





Certificate of Analysis

Project Status: PASS

Project Name: FLF_020-117002-1

Process Order: 000100291295

Product: FLF_020 - FLUAD - Filled Product With MF59 Without Thiomersal

Batch: 117002

SAP Material: RFLF25002 - FLUAD PFS 25G1 SENZA MERT. DA SPERLARE

LIMS Lot: 85488

SAP Lot Number: 30000251284

Expiry date: 31/05/2012

Grade: FLF_13_020 - Filled Product With MF59 Without Thiomersal

Storage Temperature: 2_8_C

TESTS	REQUIREMENTS	RESULTS	Units
264896_NM - Particles diameter in MF59			
result	130 <= Result <= 180	163	nm
265400 - Particles number in MF59			
result	Result <= 10000000	904580	N° part./ml
CQS_149 - Endotoxin			
Result	Result < 100	<1	UI/0,5ml
CQS_38_AP_BCA - Total Proteins (other than HA)			
Result	Result <= 120	28	mcg/0,5 ml
CQS_52_FFSS - Volume in vials			
Extracted Volume	Result >= 0,50	0,52	ml
Extracted volume single vial	Result >= 0,50	0,52	ml
Extracted volume single vial	Result >= 0,50	0,52	ml
Extracted volume single vial	Result >= 0,50	0,52	ml
Extracted volume single vial	Result >= 0,50	0,52	ml
Extracted volume single vial	Result >= 0,50	0,51	ml
CQS_64 - pH Determination, Potentiometric Method			
Result	6,9 <= Result <= 7,7	7,1	
CQS_90 - Appearance in Lyophile or Liquid Pharmaceutical Products			
Result	Equal to Conforme	Conforme	
CST_01F - Sterility (Membrane Filtration)			
Result	Equal to Sterile	Sterile	
ISU_07_T_F - Single Radial Immunodiffusion (SRID) for the HA determination in FLU vaccine			
B Strain Identity	Equal to Positiva	Positiva	
H1N1 Strain Identity	Equal to Positiva	Positiva	
H3N2 Strain Identity	Equal to Positiva	Positiva	
B Strain L.F.L.	Result >= 12	16	mcg/0,5 ml
H1N1 strain L.F.L.	Result >= 12	16	mcg/0,5 ml
H3N2 Strain L.F.L.	Result >= 12	15	mcg/0,5 ml
Identity Result		Positiva	
B Strain Titre		16	mcg/0,5 ml
H1N1 Strain Titre		16	mcg/0,5 ml
H3N2 Strain Titre		16	mcg/0,5 ml
ISU_13 - Proteins determination in flu vaccine with MF59 - Micro BCA method			
Risultato		75,7	mcg/0,5 ml
ISU_14 - Squalene determination in FLU samples			
Identity	Equal to Positiva	Positiva	
Result	1,55 <= Result <= 2,35	1,85	% P/P

