

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)
15/229

Bacterial and fungal sterility

Method	: Membrane filtration	
Media	: Thioglycollate	Soybean casein digest
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
Number of inoculated Steritest	: 1	1
Test on	: 05.12.07	
Test off	: 19.12.07	
Result	: No microbial growth - Conforms	



Specific toxicity

Method	: Vero cells
Reference standard toxin used	: FA142077-1
Volume tested	: 200 µl of a 100 Lf/ml toxoid solution
Inoculum per well	: 50 µl
Test on	: 04.01.08
Test off	: 10.01.08
Result	: Negative - Conforms

Irreversibility of toxoid

Reference standard toxin used	: FA142077-1	
Concentration of the toxoid solution	: 100 Lf/ml	100 Lf/ml
Incubation period	: 5°C ± 3°C	
Temperatures	: 37°C	
Date of beginning	: 12.12.07	
Date of end	: 23.01.08	

Method	: Vero cells	
Volume tested	: 200 µl	200 µl
Inoculum per well	: 50 µl	50 µl
Test on	: 25.01.08	
Test off	: 31.01.08	
Result	: Negative - Conforms	

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16/229

- B - PURIFIED TETANUS TOXOID


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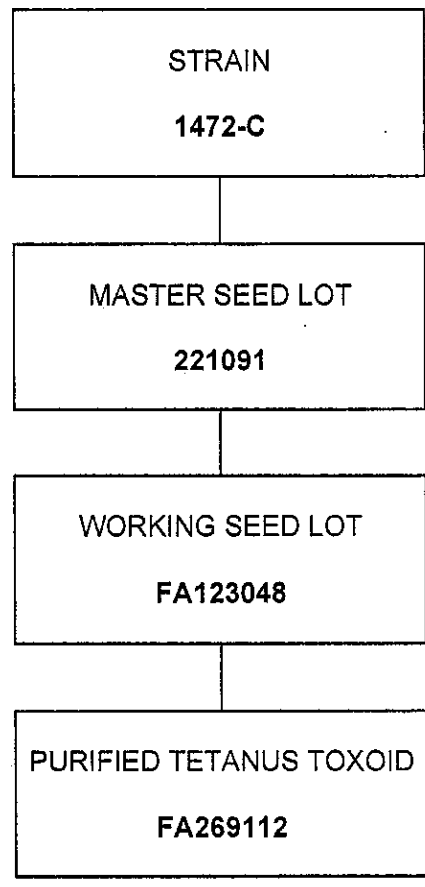
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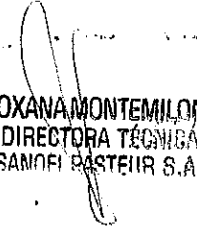
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17/229

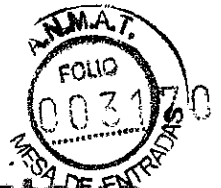


PRODUCTION FLOW SHEET


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18/229

TETANUS STRAIN
Clostridium tetani 1472-C

STRAIN


Name : Harvard 49205
Origin : Rijks Instituut (RIV), Bilthoven
Hollande (Y-IV-5 AV)
Received : 17.11.82
Institut Mérieux number : 1472-C


