SUMMARY

An *in vitro* biocompatibility study, based on the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 5: Tests for Cytotoxicity: *in vitro* Methods guidelines, was conducted on the test article, 1816 Gray, to determine the potential for cytotoxicity. A single extract of the test article was prepared using single strength Minimum Essential Medium supplemented with 5% serum and 2% antibiotics (1X MEM). This test extract was placed onto three separate confluent monolayers of L-929 mouse fibroblast cells propagated in 5% CO_2. Three separate monolayers were prepared for the reagent control, negative control and for the positive control. All monolayers were incubated at 37°C in the presence of 5% CO_2 for 48 hours. The monolayer in the test, reagent control, negative control and positive control wells was examined microscopically at 48 hours to determine any change in cell morphology.

Under the conditions of this study, the 1X MEM test extract showed no evidence of causing cell lysis or toxicity. The 1X MEM test extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity). The reagent control, negative control and the positive control performed as anticipated.

Study and Supervisory Personnel:

Michelle Weingate-Furiate, BA
Anthony M. Jackson, BA
Jan L. Koenker, BS, MS
Ryan S. Webb, BS
Jennifer N. Moritz, BA
Laura L. Tasse, BS, ALAT
Suzanne E. Brimacombe
Claire E. Chmura, B.S

Approved by:

Cherise M. McCoy for
Joshua D. Moninger, BS
Technical Reviewer

28 Oct 02
Date Completed

MERCK SHARP & DOHME ARG. Inc.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

/dt
MS

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Affiliates: France • Germany • Israel • Taiwan • United Kingdom

INTRODUCTION

The test article identified below was extracted, and the extract was subjected to an *in vitro* cytotoxicity study for biocompatibility based on the requirements of the International Organization for Standardization 10993: Biological Evaluation of Medical Devices, Part 5: Tests for Cytotoxicity: *in vitro* Methods. The test was performed to determine whether leachables extracted from the material would cause cytotoxicity. The test article was received on January 18, 2002. The cells were first exposed to the extract on January 22, 2002, and the observations were concluded on January 24, 2002.

MATERIALS

The sample provided by the sponsor was identified and handled as follows:

Test Article:	1816 Gray
Identification No.:	1816 Gray
Storage Conditions:	Room temperature
Extraction Vehicle:	Single strength Minimum Essential Medium supplemented with 5% serum and 2% antibiotics (1X MEM)
Test Article Preparation:	Based on an elastomeric ratio of 25 cm^2:20 ml, a 31.5 cm^2 portion of the test article was covered with 25 ml of 1X MEM. A single preparation was extracted at 37°C for 24 hours.
Negative Control Preparation:	High density polyethylene was used as the negative control. Based on the USP ratio of 60 cm^2:20 ml, a single 30.8 cm^2 portion of the control material was covered with 10 ml of 1X MEM. The preparation was subjected to the extraction conditions previously described for the test article.
Reagent Control Preparation:	A single aliquot of 1X MEM without test material was subjected to the same extraction conditions as described for the test article.
Positive Control Preparation:	The current NAMSA positive control, tin stabilized polyvinylchloride, was used to determine a cytotoxic end-point. Based on the USP ratio of 60 cm^2:20 ml, a single 60.8 cm^2 portion of the control material was covered with 20 ml of 1X MEM and extracted at 37°C for 24 hours. Serial dilutions were prepared (1:2, 1:4, 1:8, 1:16, 1:32) for an end-point titration.
Condition of Extracts:	Test: clear Reagent Control: clear Negative Control: clear Positive Control (undiluted): clear

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METHODS

Test System Management:

L-929, mouse fibroblast cells, (ATCC CCL 1, NCTC Clone 929, of strain L, or equivalent source) were propagated and maintained in open wells containing single strength Minimum Essential Medium supplemented with 5% serum and 2% antibiotics (1X MEM) in a gaseous environment of 5% carbon dioxide (CO_2). For this study, 10 cm^2 wells were seeded, labeled with passage number and date, and incubated at 37°C in 5% CO_2 to obtain confluent monolayers of cells prior to use. Aseptic procedures were used in the handling of the cell cultures following approved NAMSA Standard Operating Procedures.

Experimental Procedure:

Triplicate culture wells were selected which contained a confluent cell monolayer. The growth medium contained in triplicate cultures was replaced with 2 ml of the test extract. Similarly, triplicate cultures were replaced with 2 ml of the reagent control, negative control and the undiluted and each titer of the positive control. Each well was labeled with the corresponding lab number, replicate number, dilution (as applicable) and the dosing date. The wells were incubated at 37°C in 5% CO_2 for 48 hours.