Sample Review Date: 12/07/2011

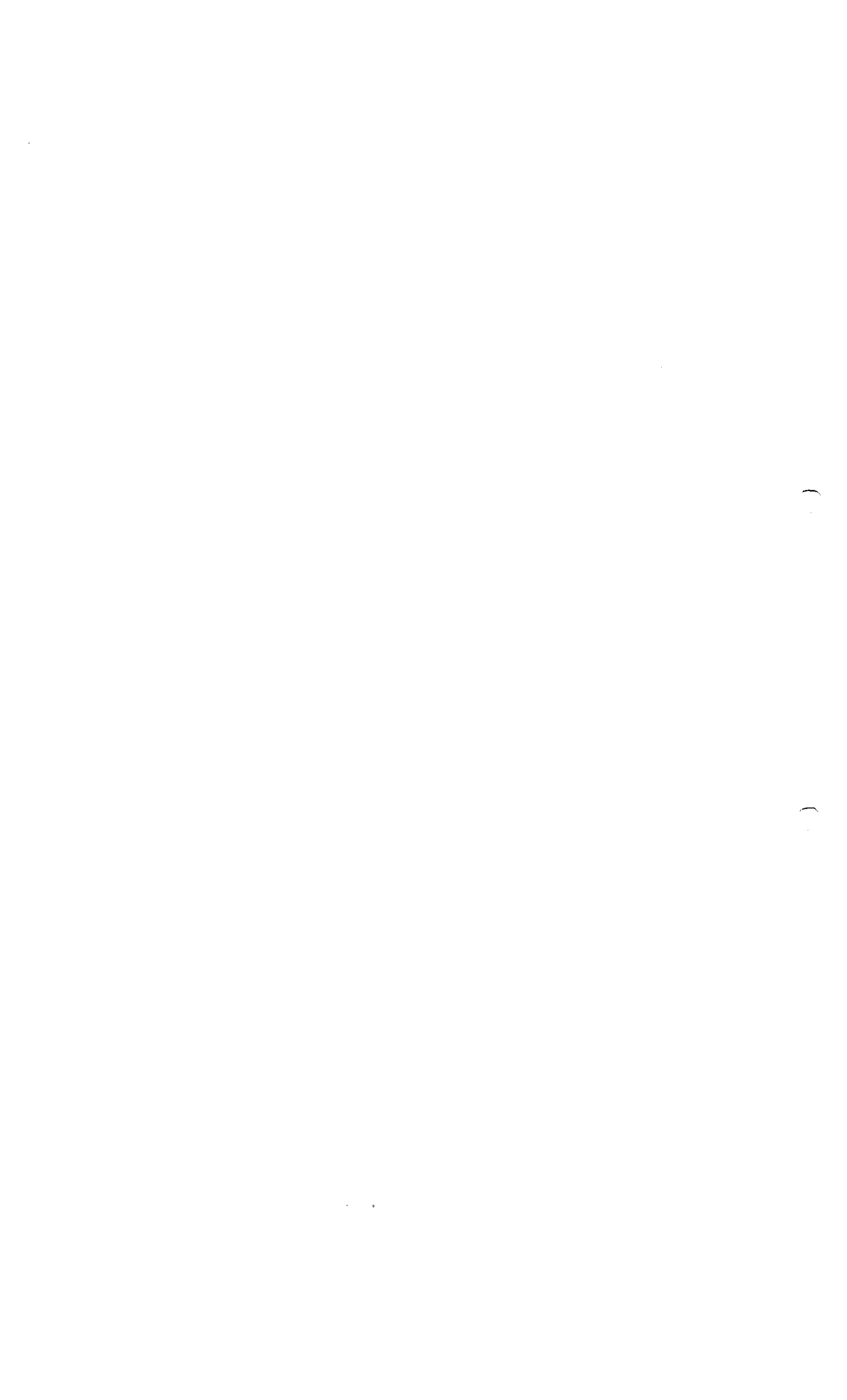
Sample Reviewed by: Fabio Ceccherini

Last Changed Date: 12/07/2011

Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840

Novartis Argentina S.A.
Vaccines Division
Farmacia Argentina
Gobernación de Buenos Aires
Aprobada

22/08/11





Certificate of Analysis

Project Status: PASS

Project Name: FLF_020-117101-1

Process Order: 000100291296

Product: FLF_020 - FLUAD - Filled Product With MF59 Without Thiomersal

Batch: 117101

SAP Material: RFLF25002 - FLUAD PFS 25G1 SENZA MERT. DA SPERLARE

LIMS Lot: 85489

SAP Lot Number: 30000251285

Expiry date: 31/05/2012

Grade: FLF_13_020 - Filled Product With MF59 Without Thiomersal

Storage Temperature: 2_8_C

TESTS	REQUIREMENTS	RESULTS	Units
264896_NM - Particles diameter in MF59			
result	130 <= Result <= 180	146	nm
265400 - Particles number in MF59			
result	Result <= 10000000	1371200	N° part./ml
CQS_149 - Endotoxin			
Result	Result < 100	<1	UI/0,5ml
CQS_38_AP_BCA - Total Proteins (other than HA)			
Result	Result <= 120	19	mcg/0,5 ml
CQS_52_FFSS - Volume in vials			
Extracted Volume	Result >= 0,50	0,52	ml
Extracted volume single vial	Result >= 0,50	0,52	ml
Extracted volume single vial	Result >= 0,50	0,53	ml
Extracted volume single vial	Result >= 0,50	0,52	ml
Extracted volume single vial	Result >= 0,50	0,51	ml
Extracted volume single vial	Result >= 0,50	0,53	ml
CQS_64 - pH Determination, Potentiometric Method			
Result	6,9 <= Result <= 7,7	7,1	
CQS_90 - Appearance in Lyophile or Liquid Pharmaceutical Products			
Result	Equal to Conforme	Conforme	
CST_01F - Sterility (Membrane Filtration)			
Result	Equal to Sterile	Sterile	
ISU_07_T_F - Single Radial Immunodiffusion (SRID) for the HA determination in FLU vaccine			
B Strain Identity	Equal to Positiva	Positiva	
H1N1 Strain Identity	Equal to Positiva	Positiva	
H3N2 Strain Identity	Equal to Positiva	Positiva	
B Strain L.F.L.	Result >= 12	15	mcg/0,5 ml
H1N1 strain L.F.L.	Result >= 12	15	mcg/0,5 ml
H3N2 Strain L.F.L.	Result >= 12	15	mcg/0,5 ml
Identity Result		Positiva	
B Strain Titre		17	mcg/0,5 ml
H1N1 Strain Titre		16	mcg/0,5 ml
H3N2 Strain Titre		16	mcg/0,5 ml
ISU_13 - Proteins determination in flu vaccine with MF59 - Micro BCA method			
Risultato		67,9	mcg/0,5 ml
ISU_14 - Squalene determination in FLU samples			
Identity	Equal to Positiva	Positiva	
Result	1,55 <= Result <= 2,35	1,76	% P/P