TETANUS TOXOID
Master seed lot n°221091

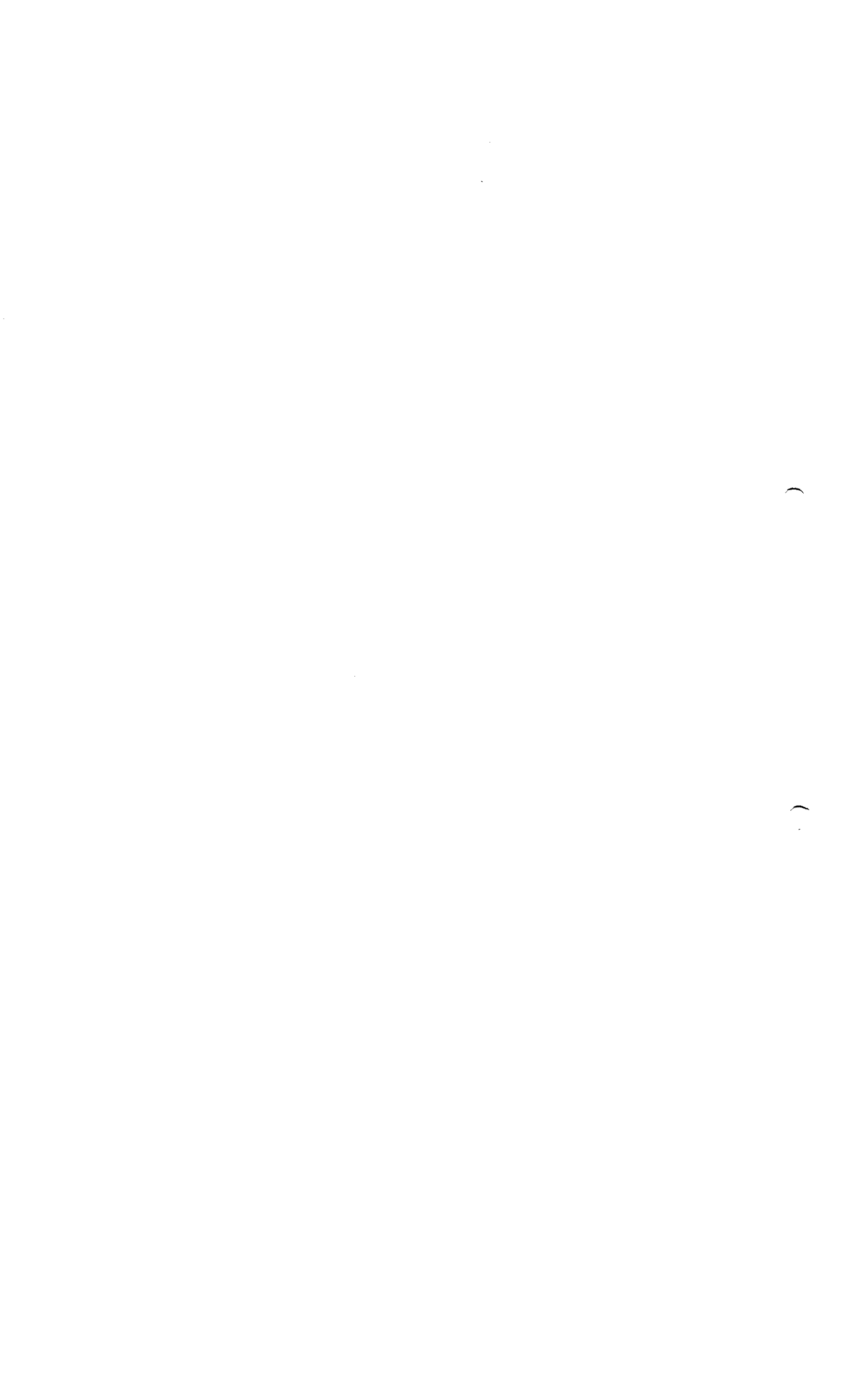
Strain number : 1472-C
Preparation date : 22.10.91
Release date : 14.11.91

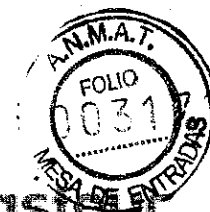
CONTROLS

- Purity
- Identification
 - Morphology
 - Growth characteristics
 - Biochemical characteristics


