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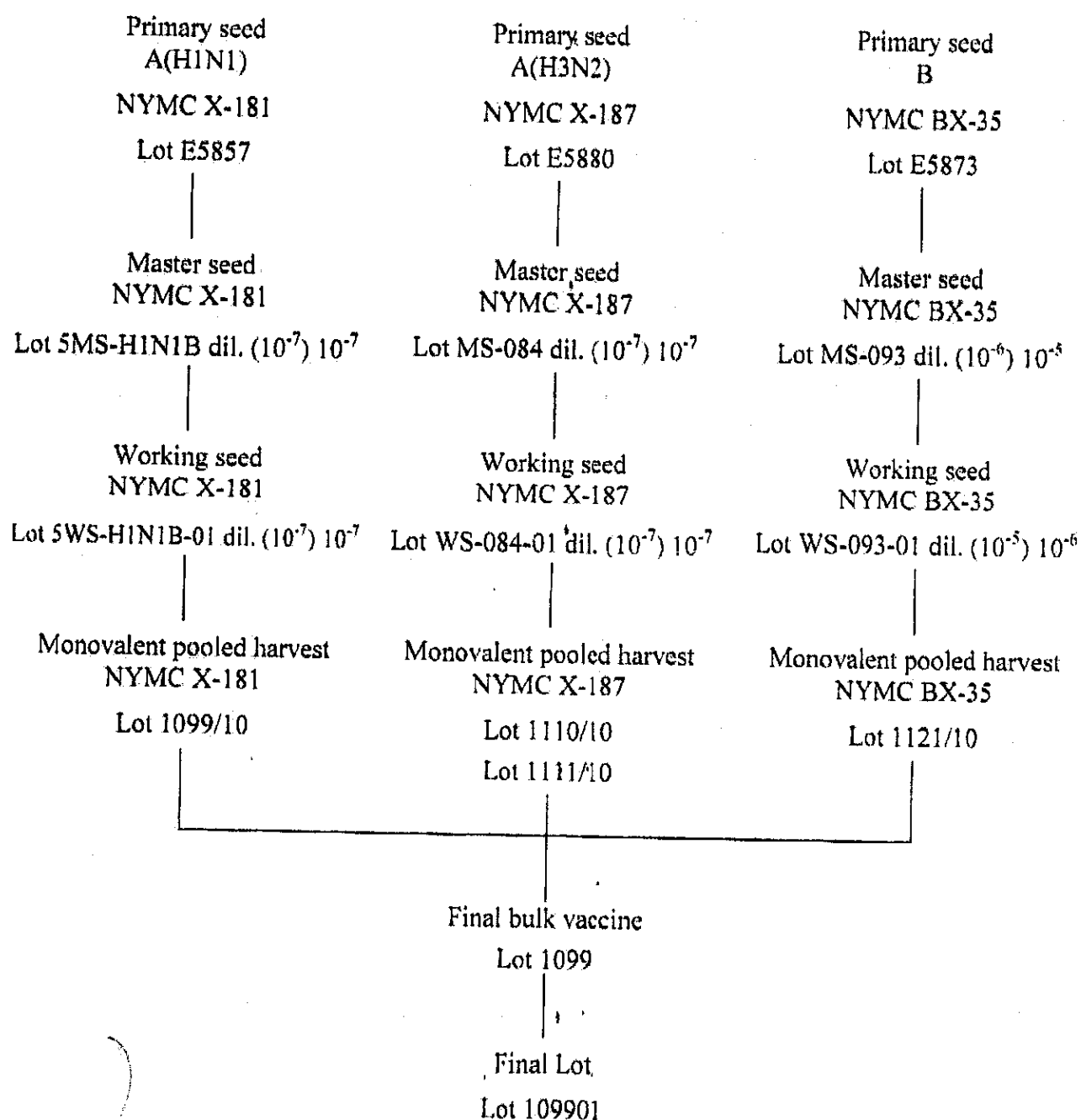
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PRODUCTION PLAN