Following incubation, the cultures were examined microscopically (100X) to evaluate cellular characteristics and percent lysis.

Evaluation Criteria:

The confluency of the monolayer was recorded as (+) if present and (-) if absent. In addition, the color of the test medium was observed and compared to the negative control medium. A color shift toward yellow was associated with an acidic pH range and a color shift toward magenta to purple was associated with an alkaline pH range. Each culture well was evaluated for percent lysis and cellular characteristics using the following criteria:

Grade	Reactivity	Observations	
0	None	Discrete intracytoplasmic granules	No lysis
1	Slight	Not more than 20% of the cells are round, loosely attached, and without intracytoplasmic granules	Not more than 20% lysis
2	Mild	Not more than 50% of the cells are round and devoid of intracytoplasmic granules	Not more than 50% lysis
3	Moderate	Not more than 70% of the cell monolayer contains rounded cells	Not more than 70% lysis
4	Severe	Nearly complete destruction of the cell monolayer	Greater than 70% lysis

For the test to be valid, the reagent control and the negative control must have had a reactivity of none (grade 0) and the positive control must have been a grade 3 or 4. The test sample met the requirements of the test if the biological response was less than or equal to grade 2 (mild). The test would have been repeated if the controls did not perform as anticipated and/or if all three test wells did not yield the same conclusion.

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A.N.M.A.T.
FOLIO
102
PASA DE ENTRADA

RESULTS

See Table I for results.

pH Observation: The test medium was similar to the negative control medium at 48 hours.

Results and conclusions apply only to the test article tested. No further evaluation of these results is made by NAMSA. Any extrapolation of these data to other samples is the responsibility of the sponsor. All procedures were conducted in conformance with good laboratory practice and ISO 17025.

CONCLUSION

Under the conditions of this study, the 1X MEM test extract showed no evidence of causing cell lysis or toxicity. The 1X MEM test extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity). The reagent control, negative control and the positive control performed as anticipated.

RECORD STORAGE

All raw data pertaining to this study and a copy of the final report are to be retained in designated NAMSA archive files.

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TABLE I

REACTIVITY GRADES FOR ELUTION TESTING

Well	Confluent Monolayer	Percent Rounding	Percent Cells Without Intracytoplasmic Granules	Percent Lysis	Grade	Reactivity
Test (1A)	(+)	0	0	0	0	None
Test (1B)	(+)	0	0	0	0	None
Test (1C)	(+)	0	0	0	0	None
Negative Control (1A)	(+)	0	0	0	0	None
Negative Control (1B)	(+)	0	0	0	0	None
Negative Control (1C)	(+)	0	0	0	0	None
Reagent Control (1A)	(+)	0	0	0	0	None
Reagent Control (1B)	(+)	0	0	0	0	None
Reagent Control (1C)	(+)	0	0	0	0	None
Positive Control (1A) 1:4 Dilution	(-)	100	100	100	4	Severe
Positive Control (1B) 1:4 Dilution	(-)	90	90	90	4	Severe
Positive Control (1C) 1:4 Dilution	(-)	90	90	90	4	Severe

(+) = Present (-) = Absent

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2261 Tracy Road - Northwood, Ohio 43619-1397 - Phone 419/666-9455

1816 Gray FC
Attachment 7

A.N.M.A.T. FOLIO 014 MESA DE ENTRADAS

LAB NO. 88T-04942-00
P.O.NO. TC-80344-15TS STAT
LOT NO. N/S

THE WEST COMPANY
TECHNICAL CENTER, ROUTE 113
PHOENIXVILLE, PA 19460

ATTN: LYNN MORABITO

CYTOTOXICITY - MEM ELUTION - MT023

Material(s): 1816 Gray PURCOAT®

Sample Size Used: 23.6 sq. cm (2.6 grams)

Procedure: A monolayer of L-929 Mouse Fibroblast cells was grown to confluency and exposed to an extract of the test sample prepared by placing the sample material in 19 ml of Minimum Essential Medium (Eagle) and bovine serum (5%) and extracting at 37 degrees C for 24 hours. An MEM aliquot was used as a negative control. After exposure to the extract, the cells were examined microscopically for cytotoxic effect (CTE). Presence (+) or absence (-) of a confluent monolayer, intracellular granulation, cellular swelling and crenation and the percentage of cellular lysis were recorded.

CTE was scored as either Nontoxic(N), Intermediate(I) or Toxic(T).

N = Indicates a negative or nontoxic response.

I = Indicates an intermediate response, a subjective assessment of the extent of cellular response.

T = Indicates a positive or toxic response consisting of greater than 50% cell death.