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19/229


TETANUS TOXOID
Working seed lot n°FA123048


Primary seed Lot n° : 221091
Preparation date : 07.08.02
Release date : 26.02.03

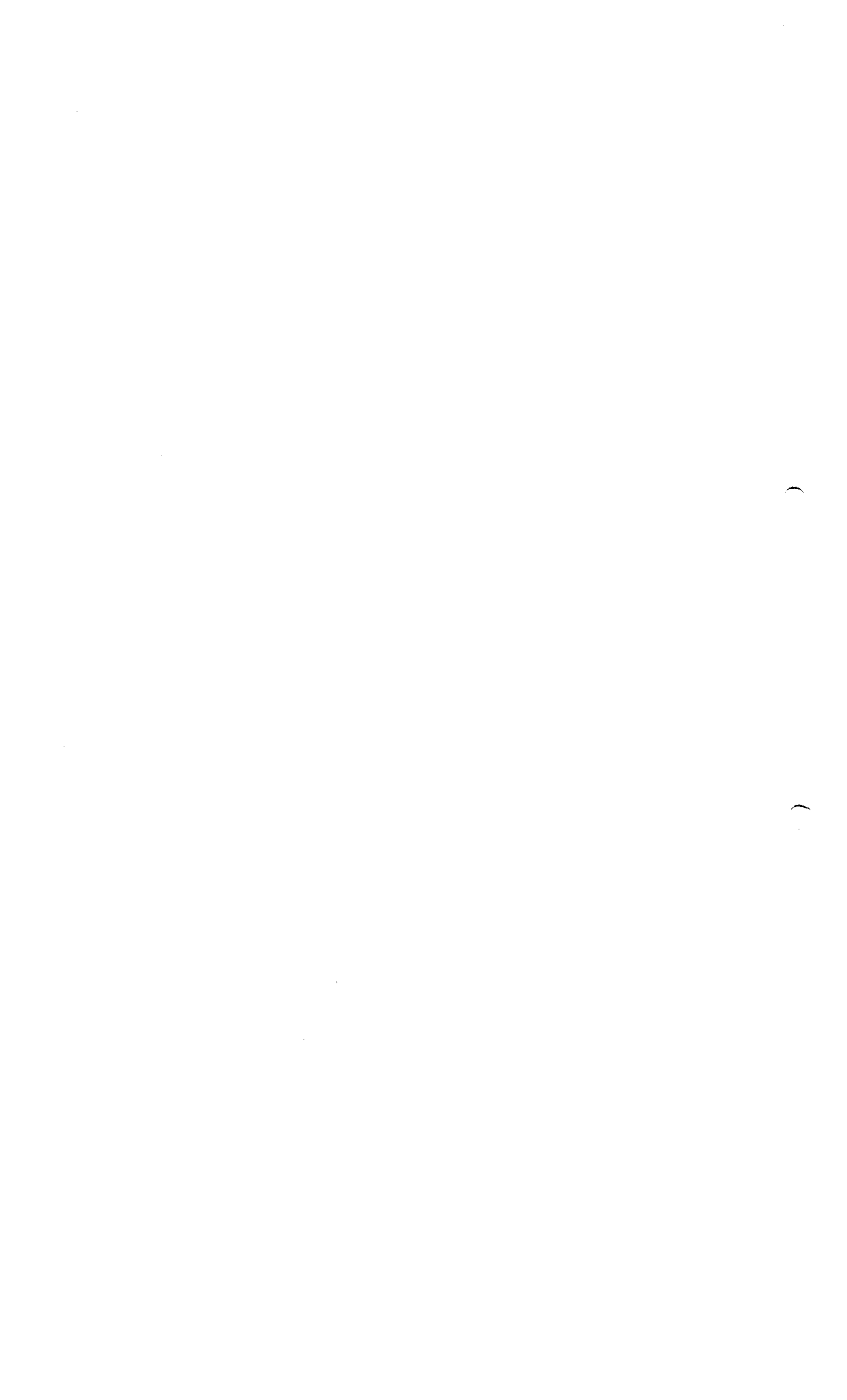
CONTROLS

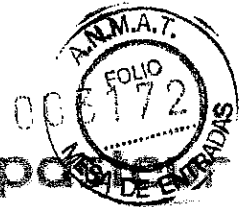
- Purity
- Identification
 - Morphology
 - Growth characteristics
 - Biochemical characteristics

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


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20/229

TETANUS TOXOID
Lot n°FA256253

Strain : 1472-C
Working seed-lot number : FA123048
Storage temperature : + 5°C ± 3°C
Approved storage period : 112 days

Single harvests :

Medium used : Massachussets
Date of reconstitution of seed lot ampoule(s) : 16.10.06
Date of inoculation : 19.10.06
Date of harvest : 26.10.06

CONTROLS

Identity test

Method : tetanus flocculation
Date : 28.11.06
Result : positive


Bacterial purity

Method : Gram coloration
Date: 26.10.06
Result : conforms

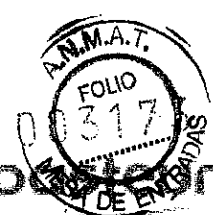
Inactivation

Method : formaldehyde treatment
Date of inactivation : 13.11.06


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21/229

TETANUS TOXOID
Lot n°FA258008

Strain : 1472-C
Working seed-lot number : FA123048
Storage temperature : + 5°C ± 3°C
Approved storage period : 112 days