Sample Review Date: 13/07/2011

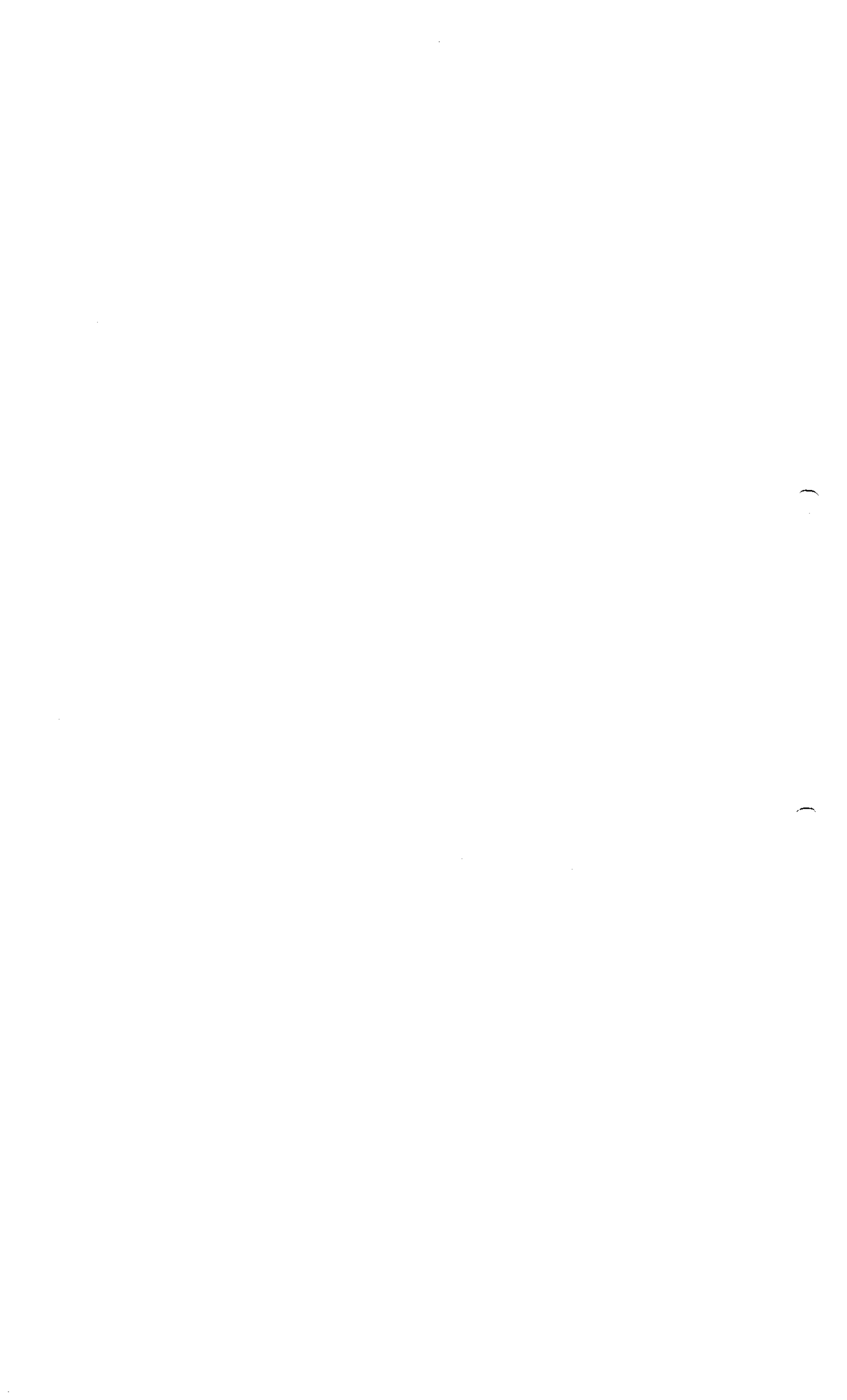
Sample Reviewed by: Fabio Ceccherini

Last Changed Date: 13/07/2011

Novartis Argentina S.A.
Vacunas y Diagnóstico
Farm. Andrés B. Álvarez
Gte. Asuntos Regulatorios
Apoderada

Novartis Argentina S.A.
Dr. Lucio Jeronip
Director Técnico
MN 14840


201081128





Proyecto de Protocolo resumido de fabricación y control del lote


Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vacunas & Diagnóstico
Farm. Adriana G. Jimenez
Gte. Asuntos Regulatorios
Apoderada

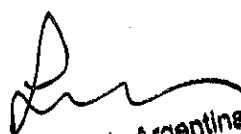




Lot 116321
Page 2 of 51
Prot. 1026/11

Summary

	Page
- Production Plan	3
- Summary protocols of monovalent pooled harvests blended in final bulk vaccine:	
NYMC X-181 monovalent pooled harvest lot 1126/10	4
NYMC X-181 monovalent pooled harvest lot 1000/11	12
NYMC X-187 monovalent pooled harvest lot 1128/10	20
NYMC BX-35 monovalent pooled harvest lot 1124/10	28
NYMC BX-35 monovalent pooled harvest lot 1130/10	36
- Summary protocol of final lot 116321	44


Novartis Argentina S.A.
Dr. Lucio Jeronimo
Director Técnico
MN 14840


Novartis Argentina S.A.
Vacunas y Productos
Farmacéuticos
Gen. Agustín Justo
Apoderada





Novartis Argentina S.A.
Fray Justo Sarmiento 2350
Olivos (B1636AKJ)
Peña. de Buenos Aires
Argentina

Dr. Lucio JERONCIC

Siena: April 23, 2011