Results:

	Confluent Monolayer	Intracellular Granulation	Swelling	Crenation	% Lysis	CTE Score
24 HOURS						
Test Extract	(+)	(-)	(-)	(-)	0	N
Negative Control	(+)	(-)	(-)	(-)	0	N
48 HOURS						
Test Extract	(+)	(-)	(-)	(-)	0	N
Negative Control	(+)	(-)	(-)	(-)	0	N
72 HOURS						
Test Extract	(+)	(-)	(-)	(-)	0	N
Negative Control	(+)	(-)	(-)	(-)	0	N

Positive control, T-6500-5-1, was toxic at a dilution of 1:2 at 24 hours.

Conclusion: Nontoxic

Comments:

Date Initiated:4-15-88 Date Terminated:4-19-88 Media Lot#:4-12-88

MERCK SHARP & DOHME ARG. INC.
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DIRECTOR TECNICO
MATRICULA NACIONAL 15436

par Completed 4-19-88 Tech. BH/LN Approved Martha Quarleda MT023-100

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TU012-500

Lab No. 02T 00878 00
P.O. No. R9AKURU174-3

WENDY MARQUARDT
WEST PHARMACEUTICAL SERVICES
101 GORDON DRIVE
PO BOX 645
LIONVILLE, PA 19341

ID No. 1816 Gray

USP SYSTEMIC TOXICITY STUDY IN THE MOUSE

Test Article: 1816 Gray

The test article was received on 1-18-02.

Preparation: Based on an elastomeric ratio of 25 cm^2:20 ml, a 31.5 cm^2 portion of the test article was covered with 25 ml of the vehicle. The test article was extracted in SC and CSO at 121°C for 1 hour. The extraction vehicles without test article were similarly prepared to serve as control blanks.

Condition of Extracts:

	Test	Control
SC:	clear with particulates*	clear
CSO:	cloudy	clear

*The test extract was filtered with a 0.8 µm filter disc to yield a clear, particulate free extract.

Experimental Procedure: Five, healthy, previously unused albino mice ranging in body weight from 17 to 19 grams were selected for each test extract and each corresponding control blank. The animals were identified by ear punch and group housed in stainless steel suspended cages. Animals received a commercial rodent feed on a daily basis and tap water was freely available.

Each animal was injected with the appropriate test extract or control blank at a dose of 50 ml/kg (SC and CSO). The SC was injected by the intravenous (IV) route while the CSO was injected by the intraperitoneal (IP) route. The animals were returned to their cages and observed for adverse reactions immediately after dosing, and at 4, 24, 48 and 72 hours. Body weights were recorded at dosing and following the 72 hour observation.

If, during the observation period, none of the mice treated with the individual test article extract exhibited a significantly greater reaction than the corresponding control mice, the test article met the USP requirements. If two or more mice died, or if abnormal behavior such as convulsions or prostration occurred in two or more mice, or if body weight loss greater than 2 grams occurred in three or more mice, the test sample did not meet the USP test requirements.

Date Prepared: 1-21-02
Date Terminated: 1-27-02

Date Injected: 1-24-02

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MERCK SHARP & DOHME ARG. INC.
Farm. ELIZABET RIVAS
Apoderada

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TU012-500 Lab No. 02T 00878 00

BODY WEIGHT AND MORTALITY DATA:

Extract, Route and Dose	TEST EXTRACT Animal Number	Weight (g) Day 0	Weight (g) Day 3	#Dead/ #Tested	CONTROL BLANK Animal Number	Weight (g) Day 0	Weight (g) Day 3	#Dead/ #Tested
0.9% sodium chloride USP solution (SC) IV; 50 ml/kg	81	18	24	0/5	41	17	23	0/5
	82	18	25		42	18	24	
	83	18	23		43	18	23	
	84	19	26		44	17	21	
	85	18	24		45	19	24	
cottonseed oil, NF (CSO) IP; 50 ml/kg	86	17	20	0/5	46	18	25	0/5
	87	18	22		47	18	23	
	88	18	23		48	18	23	
	89	17	21		49	19	24	
	90	17	20		50	18	24	

CLINICAL OBSERVATIONS:

	TEST EXTRACT SC	TEST EXTRACT CSO	CONTROL BLANK SC	CONTROL BLANK CSO
Immediate	AN	AN	AN	AN
4 Hours	AN	U	AN	U
24 Hours	AN	U	AN	U
48 Hours	AN	U	AN	U
72 Hours	AN	U	AN	AN

AN = Appeared Normal

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319-1397 / 419.666.9455 / Fax 419.666.2954

TU012-500 Lab No. 02T 00878 00

Results: The test animals injected with cottonseed oil, NF appeared ungroomed 4, 24, 48 and 72 hours after dosing. The control animals injected with cottonseed oil, NF appeared ungroomed 4, 24 and 48 hours after dosing. This was considered to be an expected effect due to the unctuous nature of the extract. All other animals appeared clinically normal throughout the study.