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SUMMARY PROTOCOL FOR PRODUCTION AND TESTING

OF INFLUENZA VACCINE (SUB - UNIT)

NYMC X-181 MONOVALENT POOLED HARVEST

Lot 1099/10

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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

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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

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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 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 SWS-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 SWS-H1N1B-01 dil. (10 ⁻⁷) 10 ⁻⁷	1280	80	40

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MONOVALENT POOLED HARVEST LOT 1099/10

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 : 327/10	October 19, 2010
Monovalent lot : 328/10	October 20, 2010
Added antibiotics	Kanamycin sulphate and neomycin sulphate
Date of harvesting:	
Monovalent lot : 327/10	October 23, 2010
Monovalent lot : 328/10	October 24, 2010
Method of inactivation	Treatment with formaldehyde
Date of inactivation:	
Monovalent lot : 327/10	October 23, 2010
Monovalent lot : 328/10	October 24, 2010
Concentration/purification procedure	Continuous zonal centrifugation in sucrose gradient, adsorption with barium sulphate and elution with sodium citrate solution

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Date of pooling of monovalent lots	October 27, 2010
Method of disruption	Treatment with Tween 80 and CTAB
Date of disruption	October 30, 2010
Date of sterile 0.2 µm final filtration	November 03, 2010
Volume of monovalent pooled harvest	50,531 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	November 09, 2010
Result	Positive for A(H1N1) strain

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

Method	SRID
Date of test	November 16, 2010
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	November 18, 2010
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	November 11, 2010
Result	< 0.4 mcg/60 mcg HA

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Residual barium (Specification: ≤ 1 mcg/mL)

Method	A. A. Spectrophotometry
Date of test	November 09, 2010
Result	< 1 mcg/mL

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

Method	HPLC
Date of test	November 08, 2010
Result	< 0.01 mg/60 mcg HA

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

Method	HPTLC
Date of test	November 08, 2010
Result	< 300 mcg/mL

Residual ovalbumin (Specification: Report result)

Method	ELISA
Date of test	November 12, 2010
Result	0.08 mcg/60 mcg HA

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

Method	Colorimetric
Date of test	November 11, 2010
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	Nov. 03 – Nov. 17, 2010
Result	Sterile

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Test for inactivation (Specification: Absence of live virus)

Method	Hemagglutination
Date of test	November 05, 2010
Result	Absence of live virus

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

Method	LAL test
Date of test	November 08, 2010
Result	< 0.4 IU/60 mcg HA

Haemagglutinin antigen content (Specification: Report result)

Method	SRID
Date of test	November 05, 2010
Result	293 mcg HA/mL



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**SUMMARY PROTOCOL FOR PRODUCTION AND TESTING
OF INFLUENZA VACCINE (SUB - UNIT)
NYMC X-187 MONOVALENT POOLED HARVEST**

Lot 1110/10

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SEED VIRUS

General information on seed virus

Name and address of manufacturer	Novartis Vaccines and Diagnostics Srl Via Fiorentina, 1 - Siena (Italy)
A(H3N2) virus strain	NYMC X-187 (A/Perth/16/2009 - like virus)
Primary seed lot	E5880
Source of primary seed	New York Medical College Valhalla, New York, USA
Date of receipt of primary seed	January 28, 2010
Number of passage of primary seed on receipt	7
Comment	None
Storage conditions of primary seed	-80 ± 10°C
Master seed lot	MS-084 dil. (10 ⁻⁷) 10 ⁻⁷
Date of manufacture of master seed	February 19, 2010
Number of passages from primary seed to master seed	3
Storage conditions of master seed	-80 ± 10°C
Working seed lot	WS-084-01 dil. (10 ⁻⁷) 10 ⁻⁷
Date of manufacture of working seed	February 23, 2010
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

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Tests on master seed

Sterility test (Specification: Sterile)

Method	Eur. Ph., direct inoculation
Media	FTM and SCDM
Volume tested	20 mL
Date of test	Feb. 22 – Mar. 08, 2010
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	Feb. 23 – Mar. 09, 2010
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	Mar. 05 – Apr. 02, 2010
Result	Sterile