Remarks: Release for Novartis Pharma Argentina S.A. supply of Influenza Vaccine Sub unit with MF59C.1 Adjuvant "FLUAD" (Argentinean Market)

We are pleased to inform you that, following to the Official Control Authority Batch Release (issued by "Istituto Superiore di Sanità"-Italy), the herebelow mentioned lot of Influenza Vaccine Sub unit with MF59C.1 Adjuvant "FLUAD", previously released under condition for shipping under quarantine, has been finally released for Novartis Pharma Argentina S.A. supply:

Product code RFLF00014

Packing lot number 116321

Kind regards.

NOVARTIS Vaccines
Novartis Vaccines and Diagnostics Srl
Dr. STEFANO VITI
Qualified Person

Novartis Argentina S.A.
Dr. Lucio Jeroncic
Director Técnico
MN 14840

Novartis Argentina S.A.
Vaccines and Diagnostics
Farm. Argentina Regulatorios
Cta. Asistencia Regulatorias
Apoderada









Lot 116321
Page 4 of 51
Prot. 1026/11

SUMMARY PROTOCOL FOR PRODUCTION AND TESTING

OF INFLUENZA VACCINE (SUB - UNIT)


NYMC X-181 MONOVALENT POOLED HARVEST

Lot 1126/10

Summary

	Page
- Seed virus:	
General information on seed virus	5
Tests on master seed	6
Tests on working seed	6
- Monovalent pooled harvest lot 1126/10:	
Production details of monovalent pooled harvest	8
Tests on monovalent pooled harvest	9


Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines and Biotechnology
Fac. Argentina G. Alimentos
Cta. Av. Regulatorios
Aplicada