The test article extracts would not be considered systemically toxic to the mouse at the prescribed USP dosage. Each test article extract met the USP requirements.

Results and conclusions apply only to the test article tested. No further evaluation of these results is made by NAMSA. Any extrapolation of these data to other samples is the responsibility of the sponsor. All procedures were conducted in conformance with good laboratory practice and ISO 17025.

Record Storage: All raw data pertaining to this study and a copy of the final report are to be retained in designated NAMSA archive files.

Test Facility: NAMSA, 2261 Tracy Road, Northwood, OH 43619-1397.

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

lag Date Completed February 1, 2002 Approved By Joshua D. Moninger, BS

RL

1816 Gray FC
Attachment 9

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TU013-800

Lab No. 02T 00878 00
P.O. No. R9AKURU174-3

WENDY MARQUARDT
WEST PHARMACEUTICAL SERVICES
101 GORDON DRIVE
PO BOX 645
LIONVILLE, PA 19341

ID No. 1816 Gray

USP INTRACUTANEOUS TOXICITY STUDY IN THE RABBIT

Test Article: 1816 Gray

The test article was received on 1-18-02.

Preparation: Based on a ratio of 25 cm^2, a 31.5 cm^2 portion of the test article was covered with 25 ml of the vehicle. The test article was extracted in SC and CSO at 121°C for 1 hour. The extraction vehicles without test article were similarly prepared to serve as control blanks.

Condition of Extracts:

	Test	Control
SC:	clear with particulates	clear
CSO:	clear with particulates	clear

Experimental Procedure: Two healthy New Zealand White rabbits, free of mechanical irritation or trauma that could interfere with the test, were selected for each extract or pair of extracts. Animals were identified by ear tag and housed individually in suspended cages. Animals received a commercial rabbit feed on a daily basis and tap water was freely available. Prior to injection, the fur was closely clipped from the back and from both sides of the spinal column of each rabbit. A 0.2 ml dose of the test article extract was injected intracutaneously into five separate sites on the right side of the back of each animal while 0.2 ml of the control blank was injected into five separate sites on the left side. Injection sites were examined 24, 48 and 72 hours after injection for erythema and edema. The average tissue reaction to the extract of the test article was compared with the control. The requirements of the test were met if the difference was 1.0 or less.

Date Prepared: 1-18-02 Date Injected: 1-23-02
Date Terminated: 1-26-02

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TU013-800

Lab No. 02T 00878 00

Results:

ERYTHEMA (ER)		EDEMA (ED)	
0	No erythema	0	No edema
1	Very slight (barely perceptible)	1	Very slight (barely perceptible)
2	Well-defined (pink)	2	Slight (edges of area well-defined by definite swelling)
3	Moderate to severe (red)	3	Moderate (raised approximately 1 mm)
4	Severe (beet redness) to slight eschar formation (injuries in depth)	4	Severe (raised more than 1 mm, may extend beyond the area of exposure)

Rabbit Number	Gender	Extract	Scoring Interval											
			24 Hours				48 Hours				72 Hours			
			Test		Control		Test		Control		Test		Control	
			ER	ED	ER	ED	ER	ED	ER	ED	ER	ED	ER	ED
28268	Female	SC	0	0	0	0	0	0	0	0	0	0	0	0
28269	Female	SC	0	0	0	0	0	0	0	0	0	0	0	0
28268	Female	CSO	1	1	1	0	1	0	1	0	1	0	1	0
28269	Female	CSO	1	0	0	0	1	0	1	0	1	0	1	0

ER = Erythema
ED = Edema

SC = 0.9% sodium chloride USP solution
CSO = cottonseed oil, NF

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TU013-800 Lab No. 02T 00878 00

Extract	Average Test (-) Average Control = Difference = Assessment			
SC	0.0	0.0	0.0	Passed
CSO	0.6	0.4	0.2	Passed

Results and conclusions apply only to the test article tested. No further evaluation of these results is made by NAMSA. Any extrapolation of these data to other samples is the responsibility of the sponsor. All procedures were conducted in conformance with good laboratory practice and ISO 17025.

Record Storage: All raw data pertaining to this study and a copy of the final report are to be retained in designated NAMSA archive files.

Test Facility: NAMSA, 2261 Tracy Road, Northwood, OH 43619-1397.