Single harvests :

Medium used : Massachussets
Date of reconstitution of seed lot ampoule(s) : 06.11.06
Date of inoculation : 09.11.06
Date of harvest : 16.11.06

CONTROLS

Identity test
Method : tetanus flocculation
Date : 12.12.06
Result : positive

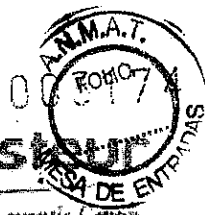
Bacterial purity
Method : Gram coloration
Date: 16.11.06
Result : conforms

Inactivation
Method : formaldehyde treatment
Date of inactivation :04.12.06

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influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 22/229

TETANUS TOXOID
Lot n°FA258899

Strain : 1472-C
Working seed-lot number : FA123048
Storage temperature : + 5°C ± 3°C
Approved storage period : 112 days

Single harvests :


Medium used : Massachussets
Date of reconstitution of seed lot ampoule(s) : 13.11.06
Date of inoculation : 16.11.06
Date of harvest : 23.11.06


CONTROLS

Identity test
Method : tetanus flocculation
Date : 10.12.06
Result : positive

Bacterial purity
Method : Gram coloration
Date: 23.11.06
Result : conforms

Inactivation
Method : formaldehyde treatment
Date of inactivation : 12.12.06


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23/229

TETANUS TOXOID
Lot n°FA261338

Strain : 1472-C
Working seed-lot number : FA123048
Storage temperature : + 5°C ± 3°C
Approved storage period : 112 days

Single harvests :

Medium used : Massachussets
Date of reconstitution of seed lot ampoule(s) : 04.12.06
Date of inoculation : 07.12.06
Date of harvest : 14.12.06

CONTROLS

Identity test

Method : tetanus flocculation
Date : 11.01.07
Result : positive

Bacterial purity

Method : Gram coloration
Date: 14.12.06
Result : conforms

Inactivation

Method : formaldehyde treatment
Date of inactivation : 01.01.07


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influenzae type b conjugate vaccine (adsorbed) lot n° S4312 (clinical batch) 24/229

TETANUS TOXOID
Lot n°FA264426

Strain : 1472-C
Working seed-lot number : FA123048
Storage temperature : + 5°C ± 3°C
Approved storage period : 112 days

Single harvests :


Medium used : Massachussets
Date of reconstitution of seed lot ampoule(s) : 15.01.07
Date of inoculation : 18.01.07
Date of harvest : 25.01.07