Lot 116321
Page 5 of 51
Prot. 1026/11

SEED VIRUS

General information on seed virus

Name and address of manufacturer	Novartis Vaccines and Diagnostics Srl Via Fiorentina, 1 - Siena (Italy)
A(H1N1) virus strain	NYMC X-181 (A/California/7/2009 - like virus)
Primary seed lot	E5857
Source of primary seed	New York Medical College Valhalla, New York, USA
Date of receipt of primary seed	August 17, 2009
Number of passage of primary seed on receipt	6
Comment	None
Storage conditions of primary seed	- 80 ± 10°C
Master seed lot	5MS-H1N1B dil. (10 ⁻⁷) 10 ⁻⁷
Date of manufacture of master seed	December 08, 2009
Number of passages from primary seed to master seed	5
Storage conditions of master seed	- 80 ± 10°C
Working seed lot	5WS-H1N1B-01 dil. (10 ⁻⁷) 10 ⁻⁷
Date of manufacture of working seed	December 11, 2009
Number of passages from master seed to working seed	1
Added antibiotics	Kanamycin sulphate and neomycin sulphate
Storage conditions of working seed	- 80 ± 10°C


Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines and Diagnostics
Ejército de los Andes G. Jimenez
Cda. Avellaneda Reguladorías
Apoderada



Lot 116321
Page 6 of 51
Prot. 1026/11

Tests on master seed

Sterility test (Specification: Sterile)

Method	Eur. Ph., direct inoculation
Media	FTM and SCDM
Volume tested	20 mL
Date of test	Dec. 09 – Dec. 23, 2009
Result	Sterile

Tests on working seed

Sterility test (Specification: Sterile)

Method	Eur. Ph., direct inoculation
Media	FTM and SCDM
Volume tested	20 mL
Date of test	Dec. 15 – Dec. 29, 2009
Result	Sterile

Test for mycoplasma (Specification: Sterile)

Method	Eur. Ph.
Media	Basic agar / broth and modified 1699 plus agar / broth
Volume tested	8.7 mL
Date of test	Dec. 21, 2009 – Jan. 20, 2010
Result	Sterile

Infectivity titre (Specification: $\geq 10^{5.0}$ EID₅₀/mL)

Method	HA titration
Date of test	December 17, 2009
Result	$5 \times 10^{8.4}$ EID ₅₀ /mL


Novartis Argentina S.A.
Dr. Lucio Jerencic
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines and Biologicals
Regulatory Affairs
Buenos Aires
Moderada



Lot 116321
Page 7 of 51
Prot. 1026/11

Identity of neuraminidase (Specification: Positive for A(H1N1) strain)

Method ELISA
Date of test January 25, 2010
Result Positive for A(H1N1) strain

NI titre				
Antigen	Antiserum			
	[A(H1N1)] Anti-N1 NA X-181/09/152	[A(H1N1)] Anti-N1 NA IVR-148/08/112	[A(H3N2)] Anti-N2 NA X-175C/08/246	[B] Anti-B NA B/Brisbane/AS397
X-181 Working seed Lot 5WS-H1N1B-01 dil. (10 ⁻⁷) 10 ⁻⁷	444	< 10	< 10	< 10

Identity of haemagglutinin (Specification: Positive for A(H1N1) strain)

Method Haemagglutination – inhibition test
Date of test February 09, 2010
Result Positive for A(H1N1) strain

HI titre			
Antigen	Antiserum		
	[A(H1N1)] X-181/09/152	[A(H3N2)] X-175C/08/246	[B] B/Brisbane/AS397IM10001
NYMC X-181 Working seed Lot 5WS-H1N1B-01 dil. (10 ⁻⁷) 10 ⁻⁷	1280	80	40

Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840

Novartis Argentina S.A.
Vaccines Division
Dr. Juan Carlos Arneroz
Gerente Asesor Regulatorio
Apoderada




Lot 116321
Page 8 of 51
Prot. 1026/11

MONOVALENT POOLED HARVEST LOT 1126/10

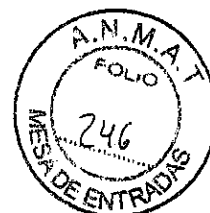
Production details of monovalent pooled harvest

Name and address of manufacturer	Novartis Vaccines and Diagnostics Srl Via Fiorentina, 1 - Siena (Italy)
A(H1N1) virus strain	NYMC X-181 (A/California/7/2009 - like virus)
Working seed lot used in manufacture	5WS-H1N1B-01 dil. (10 ⁻⁷) 10 ⁻⁷
Date of inoculation:	
Monovalent lot : 390/10	December 21, 2010
Monovalent lot : 391/10	December 22, 2010
Added antibiotics	Kanamycin sulphate and neomycin sulphate
Date of harvesting:	
Monovalent lot : 390/10	December 25, 2010
Monovalent lot : 391/10	December 26, 2010
Method of inactivation	Treatment with formaldehyde
Date of inactivation:	
Monovalent lot : 390/10	December 25, 2010
Monovalent lot : 391/10	December 26, 2010
Concentration/purification procedure	Continous zonal centrifugation in sucrose gradient. adsorption with barium sulphate and elution with sodium citrate solution


Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines and Diagnostics
Estrada de la Libertad 1000
Calle Aurore, Reguladoras
Apoderada





Lot 116321
Page 9 of 51
Prot. 1026/11

Date of pooling of monovalent lots	December 29, 2010
Method of disruption	Treatment with Tween 80 and CTAB
Date of disruption	December 31, 2010
Date of sterile 0.2 µm final filtration	January 04, 2011
Volume of monovalent pooled harvest	52,731 mL
Storage conditions of monovalent pooled harvest	2 - 8°C

Tests on monovalent pooled harvest

Identity of neuraminidase (Specification: Positive for A(H1N1) strain)

Method	ELISA
Date of test	January 14, 2011
Result	Positive for A(H1N1) strain

Identity of haemagglutinin (Specification: Positive for A(H1N1) strain)

Method	SRID
Date of test	January 13, 2011
Result	Positive for A(H1N1) strain


Purity (Specification: Evidence of HA bands and absence or traces of NP and M components)

Method	SDS-PAGE, reducing conditions
Date of test	January 12, 2011
Result	Evidence of HA bands and absence or traces of NP and M components

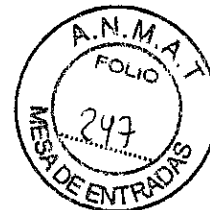
Residual CTAB (Specification: ≤ 12 mcg/60 mcg HA)

Method	Colorimetric
Date of test	January 12, 2011
Result	< 3 mcg/60 mcg HA


Novartis Argentina S.A.
Dr. Luolo Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines Division
Patricia G. Jimenez
Gte. Asesoría Regulatoria
Apoderada





Lot 116321
Page 10 of 51
Prot. 1026/11

Residual barium (Specification: ≤ 1 mcg/mL)

Method	A. A. Spectrophotometry
Date of test	January 07, 2011
Result	< 1 mcg/mL

Residual sodium citrate (Specification: ≤ 1 mg/60 mcg HA)

Method	HPLC
Date of test	January 11, 2011
Result	< 0.01 mg/60 mcg HA

Residual Tween 80 (Specification: ≤ 300 mcg/mL)

Method	HPTLC
Date of test	January 11, 2011
Result	< 300 mcg/mL

Residual ovalbumin (Specification: Report result)

Method	ELISA
Date of test	January 14, 2011
Result	0.10 mcg/60 mcg HA


Residual formaldehyde (Specification: ≤ 1 mcg/60 mcg HA)

Method	Colorimetric
Date of test	January 10, 2011
Result	0.4 mcg/60 mcg HA

Sterility test (Specification: Sterile)

Method	Eur. Ph., membrane filtration
Media	FTM and SCDM
Volume tested	30 mL
Date of test	Jan. 04 - Jan. 18, 2011
Result	Sterile


Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines Production
Ejército de los Andes, Tucumán
Gisela Martínez
Gis. Autor. de Regulaciones
Agoderada





Lot 116321
Page 11 of 51
Prot. 1026/11

Test for inactivation (Specification: Absence of live virus)

Method	Hemagglutination
Date of test	January 07, 2011
Result	Absence of live virus

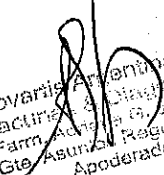
Endotoxin content (Specification: < 100 IU/60 mcg HA)

Method	LAL test
Date of test	January 11, 2011
Result	< 0.4 IU/60 mcg HA

Haemagglutinin antigen content (Specification: Report result)

Method	SRID
Date of test	January 10, 2011
Result	274 mcg HA/mL


Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines & Diagnostics
Farm. Adolfo G. Jimenez
Gte. Asuntos Regulatorios
Apoderada





Lot 116321
Page 12 of 51
Prot. 1026/11

SUMMARY PROTOCOL FOR PRODUCTION AND TESTING

OF INFLUENZA VACCINE (SUB - UNIT)