MERCK SHARP & DOHME Arg. Inc.
Farm. Sebastián Dario Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

rl
LAG

Date Completed February 4, 2002 Approved By
Joshua D. Moninger, BS

MERCK SHARP & DOHME Argentina Inc.

A.N.M.A.T. FOLIO 121 MESA DE ENTRADAS

Declaración Jurada

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

A.N.M.A.T. FOLIO 1022 MESA DE ENTRADAS

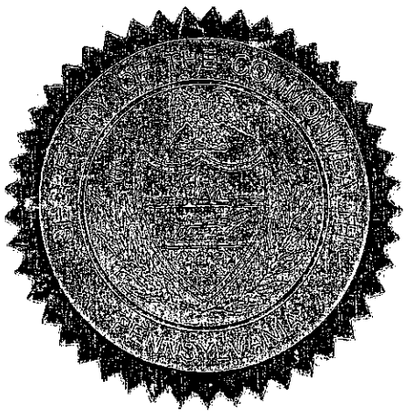
PABLO M. HORTIGUERA
NOTARIO

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country : United States of America
2. This public document has been signed by HEATHER L SINSEL
3. acting in the capacity of NOTARY PUBLIC
4. bears the seal/stamp HEATHER L SINSEL , NOTARY PUBLIC, MONTGOMERY COUNTY, COMMONWEALTH OE PENNSYLVANIA

Certified

5. a arrisburg, Pennsylvania
6. The 13th day of July, 2011
7. by Carol Aichele, Secretary of the Commonwealth of Pennsylvania
8. No: 201124036
9. Seal/Stamp
10. Signature



Carol Aichele

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This Apostille does not certify the content of the document for which it was issued.

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Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

MERCK
Manufacturing Division

10-June-2011

DECLARATION

ZOSTAVAX™ (Zoster Vaccine Live [Oka/Merck])

Dear Sir or Madam:

Merck, Sharpe and Dohme, Corp. (Merck) certifies that the stoppers used to manufacture ZOSTAVAX™ (Zoster Vaccine Live [Oka/Merck]) are compliant with the testing requirements described in the United States Pharmacopeia (USP) chemical test chapter *Elastomeric Closures for Injection, Biological Tests* <381>. The stoppers (1816 Gray) are manufactured by West Pharmaceutical Services (West). The elastomeric compound used to manufacture the stoppers was tested in accordance with the USP for *in vitro* and *in vivo* toxicity by NAMSA Laboratory, a subcontractor of West. The elastomeric compound was tested for *in vitro* biocompatibility based on International Organization for Standardization (ISO) 10993: Biological Evaluation of Medical Devices, Part 5: Tests for Cytotoxicity: *in vitro* methods guidelines. ISO 10993 is equivalent to USP general test chapter *Biological Reactivity Tests, In Vitro* <87>, a required test within USP <381>. Merck reviewed the *In Vitro* <87> testing results provided by West/NAMSA and the data were satisfactory. In addition, the elastomeric compound was tested for USP systemic toxicity in mouse and USP intracutaneous toxicity in rabbit according to USP general test chapter *Biological Reactivity Tests, In Vivo* <88>. Merck reviewed the *In Vitro* <88> testing results provided by West/NAMSA and the data were satisfactory.

Merck does not have a contract with West that includes the use of the NAMSA testing laboratory. Merck has reviewed West's GMP standard operating procedures and has concluded they adhere to relevant industry guidelines and are acceptable to Merck.

Sincerely,

Scott Wendler

Scott Wendler
Sr. Regulatory Coordinator, Vaccines CMC

Commonwealth of Pennsylvania SS:
County of
On this, the 10 day of June 2011
before me a notary public, the undersigned
officer, personally appeared Scott Wendler
known to me (or satisfactorily proven) to be the
person whose name is subscribed to the within
instrument, and acknowledged that he executed
The same for the purposes therein contained.
In witness whereof, I hereunto set my hand and
official seal.

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Heather L. Sinsel, Notary Public
Upper Gwynedd Twp., Montgomery County
My Commission Expires Dec. 19, 2011
Member, Pennsylvania Association of Notaries

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

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925

COLEGIO DE TRADUCTORES PUBLICOS
DE LA CIUDAD DE BUENOS AIRES

República Argentina — Ley 20.305

ACTUACION PROFESIONAL

A.N.M.A.T. FOLIO 1024 MESA DE ENTRADAS

PABLO M. IRURZUN GUERRA
NOTARIO

TRADUCCIÓN PÚBLICA: ZOSTAVAX™ - DECLARACIÓN ----------

APOSTILLA (Convención de La Haya del 5 de octubre de 1961) -----

1. País: Estados Unidos de América ----------

2. Este documento público ha sido firmado por HEATHER L. SINSEL

3. quien actuó en su carácter de Escribana Pública ----------

4. lleva el sello de HEATHER L. SINSEL, Escribana Pública, Montgomery County, Mancomunidad de Pensilvania ----------

