

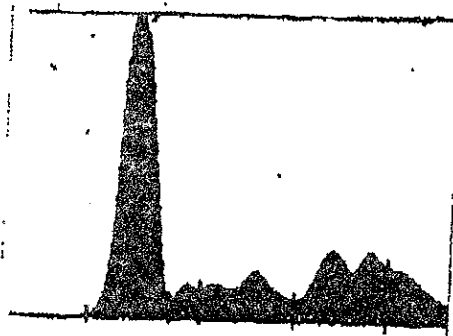


HyClone New Zealand
Omokoroa Farm
441 Old Highway
P.O. Box 058
Tauranga, New Zealand

Product: **DONOR BOVINE SERUM**
Collected and Processed in New Zealand
Custom Filtered for NVI
Catalog#: **SH3A1248.01** Manufacture Date: **OCT/2006**
Lot#: **DRK0265** Expiration Date: **OCT/2011**
Filtration: **0.2 µm Sterile Filtered** Total Batch Volume: **1034.7 L**

ELECTROPHORETIC PROFILE

Electrophoretic Region	%TP
Albumin	50.0
Alpha - 1	3.8
Alpha - 2	13.9
Beta	21.9
Gamma	10.4



Biological Containers • Media • Buffers • Reagents • Serum free media • FCS alternatives • Vitamins

Phone: + 64 7 548 0225
Fax: + 64 7 548 1295

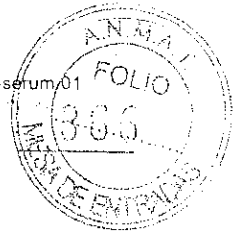
Toll Free: 800-522-5385

Internet: www.hyclone.com
Email: info@hyclone.com

CAIF SA
Dra. Bernarda Belay
Co-Directora Tecnica
M.N. 15.148

CAIF
Compañia Argentina de
Investigaciones Farmacológicas S.A.
Dra. María Bernarda Belay
Acreditada
ONI 29378925





13 Jun 2007 13:22

Nº0971 P. 1/6

05-187-OP-PRO-309 Rev.)



CERTIFICAT D'IRRADIATION N° 95816
BEWIS VAN BESTRALING Nr.
CERTIFICATE OF IRRADIATION N°

STERIGENICS Belgium (Fleurus) s.a. Zoning industriel B-6220 certifie avoir traité dans ses installations par rayonnement gamma (cobalt-60) sur base de l'autorisation d'exploitation délivrée en application de P.A.R. du 12 mars 2002 par l'Agence Fédérale de Contrôle Nucléaire et en conformité avec les normes EN 552 et ISO 11137.

STERIGENICS Belgium (Fleurus) s.a. Zoning industriel B-6220 verklaart door middel van gammastralen (cobalt-60) te hebben behandeld in haar installaties waarvoor een uitbatingvergunning werd bekomen in toepassing van het K.B. van 12 maart 2002 door het Federaal Agentschap voor Nucleaire Controle en overeenkomstig met normen EN 552 en ISO 11137.

STERIGENICS Belgium (Fleurus) s.a. Zoning industriel B-6220 certifies the treatment by gamma irradiation (cobalt-60) at its plant according to the licence delivered in compliance to the Belgian Royal Decree of March 12, 2002 by the Federal Agency for Nuclear Control and in accordance with norms EN 552 and ISO 11137.

Pour le compte de : PERBIO
Voor rekening van :
For the account of :

"Produit maintenu à l'état congelé pendant l'irradiation - Product kept frozen during irradiation"

Les colis suivants : nombre : 56 COLIS DONOR BOVINE SERUM, NZ
De volgende colli : aantal :
Following parcels : quantity :

Réf. STERIGENICS: 8543

Identification suivant déclaration du client : SH3A1244.01/NVI
Identificatie volgens verklaring van de klant : Product Lot N°: DRK0265
Identification following the declaration of the customer : 1006 L

*Bestraling v.o.f.
party (56 colli)
Wol
17/NEC/rooy*

Répartis dans les unités de traitement numérotées : 354826 à 354853
Verdeeld in de genummerde behandelingsenheden :
Divided into the numbered treated units :