NYMC X-181 MONOVALENT POOLED HARVEST

Lot 1000/11

Summary

	Page
- Seed virus:	
General information on seed virus	13
Tests on master seed	14
Tests on working seed	14
- Monovalent pooled harvest lot 1000/11:	
Production details of monovalent pooled harvest	16
Tests on monovalent pooled harvest	17


Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines & Biotechnology
Farmacia S. Gimenez
Cte. Asunción, Regulatorias
Apoderada





Lot 116321
Page 14 of 51
Prot. 1026/11

Tests on master seed

Sterility test (Specification: Sterile)

Method	Eur. Ph., direct inoculation
Media	FTM and SCDM
Volume tested	20 mL
Date of test	Dec. 09 – Dec. 23, 2009
Result	Sterile

Tests on working seed

Sterility test (Specification: Sterile)

Method	Eur. Ph., direct inoculation
Media	FTM and SCDM
Volume tested	20 mL
Date of test	Dec. 15 – Dec. 29, 2009
Result	Sterile

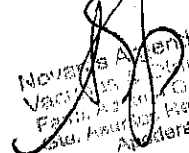
Test for mycoplasma (Specification: Sterile)

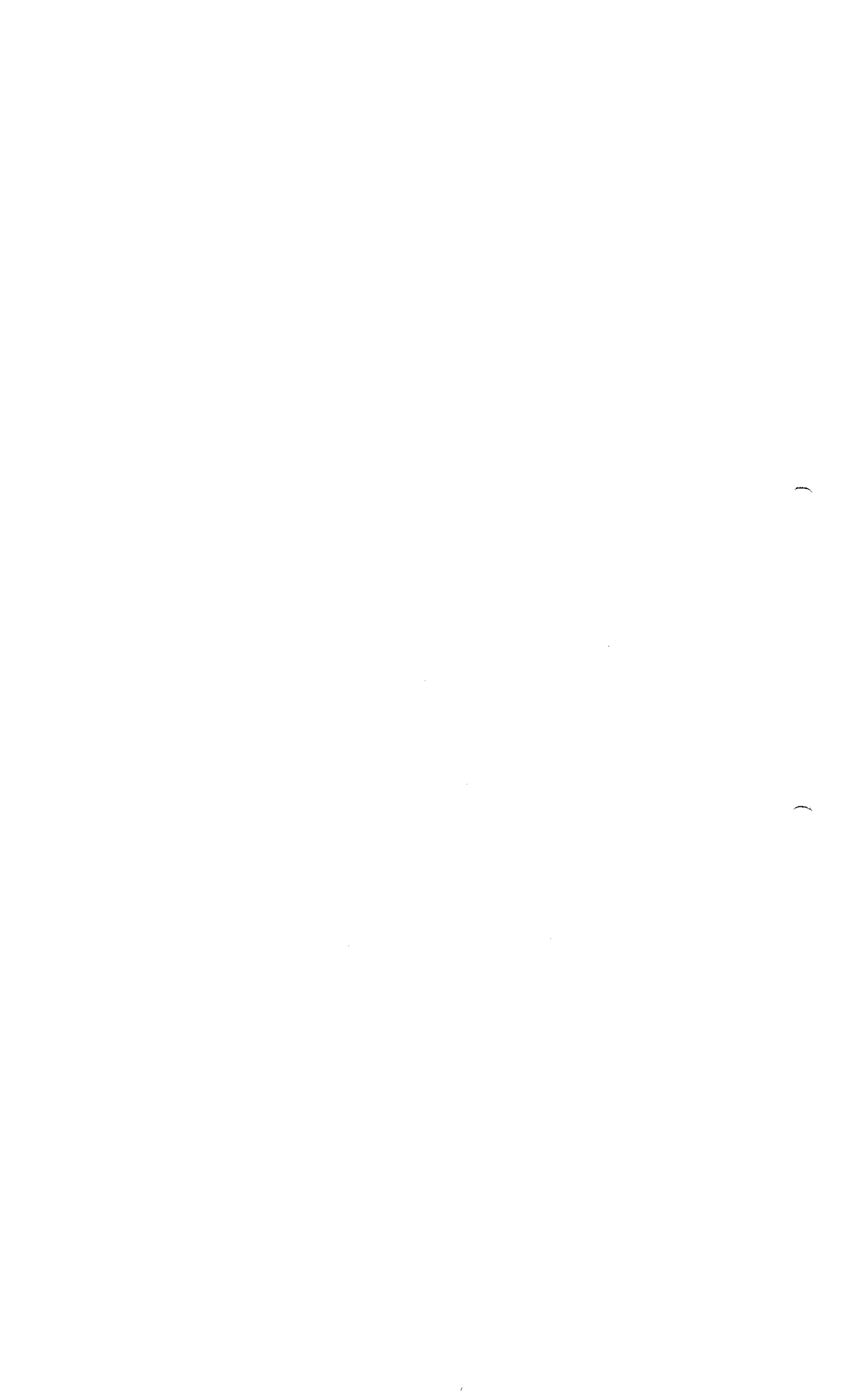
Method	Eur. Ph.
Media	Basic agar / broth and modified 1699 plus agar / broth
Volume tested	8.7 mL
Date of test	Dec. 21, 2009 – Jan. 20, 2010
Result	Sterile