CONTROLS

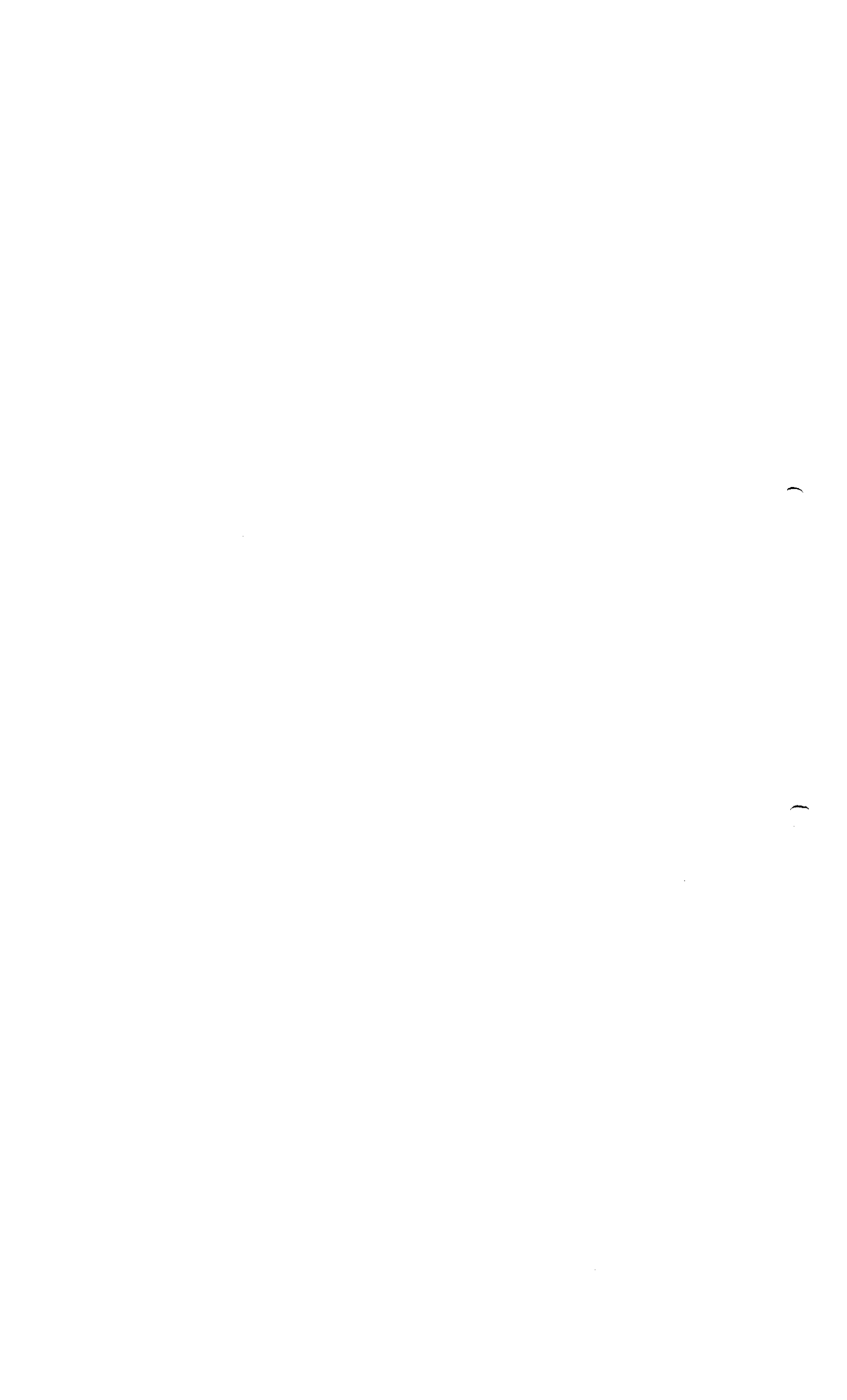
Identity test
Method : tetanus flocculation
Date : 23.02.07
Result : positive

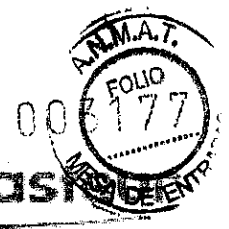
Bacterial purity
Method : Gram coloration
Date: 25.01.07
Result : conforms