Date d'irradiation :
Bestralingsdatum : 10/06/07 Fleurus, le 13 Jun 2007
Irradiation date :

Dose garantie : 27,53 kGy min
Gewaarborgde dosis : 32,06 kGy max
Guaranteed dose of :

[Signature]
A. BOUXIN
Ingénieur Assurance Qualité

[Signature]
P. BERNARDI
Central Quality

STERIGENICS Belgium (Fleurus) S.A.
Zoning Industriële B-6220 Fleurus
www.sterigenics.com 071: 438 71 81 80 84 Fax: +32 71 81 82 82

TIR 05 042042.004 RPM Control Page 1 sur 1
Forma 210-1530298-01
IRAN 8173100002001
Swift code: BSAAB333
Crédit de l'état: 80070-0-228-0-00000-000-01

CAIF SA
Dra. Bernarda Belay
Co-Directora Técnica
M.N. 15.148

CAIF
Compañía Argentina de
Investigaciones Farmacéuticas S.A.
Dra. María Bernarda Belay
Apoderada
DNI 23376925



13. Juin 2007 13:22

Nº0971 P. 2/6

DELIVERY NOT / AFLEVERINGSBON / BON DE LIVRAISON / LIEPERSCHEIN

Parbio Science BVEBA

Shipping Customer: STERGENICS MIR JUMET ZONING INDUSTRIEL FLEURUS B-6220 BELGIUM	Seller Customer: STERGENICS SERVICE ACHATS ZONING INDUSTRIEL FLEURUS B-6220 BELGIUM	Shipping Ref: 040 547837 040 43255 04-JUN-07 NVI (PFR 2.5 MEGARAD) MIR JUMET +32 71810084 +32 71816853	Page: 1/1
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Customer Ref: GRIFFINE Bill No: BEST WAY Billing Date: 04-JUN-07 Billing Amount:	Customer Ref: GRIFFINE Bill No: BE42846264 Payment Terms: NET 30 DAYS	Subject Page: ZNONE Invoice No: SNPT Freight and Labels: Prepay & Add Freight & Ica
--	--	--

Line	Qty	Unit	Lot Number	Expiration Date	Qty Ordered	Dry Shipped	UOM	Weights	Commodity	Description
1.1	1	EA	04000205	30-OCT-11	503	503	EA	2	8002.1089	DONOR BOVINE SERUM, NZ, 2L, CUSTOM FOR NVI
Unit of Measure: EA Expiration Date: 30-OCT-11 Description: production 2.5 Megard. Dry Ice is only required for freight. Total number of boxes										

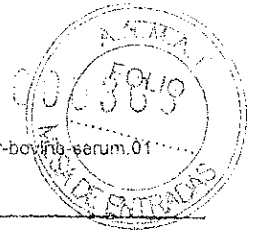
Address: INDUSTRIEZONE M - INDUSTRIELAAN 27 6500 EREMBODESEM - ZAAFT BELGIUM 01452.612-123	Phone/Fax: +32 63 857 104 +32 63 857 431 Cell Number: 0498 059 551	Best Account: BE3 ANELWYSTRANT 27 B-2000 Antw	Bank Account Number: 303-0017062-01
--	---	---	---

CAIF SA
Compañía Belay

Cg-Dirección
M.N. 15.148

CAIF
 Compañía Argentina de
 Investigaciones Farmacéuticas S.A.
 Dra. María Bernadita Belay
 Apodemia
 CUIT 29376924





13. Jun 2007 13:23

Nº0971 P. 3/6

Stergenics FleUTUS Single Dose Sheet (AerODE Vers. 4.3.0b) (Current data)

Sheet ID: S2007/08/13-07
 Operator: Pascal QUERTINMONT
 Mode: Measure (mean BGD)
 Entry: 8843
 Calibration ID: C2007/03/18-00
 Batch (Type): 4034 JN (Sarni - Red Porapak)
 W, L (mm): 840
 Range-L (kGy): 8.0
 Range-H (kGy): 50.0
 Ref. mean BGD: 0.0
 Cur. mean BGD: 0.0
 Ref. UOY (%): 4.0
 Mode of fitting Log(R)=f(Log(D))