Infectivity titre (Specification: $\geq 10^{5.0}$ EID₅₀/mL)

Method	HA titration
Date of test	December 17, 2009
Result	$5 \times 10^{8.4}$ EID ₅₀ /mL


Novartis Argentina S.A.
Dr. Lucio Jeronimo
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccinas y Productos Químicos
Fac. de Agronomía y G. Jirónes
Sta. Lucía de Bariles, Argentina





Lot 116321
Page 15 of 51
Prot. 1026/11

Identity of neuraminidase (Specification: Positive for A(H1N1) strain)

Method ELISA
Date of test January 25, 2010
Result Positive for A(H1N1) strain

Antigen	NI titre			
	Antiserum			
	[A(H1N1)] Anti-N1 NA X-181/09/152	[A(H1N1)] Anti-N1 NA 1VR-148/08/112	[A(H3N2)] Anti-N2 NA X-175C/08/246	[B] Anti-B NA B/Brisbane/AS397
X-181 Working seed Lot 5WS-H1N1B-01 dil. (10 ⁻⁷) 10 ⁻⁷	444	< 10	< 10	< 10

Identity of haemagglutinin (Specification: Positive for A(H1N1) strain)

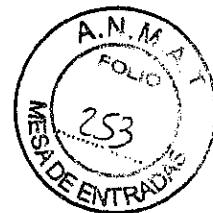
Method Haemagglutination – inhibition test
Date of test February 09, 2010
Result Positive for A(H1N1) strain

Antigen	HI titre		
	Antiserum		
	[A(H1N1)] X-181/09/152	[A(H3N2)] X-175C/08/246	[B] B/Brisbane/AS397IM10001
NYMC X-181 Working seed Lot 5WS-H1N1B-01 dil. (10 ⁻⁷) 10 ⁻⁷	1280	80	40

Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840

Novartis Argentina S.A.
Vaduz, Liechtenstein
Parte de la División de
Control de Medicamentos
Apoderada






Lot 116321
Page 16 of 51
Prot. 1026/11

MONOVALENT POOLED HARVEST LOT 1000/11

Production details of monovalent pooled harvest

Name and address of manufacturer	Novartis Vaccines and Diagnostics Srl Via Fiorentina, 1 - Siena (Italy)
A(H1N1) virus strain	NYMC X-181 (A/California/7/2009 - like virus)
Working seed lot used in manufacture	5WS-H1N1B-01 dil. (10^{-7}) 10^{-7}
Date of inoculation:	
Monovalent lot : 100/11	January 06, 2011
Monovalent lot : 101/11	January 07, 2011
Monovalent lot : 102/11	January 08, 2011
Added antibiotics	Kanamycin sulphate and neomycin sulphate
Date of harvesting:	
Monovalent lot : 100/11	January 10, 2011
Monovalent lot : 101/11	January 11, 2011
Monovalent lot : 102/11	January 12, 2011
Method of inactivation	Treatment with formaldehyde
Date of inactivation:	
Monovalent lot : 100/11	January 10, 2011
Monovalent lot : 101/11	January 11, 2011
Monovalent lot : 102/11	January 12, 2011
Concentration/purification procedure	Continuous zonal centrifugation in sucrose gradient, adsorption with barium sulphate and elution with sodium citrate solution


Novartis Argentina S.A.
Dr. Lucio Jeroncio
Director Técnico
MN 14840


Novartis Argentina S.A.
Vaccines and Diagnostics
Farm. Adh. C. Jimenez
Gte. Asuntos Regulatorios
Apoderada