Certificado ----------

5. en Harrisburg, Pensilvania 6. el día 13 de julio de 2011 -------

7. por Carol Aichele, Secretario de la Mancomunidad de Pensilvania-

8. Nº: 201124036 ----------

9. Sello: Se observa adherida una oblea dorada en la cual se lee: Secretario de la Mancomunidad – Pensilvania ----------

10. Firma: Se observa una firma que dice Carol Aichele. Abajo, aclarado figura: Carol Aichele. ----------

Esta Apostilla certifica únicamente la autenticidad de la firma y el carácter de la persona que firmó el documento público, y, cuando corresponde, la identidad del sello que lleva el documento público. ----------

Esta Apostilla no certifica el contenido del documento para el cual se emitió. ----------

Esta Apostilla no es válida para ser utilizada dentro de los Estados Unidos de América, sus territorios o posesiones. -----

En una hoja con membrete de Merck Manufacturing Division, se lee lo siguiente: ----------

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

10 de junio de 2011. ----------

DECLARACIÓN – ZOSTAVAX™ (Vacuna con virus vivos [Oka/Merck] del herpes Zoster) ----------

De nuestra consideración: ----------

Merck, Sharpe and Dohme, Corp (Merck) certifica que los tapones empleados para elaborar ZOSTAVAX™ (Vacuna con virus vivos [Oka/Merck] del herpes Zoster) cumplen con los requisitos de análisis descritos en el capítulo de análisis clínicos de la Farmacopea de Estados Unidos (USP) *Cierres Elastoméricos para Inyectables, Análisis Biológicos* <381>. Los tapones (1816 Gris) son fabricados por West Pharmaceutical Services (West). El compuesto elastómero utilizado para fabricar los tapones fue analizado por NAMSA Laboratory, un subcontratista de West, de acuerdo con la USP para establecer la toxicidad *in vitro* e *in vivo*. El compuesto elastómero se analizó para establecer la biocompatibilidad *In vitro* sobre la base de la norma 10993 de la Organización Internacional de Estandarización (ISO): Evaluación Biológica de Dispositivos Médicos, Parte 5: Pruebas de citotoxicidad: pautas para los métodos *in vitro*. La ISO 10993 es equivalente al capítulo de análisis general de la USP *Pruebas de Reactividad Biológica, In Vitro* <87>, una prueba exigida dentro de la USP <381>. Merck revisó los resultados de las pruebas *In Vitro* <87> proporcionados por West/ NAMSA, y los datos fueron satisfactorios. Además, el compuesto elastomérico fue analizado para establecer la toxicidad sistémica según la Farmacopea de EE.UU. en ratones, y la toxicidad intracutánea en

COLEGIO DE TRADUCTORES PUBLICOS
DE LA CIUDAD DE BUENOS AIRES

República Argentina — Ley 20.305

ACTUACION PROFESIONAL

A.N.M.A.T. FOLIO 025 MESA DE ENTRADAS

PABLO M. HORTIGUERA NOTARIO

conejos, de acuerdo con el capítulo de análisis generales de la USP *Pruebas de Reactividad Biológica, In Vivo* <88>. Merck revisó los resultados de las pruebas *In Vitro* <88> proporcionados por West/ NAMSA, y los datos fueron satisfactorios. ----------

Merck no tiene un contrato con West que incluya el uso del laboratorio de análisis NAMSA. Merck revisó los procedimientos operativos estándar de Buenas Prácticas Clínicas de West, y llegó a la conclusión que cumplen con las pautas relevantes de la industria y son aceptables para Merck. ----------

Atentamente, ----------

Se observa una firma que dice Scott Wendler. Abajo de la firma se lee aclarado: Scott Wendler – Coordinador de Asuntos Regulatorios Senior, Vacunas CMC. ----------

Sobre la derecha se observa un sello en tinta negra en el cual se lee: Mancomunidad de Pensilvania. Declaración Jurada ----------

Condado de (en blanco) ----------

El 10 de junio de 2011, ante mí, escribana pública, compareció en persona el directivo que suscribe, conocido por mí como (o quien comprobó ser) la persona cuyo nombre figura suscrito en este instrumento, y reconoció haberlo formalizado a los fines que en él figuran. En fe de lo cual, firmo y coloco mi sello oficial. ----------