RMS of fitting: 1.94 %
 C5 =
 C4 =
 C3 = -0.2058360276342
 C2 = 0.8887478788817
 C1 = 0.2941879304368
 C0 = -0.6732444866888

Measure T? Yes
 Mean T(µm):
 Control mode: Beep-beep
 Standard T:
 Temperature (°C):

NOTE:

Sample-Nº	Position	BGD	Cal	AB2	T (µm)	(A-R)T (µm)	Dose (kGy)	Mean (kGy)	UOY (kGy/µm)	Req-dose (kGy)
3548280				0.802	3080.8	2.6181	30.88		27.8	
3548281				0.784	2780.8	1.8477	27.08		30.1	
3548282				0.875	3890.8	2.2907	38.97		25.7	
3548283				0.768	2768.8	1.6704	27.68		27.5	
3548284				0.758	3068.8	2.4328	27.58		24.3	
3548285				0.746	1860.8	2.4443	23.07		24.0	

S2007/08/13-07 pag 3 de 1/1 *03-15/07-LAB-001 rev. 0

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 Dra. Bernarda Belay
 Co-Directora Técnica

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 Compañía Argentina de
 Investigaciones Farmacéuticas S.A.
 Dra. María Bernarda Belay
 Apoderada
 DNI 29376925



CERTIFICAT D'IRRADIATION N° 96457
BEWIJS VAN BESTRALING Nr
CERTIFICATE OF IRRADIATION N°

STERIGENICS Belgium (Fleurus) s.a. Zoning industriel B-6220 certifie avoir traité dans ses installations par rayonnement gamma (cobalt-60) sur base de l'autorisation d'exploitation délivrée en application de l'A.R. du 12 mars 2002 par l'Agence Fédérale de Contrôle Nucléaire et en conformité avec les normes EN 552 et ISO 11137.

STERIGENICS Belgium (Fleurus) n.v. Zoning industriel B-6220 verklaart door middel van gammastralen (cobalt-60) te hebben behandeld in haar inrichtingen waarvoor een uitbatingvergunning werd bekomen in toepassing van het K.B. van 12 maart 2002 door het Federaal Agentschap voor Nucleaire Controle en overeenkomstig met normen EN 552 en ISO 11137.

STERIGENICS Belgium (Fleurus) s.a. Zoning industriel B-6220 certifies the treatment by gamma irradiation (cobalt-60) at its plant according to the licence delivered in compliance to the Belgium Royal Decree of March 12, 2002 by the Federal Agency for Nuclear Control and in accordance with norms EN 552 and ISO 11137.

Pour le compte de : PERBIO
Voor rekening van :
For the account of :

"Produit maintenu à l'état congelé pendant l'irradiation - Product kept frozen during irradiation"

Les colis suivants : nombre : 1 carton DONOR BOVINE SERUM
De volgende colli : aantal :
Following parcels : quantity :

Réf. STERIGENICS: 8689

Identification suivant déclaration du client : SH 3A 1248.02
Identificatie volgens verklaring van de klant : Product Lot N°: DRK0265
Identification following the declaration of the customer :

Répartis dans les unités de traitement numérotées :
Verdeeld in de genummerde behandelingseenheden : 370872
Divided into the numbered treated units :

Date d'irradiation :
Bestralingsdatum : 14/07/07 Fleurus, le 16 juillet 2007
Irradiation date :

Dose garantie : 26,86 kGy min
Gewaarborgde dosis : 31,79 kGy max
Guaranteed dose of :

BOUXIN
Ingénieur Assurance Qualité

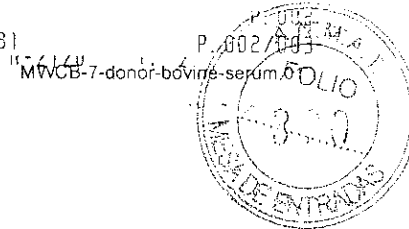
P. QUERTINMONT
Contrôle Qualité
CAIF SA

Dra. Bernarda Belay
Directora Técnica
Page 1 sur 1

TVA BE 0442 022 054, N°RM CH 00148
Forme 230-0060250-51
IBAN BE75210001025051
Swift code DEBABELB
Crédit du Nord 00076-0420-00032204200-05 Page 8 of 12