Inactivation
Method : formaldehyde treatment
Date of inactivation : 12.02.07


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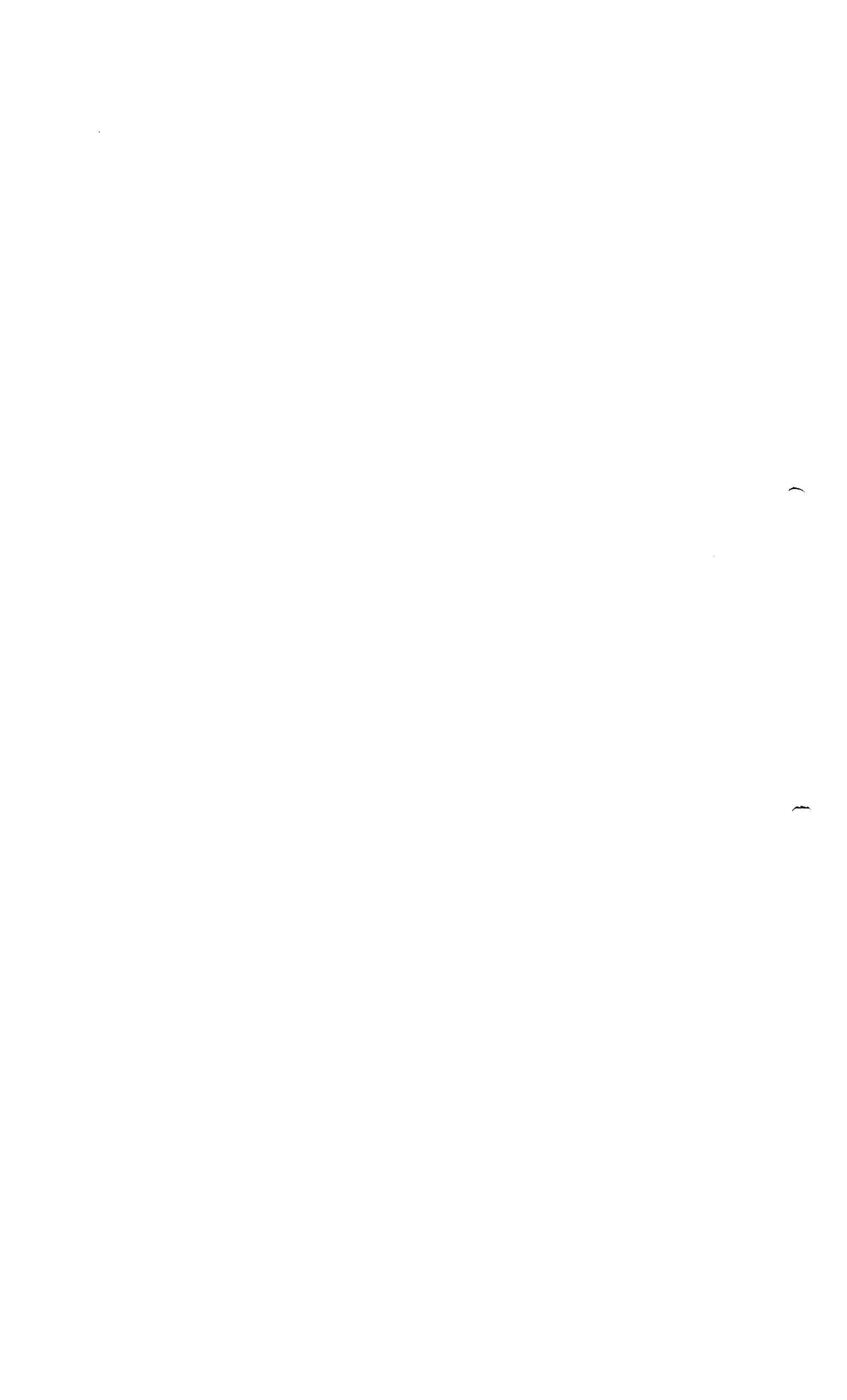
25/229

PURIFIED TETANUS TOXOID
FA269112

TESTS	SPECIFICATIONS
PROTEIN NITROGEN CONTENT	For antigenic purity calculation
FREE FORMALDEHYDE CONTENT	For formulation (used for formulation in final bulk product where appropriate)
FLOCCULATING TITER	For antigenic purity calculation
ANTIGENIC PURITY	≥ 1000 Lf/mg of protein nitrogen
BACTERIAL AND FUNGAL STERILITY	No microbial growth
ABSENCE OF TOXIN (SPECIFIC TOXICITY) AND IRREVERSIBILITY OF TOXOID	No tetanus symptom and at least 93 % of survival


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26/229

PURIFIED TETANUS TOXOID
Lot n° FA269112

Working seed Lot n° : FA123048

Tetanus toxoid Lot number :	FA256253	FA258008	FA258899	FA261338	FA264426
Volume used (liters) :	200	230	303	286	225

Volume : 59.800 liters
 Storage temperature : + 5°C ± 3°C
 Date of manufacture : 05.03.07
 Expiry date : 05 MARCH 2010
 Approved storage period : 3 years

CONTROLS

Protein nitrogen content

Method : Kjeldahl after trichloroacetic acid precipitation
 Date : 12.03.07
 Result : 4.11 mg/ml