Sigue luego un sello rectangular, también en tinta negra, en el cual se lee: Mancomunidad de Pensilvania – Sello notarial – Heather L. Sinsel, Escribana Pública – Upper Gwynedd Twp., Condado de Montgomery – Mi comisión vence el 19 de diciembre de 2011. ------

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

Miembro del Colegio de Escribanos de Pensilvania. ----------

ES TRADUCCIÓN FIEL al idioma español, del documento adjunto en idioma inglés y francés, que tengo ante mí, y al cual me remito en Buenos Aires, a los veintitrés días del mes de julio de 2011. ------

EL COLEGIO DE TRADUCTORES PUBLICOS
DE LA CIUDAD DE BUENOS AIRES
Corresponde a la Legalización
Nº 61485/11
WALTER FABIAN GOSTANZI

BEATRIZ BARROSO
TRADUCTORA PUBLICA
INGLES T° VII F° 186 CAP. FED.
FRANCES T° IX F° 480 CAP. FED.
INSCRIP. CTPCBA N° 1223

84317 61485
26/07/2011

COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES

REPÚBLICA ARGENTINA
LEY 20.305

A.N.M.A.T. FOLIO 1026 MESA DE ENTRADAS

LEGALIZACIÓN

Por la presente, el *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES*, en virtud de la facultad que le confiere el artículo 10, inc.d) de la ley 20.305, certifica únicamente que firma y el sello que aparecen en la traducción adjunta concuerdan con los correspondientes a/la Traductor/a Público/a BARROSO, BEATRIZ

que obran en los registros de esta institución en el folio 480 del Tomo 9 en el idioma FRANCES
166 7 en el idioma INGLES

Legalización Número: 61485

Buenos Aires, 26/07/2011

CPCIBA

Julio 20

GUSTAVO A. SIGALOFF
DTO. DE LEGALIZACIONES
COLEGIO DE TRADUCTORES PUBLICOS
DE LA CIUDAD DE BUENOS AIRES

ESTA LEGALIZACIÓN NO SE CONSIDERARÁ VÁLIDA SIN EL CORRESPONDIENTE TIMBRADO DE CONTROL EN LA ÚLTIMA HOJA DE LA TRADUCCIÓN ADJUNTA

Control Interno: 8431761485

Av. Corrientes 1834 - C1045AAN - Ciudad Autónoma de Buenos Aires - 4373-7173 y líneas rotativas

MERCK SHARP & DOHME ARG.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15438

THE *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Sworn translators association of the city of Buenos Aires) pursuant to 20305 act, section 10, subsection d, hereby certifies that the signature and the seal on the translation attached hereto match the signature and seal of the Sworn Translator (Traductor Público) in our files.

THIS CERTIFICATION IS NOT VALID WITHOUT THE PERTINENT CONTROL STAMP ON THE LAST PAGE OF THE TRANSLATION ATTACHED HERETO.

Vu par le *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Ordre de Traducteurs Officiels de la ville de Buenos Aires), en vertu des attributions que lui ont été accordées par l'article 10, alinéa d) de la Loi nº 20.305, pour la seule légalisation matérielle de la signature et du sceau du Traductor Público (Traducteur Officiel) apposés sur la traduction du document ci-joint, qui sont conformes à ceux déposés aux archives de cette Institution.

LE TIMBRE APPOSÉ SUR LA DERNIÈRE PAGE DE LA TRADUCTION FERA PREUVE DE LA VALIDITÉ DE LA LÉGALISATION.

Con la presente il *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Collegio dei Traduttori Giurati della Città di Buenos Aires) ai sensi della facoltà conferitagli dall'articolo 10, comma d), della Legge 20.305, CERTIFICA, esclusivamente, la firma ed il timbro del Traductor Público (Traduttore Giurato), apposti in calce alla qui unita traduzione, in conformità alla firma ed al timbro depositati nei propri registri.

LA PRESENTE LEGALIZZAZIONE SARÀ PRIVA DI VALIDITÀ OVE NON VENGA TIMBRATA NELL' ULTIMO FOGLIO DELLA TRADUZIONE.

Através da presente, o *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Colégio de Tradutores Públicos da Cidade de Buenos Aires), no uso de suas atribuições, de conformidade com o artigo 10, alínea "d", da Lei 20.305, certifica unicamente que a assinatura e o carimbo do Traductor Público (Tradutor Público) que subscreve a tradução anexa conferem com a assinatura e o carimbo arquivados nos registros desta instituição.

