	Activity ≥30 IU/dose Lower confidence limit (P = 0.95) of the estimated potency ≥ 20 IU/dose
TETANUS POTENCY	Lower confidence limit (P = 0.95) of the estimated potency ≥ 40 IU/dose
IMMUNOGENICITY PERTUSSIS IN MICE	Anti-PT and anti-FHA antibody GMTs for the vaccine are not significantly lower than those of the reference vaccine (analysis of variance) at the level 5%.
D-ANTIGEN CONTENT	TYPE 1 : 20.0 – 43.0 DU/DOSE TYPE 2 : 5.0 – 9.0 DU/DOSE TYPE 3 : 17.0 – 36.0 DU/DOSE
HEPATITIS B IN VITRO RELATIVE POTENCY (IVRP)	≥0.70 At time of release, this acceptance criterion was not defined


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FINAL BULK
 Lot number : FDV01416

Date of manufacture : 18.11.2009
 Storage temperature : + 5°C ± 3°C
 Expiry date : 18 August 2010

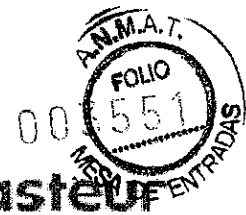
Composition

INGREDIENT	Lot number	Volume (ml)
Purified Diphtheria Toxoid	FA293606	2 728
Purified Tetanus Toxoid	FA276217	1 000
Adsorbed Pertussis Toxoid	FA326717	17 944
Adsorbed FHA Pertussis	FA344108	17 620
Concentrated Polio Trivalent (5C)	FA328827	50 020
Hepatitis B Surface Antigene C	AC004	1 712
	AC012	1 656
Haemophilus Polysaccharide Conjugate	FA328213	28 966
Aluminium hydroxide	FA365289	34 323
Buffer solution (Disodium hydrogen phosphate and potassium dihydrogen phosphate)	FA363235	20 002
Essential Amino acids solution	FA367791	25 000
Buffer solution (trometamol and saccharose)	FA363236	6 707
Water for injections	ABS2E321A	42 361
	ABS2E322A	
APPROXIMATE TOTAL VOLUME		240 800

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CONTROLS :

Osmolality

Method : Measure of the freezing point reduction
Date : 02.12.2009
Result : 338 mosmol/kg - **Conforms**

Free formaldehyde content

Method : Spectrophotometry / colorimetric assay
Date : 04.12.2009
Result : 3.34 µg/ml - **Conforms**

Bacterial and fungal sterility

Method	:	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	:	26.11.2009
Test off	:	10.12.2009
Result	:	No microbial growth - Conforms

Histamine-sensitizing activity

Injection (Day 0)

Animals and sex : mice CD1 - Female
Number of animals : 20
Route : Intraperitoneal
Dose tested per mouse : 2 human doses (1ml)
Date of injection : 23.12.2009

Histamine challenge (Day 5)

Challenge dose per mouse : 2 mg histamine base
Route : Intraperitoneal
Date of injection : 28.12.2009

Reading date (Day 6)

Result : 29.12.2009
: 100 % of survival - **Conforms**

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Polysaccharide content :


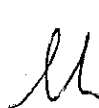
Method	: High Performance Anion Exchange Chromatography with Pulsed Amperometric Detection method (HPAEC-PAD)
Standard	: CP09E055
Date	: 10.12.2009
Non adsorbed PRP	: 10 µg/dose
Depolymerized PRP	: 3.7 % - Conforms

Percent adsorption – Diphtheria toxoid:

Method	: Rocket Immuno-electrophoresis method
Date	: 01.12.2009
Result	: 54 %

Percent adsorption – Hepatitis B:

Method	: ELISA
Date	: 27.11.2009
Result	: 97 %

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