Free formaldehyde content

Method : Nash
 Date : 21.03.07
 Result : 58.19 µg/ml

Flocculating titer

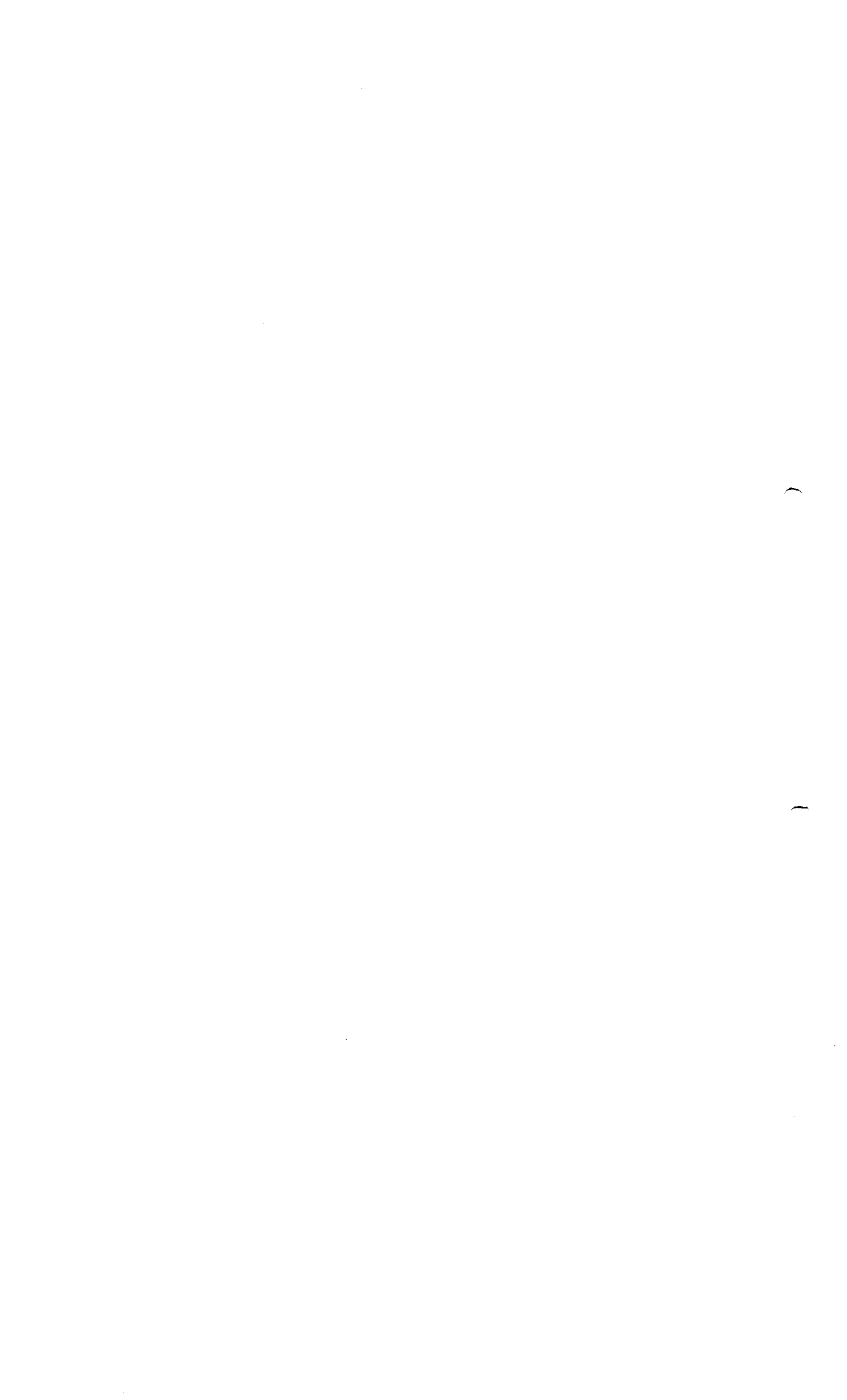
Method : Flocculation in comparison with in house
reference
 Date : 13.03.07
 Result : 5000 Lf/ml

Antigenic purity

Date : 27.03.07
 Result : 1217 Lf/mg of protein nitrogen - **Conforms**

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Bacterial and fungal sterility

Method	:	Membrane filtration	
Media	:	Thioglycollate	Soybean casein digest
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
Number of inoculated Steritest	:	1	1
Test on	:	07.03.07	
Test off	:	21.03.07	
Result	:	No microbial growth - Conforms	

Absence of toxin (specific toxicity)



Animals	:	Guinea-pigs
Number of animals	:	5
Lf of toxoid injected per animal	:	2000
Route of injection	:	Subcutaneous
Test on	:	16.03.07
Test off	:	06.04.07
Result	:	No tetanus symptom and at least 93% of survival - Conforms