A PRESENTE LEGALIZAÇÃO SÓ SERÁ CONSIDERADA VÁLIDA COM A CORRESPONDENTE CHANCELA MECÂNICA APOSTA NA ÚLTIMA FOLHA DA TRADUÇÃO

BEGLAUBIGUNG. Der *COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES* (Kammer der Vereidigten Übersetzer der Stadt Buenos Aires), kraft der Befugnisse, die ihr nach Artikel 10, Abs.d) des Gesetzes 20.305 zustehen, bescheinigt hiermit lediglich die Übereinstimmung der Unterschrift und des Siegelabdruckes auf der beigefügten Übersetzung mit der entsprechenden Unterschrift und dem Siegelabdruck des Traductor Público (VereidigtenÜbersetzers), die in den Registern dieser Institution hinterlegt worden sind.

DIESE BEGLAUBIGUNG IST NICHT GÜLTIG OHNE DEN ENTSPRECHENDEN GEBÜHRENSTEMPEL AUF DEM LETZTEN BLATT DER BEIGEFÜGTEN ÜBERSETZUNG.

CERTIFICO QUE LA ATESTACION CORRESPONDIENTE A ESTA FOTOCOPIA SE FORMALIZA EN EL FOLIO DE ACTUACION NOTARIAL Nº E AA 0713 5153

VICENTE LOPEZ PCIA. BS. AS. 1- Agosto - 2011

PABLO M. HORTIGUERA
NOTARIO

CERTIFICACIÓN DE REPRODUCCIONES

EAA07135193

A.N.M.A.T. FOLIO 1027 MESA DE ENTRADAS

CERTIFICO que el documento adjunto que consta de CINCO fojas que llevan mi sello y firma, es copia fiel de su original, que tengo a la vista, doy fe.- Registro número 33 del Distrito de Vicente López. Lugar y fecha: Vicente López, Provincia de Buenos Aires, uno de agosto de dos mil once.-

PABLO M. [illegible]
NOTARIO

MERCK SHARP & DOHME ARG. INC.
Farm. Sebastián Darío Goldentul
DIRECTOR TECNICO
MATRICULA NACIONAL 15436

MESA DE ENTRADAS INAME

Notifíquese al Laboratorio: *MERCK SHARP & DOHME ARGENTINA INC.*

en relación al expediente 1-0047-0000-001896-07-5

presentado en un Formulario 1.2 5

para el producto: ZOSTAVAX

Ie a partir del día de la fecha se suspenden los plazos a los que hace referencia el Decreto 150/92, producido por la ADMINISTRACION NACIONAL DE MEDICAMENTOS, ALIMENTOS y TECNOLOGIA MEDICA.
Dicha suspensión fue solicitada por los siguientes Departamentos del INAME por los motivos que se detallan a continuación:

DEPARTAMENTO DE FARMACOLOGIA
Forma Farmacéutica: POLVO LIOF INYEC [1]
De las Composiciones
CEPA OKA/MERK DE VIRUS VIVO ATENUADO DE VARICELA-ZOSTER 19400,00000 UFP
: Los tests de reactividad biológica aportados datan del año 2002. Remitir tests mas recientes o bien justificar la antiguedad de los mismos.

18 AGO 2011

Lic. MARTA E. SPINETTO
DIRECTORA
Instituto Nacional de Medicamentos

Firma y Sello

DIRECCION INAME

Buenos Aires, 18 de Agosto de 2011

Russi Patricia

Fecha 24/08/2017

INS 14492215

Merck Sharp & Dohme (Argentina) Inc.
Av. Del Libertador 1406/10
B1638BGN Vicente López - Buenos Aires
Tel. (54-11) 4796-8200

1029

MSD

Merck Manufacturing Division

PARA SER AGREGADO AL EXPEDIENTE N° 1-0047-1896-07-5

Buenos Aires, Septiembre de 2011

Señor
Interventor de la Administración Nacional de
Medicamentos, Alimentos y Tecnología Médica
Dr. Carlos A. Chiale
S / D.

ASUNTO: Responder corte.

Registro nuevo Producto: Zostavax

MERCK SHARP & DOHME (ARGENTINA INC.), (Legajo N° 6.312), con domicilio real y legal en Av. Del Libertador 1406/10, Vicente López, Prov. de Buenos Aires, Código 1638, se dirige al Señor Interventor a los efectos de responder al corte realizado.

Por tal motivo, informamos lo siguiente:

La composición de los tapones elastoméricos de Zostavax no ha cambiado desde el año 2002; adicionalmente, no hubo cambios que podrían requerir la realización de tests de reactividad biológica a los ismos. Los datos de biorreactividad del 2002 son los más recientes y todavía aplicables. Se informa además que los tapones elastoméricos de Zostavax cumplen con los requerimientos de evaluación USP.

Sin otro particular y a la espera de una resolución favorable,

12 SEP

Apoderado

06/Sep/2011