Compañía Argentina de
Investigaciones Farmacéuticas S.A.
Dra. María Bernarda Belay
Acreditada
DNI 29279925

Bestraling v.b.
mutter (2x 500 ml)
Wille
13/07/2007



Sterigenics Fleuruss Single Dose Sheet (AerODE Vers. 4.3.0b) (Current data)

Sheet ID: S2007/07/15-04	RMS of fitting: 1.94 %
Operator: Anne BOUXIN	C5 =
Mode: Measure (mean BGD)	C4 =
Entry: 8689	C3 = -0.2058350276342
Calibration ID: C2007/03/19-00	C2 = 0.5587478753817
Batch (Type): 4034 JN (Semi - Red Perspex)	C1 = 0.2941879304388
W. L. (nm): 640	C0 = -0.6733444656698
Range-L (kGy): 5.0	Measure T ? Yes
Range-H (kGy): 50.0	Mean T (µm):
Ref. mean BGD: 0.0	Control mode: Beep-beep
Curr. mean BGD: 0.0	Standard T:
Ref. UCTY (%): 4.0	Temperature (°C):
Mode of fitting Log(R)≠f(Log(D))	

Note:

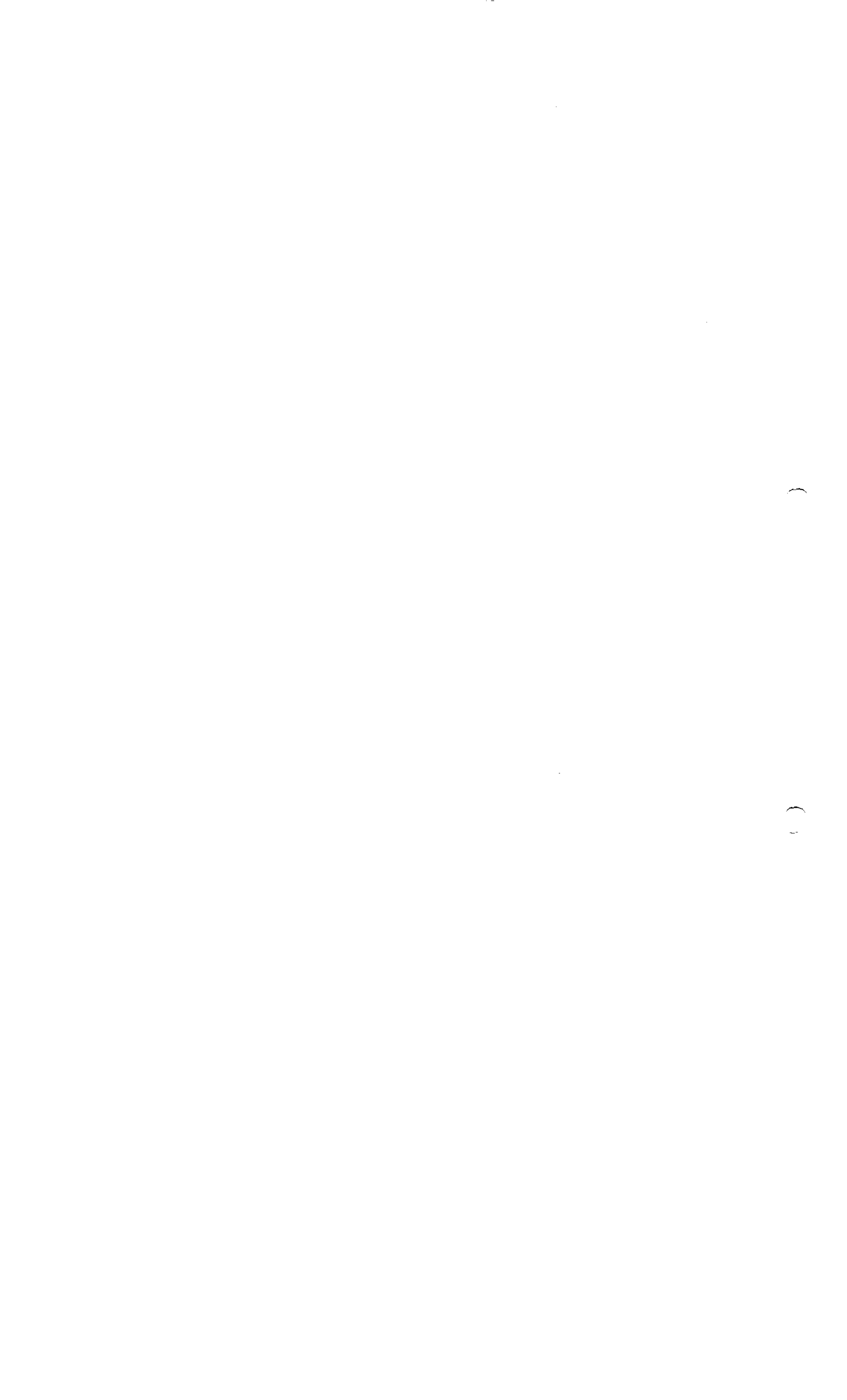
Sample-N°	Position	BGD	Cell	ABS	T (µm)	[A-B]/T (1/cm)	Dose (kGy)	Mean (kGy)	UCTY (kGy, k=2)	Req. doses (kGy)
370872b				0.788	3250.4	2.4181	28.85		23.3	
370872h				0.573	2518.0	2.6748	31.79		30.1	