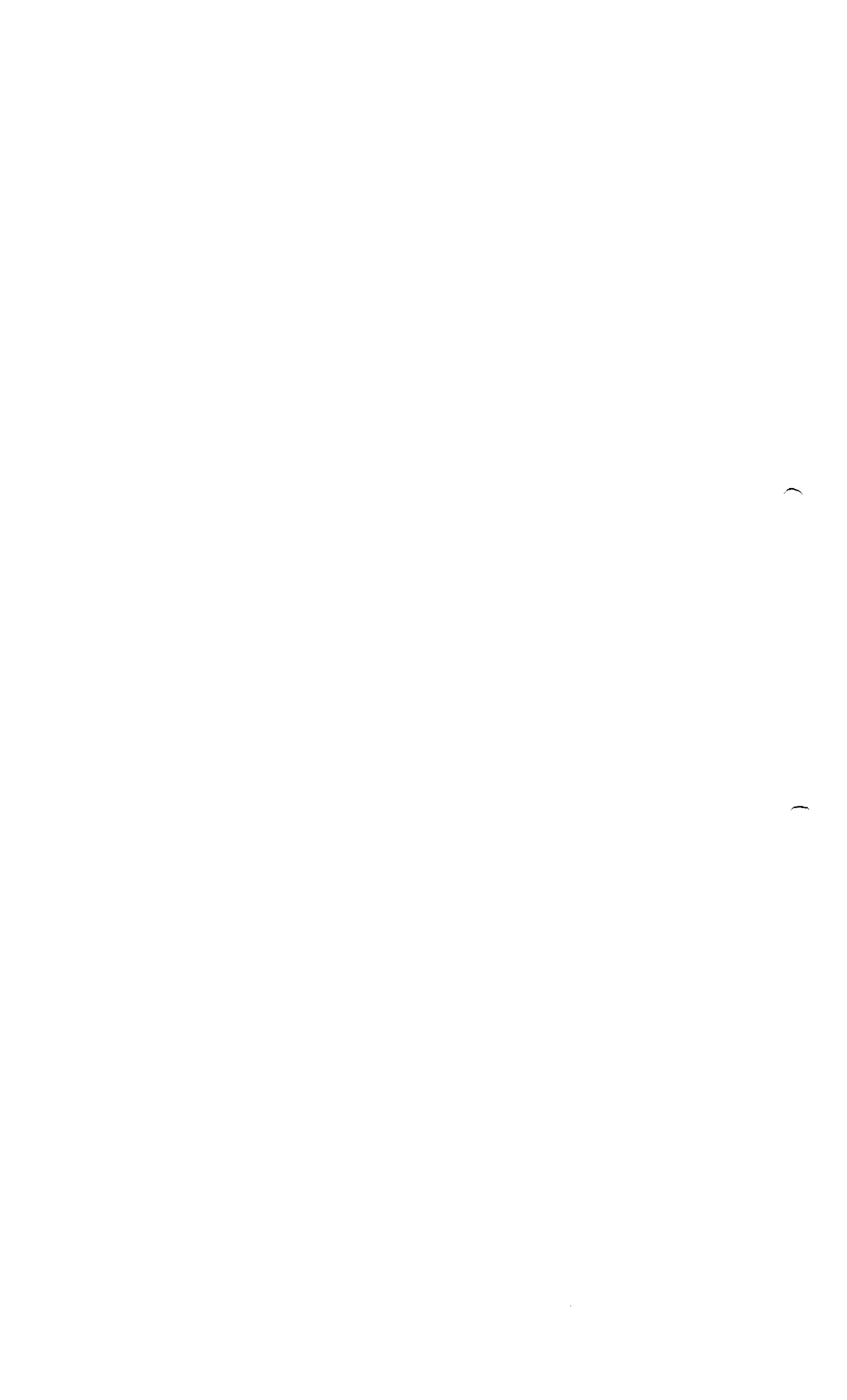
Irreversibility of toxoid

Concentration of the toxoid solution	:	20 Lf/ml	20 Lf/ml
Incubation period	:		
Temperatures	:	5°C ± 3°C	37°C
Date of beginning	:	03.05.07	
Date of end	:	14.06.07	

Test in animals

Number of guinea pigs injected	:	5	5
Route	:	Subcutaneous	
Volume injected	:	5 ml	5 ml
Date of inoculation	:	14.06.07	
Date of end of observation	:	05.07.07	
Result	:	No tetanus symptom and at least 93% of survival - Conforms	


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28/229

- C - 2 COMPONENT ACELLULAR PERTUSSIS

	
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