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

Method	HA titration
Date of test	February 26, 2010
Result	$5 \times 10^{7.5}$ EID ₅₀ /mL

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Identity of neuraminidase (Specification: Positive for A(H3N2) strain)

Method ELISA
Date of test May 28, 2010
Result Positive for A(H3N2) strain

NI titre			
Antigen	Antiserum		
	[A(H1N1)] Anti-N1 NA A/California/7/2009 09/152	[A(H3N2)] Anti-N2 NA A/Perth/16/2009 09/270	[B] Anti-B NA B/Brisbane/60/2008 08/354
NYMC X-187 Working seed Lot WS-084-01 dil. (10 ⁻⁷) 10 ⁻⁷	< 10	161	21

Identity of haemagglutinin (Specification: Positive for A(H3N2) strain)

Method Haemagglutination – inhibition test
Date of test May 28, 2010
Result Positive for A(H3N2) strain

HI titre			
Antigen	Antiserum		
	[A(H3N2)] X-175C/08/246	[A(H3N2)] X-187/09/270	[B] B/Brisbane/60/2008 08/354
NYMC X-187 Working seed Lot WS-084-01 dil. (10 ⁻⁷) 10 ⁻⁷	320	2560	80

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Date of pooling of monovalent lots	November 22, 2010
Method of disruption	Treatment with Tween 80 and CTAB
Date of disruption	November 25, 2010
Date of sterile 0.2 µm final filtration	December 02, 2010
Volume of monovalent pooled harvest	71,031 mL
Storage conditions of monovalent pooled harvest	2 - 8°C

Tests on monovalent pooled harvest

Identity of neuraminidase (Specification: Positive for A(H3N2) strain)

Method	ELISA
Date of test	December 13, 2010
Result	Positive for A(H3N2) strain

Identity of haemagglutinin (Specification: Positive for A(H3N2) strain)

Method	SRID
Date of test	December 16, 2010
Result	Positive for A(H3N2) strain

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

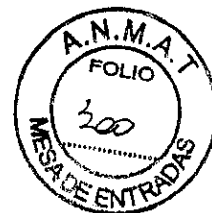
Method	SDS-PAGE, reducing conditions
Date of test	December 16, 2010
Result	Evidence of HA bands and absence or traces of NP and M components

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

Method	Colorimetric
Date of test	December 16, 2010
Result	1, mcg/60 mcg HA

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Residual barium (Specification: ≤ 1 mcg/mL)

Method	A. A. Spectrophotometry
Date of test	December 13, 2010
Result	< 1 mcg/mL

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

Method	HPLC
Date of test	December 09, 2010
Result	< 0.01 mg/60 mcg HA

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

Method	HPTLC
Date of test	December 06, 2010
Result	≤ 300 mcg/mL

Residual ovalbumin (Specification: Report result)

Method	ELISA
Date of test	December 09, 2010
Result	0.03 mcg/60 mcg HA

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

Method	Colorimetric
Date of test	December 13, 2010
Result	0.3 mcg/60 mcg HA

Sterility test (Specification: Sterile)

Method	Eur. Ph., membrane filtration
Media	FTM and SCDM
Volume tested	30 mL
Date of test	Dec. 02 – Dec. 16, 2010
Result	Sterile

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Test for inactivation (Specification: Absence of live virus)


Method	Hemagglutination
Date of test	December 03, 2010
Result	Absence of live virus

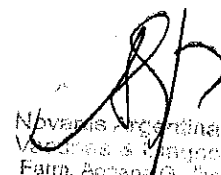
Endotoxin content (Specification: < 100 IU/60 mcg HA)

Method	LAL test
Date of test	December 09, 2010
Result	< 0.3 IU/60 mcg HA

Haemagglutinin antigen content (Specification: Report result)

Method	SRID
Date of test	December 09, 2010
Result	396 mcg HA/mL


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