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 M.N. 15.148

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 Apoderada
 DNI 29328065

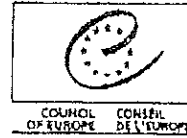
26 Jul 2007

Page 9 of 12





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European Directorate for the Quality of Medicines
Certification Unit

Certificate of suitability
No. R1-CEP 2000-341-Rev 00

- 1 *Name of the substance:*
- 2 **DONOR BOVINE SERUM**

- 3 *Name of holder:*
- 4 **SOUTH PACIFIC SERA LIMITED**
- 5 **Blue Cliffs Rd 24**
- 6 **NZ - 8790 Timaru**

- 7 *Site of production:*
- 8 **SOUTH PACIFIC SERA LIMITED**
- 9 **Blue Cliffs Rd 24**
- 10 **NZ - 8790 Timaru**

- 11 **THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE**
- 12 **R0-CEP 2000-341-REV 02**
- 13 After examination of the information provided on the origin of raw material(s) and type of
- 14 tissue(s) used and on the manufacturing process for this substance on the site of production
- 15 mentioned above, NZ - 8790 Timaru, we certify that the substance **DONOR BOVINE SERUM**
- 16 meets the criteria described in the current version of the monograph Products with risk of
- 17 transmitting agents of animal spongiform encephalopathies no. 1483 of the European
- 18 Pharmacopoeia, current edition including supplements.

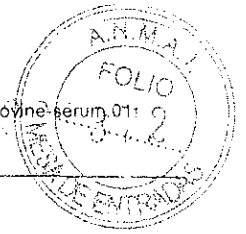
- 19 - country of origin of source materials: **New Zealand**
- 20 - nature of animal tissues used in manufacture: **Donor bovine blood**

- 21 The submitted dossier must be updated after any significant change that may alter the quality,
- 22 safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform
- 23 encephalopathy agents.
- 24 Manufacture of the substance shall take place in accordance with a suitable quality assurance
- 25 system such as GMP and ISO 9002, and in accordance with the dossier submitted.
- 26 Failure to comply with these provisions will render this certificate void.
- 27 The certificate is valid provided that there has been no deterioration in the TSE status of the
- 28 country(ies) of origin of the source material.

Postal Address: 226 Avenue de Colmar (entrance via Schertz) B.P. 907 - F 87028 Strasbourg Cedex 1
Telephone: 03.88.41.30.30 - Fax 03.88.41.27.71 - Web site : <http://www.pharuc.org>

CAIF SA
Dra. Bernarda Belay
Co-Directora Técnica
15.148

CAIF
Compania Argentina de
Investigaciones Farmaceuticas
Dra. Maria Bernarda Belay
Aptoderada
DNI 29278925



- 29 This certificate is renewed from 11 May 2006 according to the provisions of Resolution AP-CSP
- 30 (93) 5 as amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent
- 31 amendment, and the related guidelines.
- 32: This certificate has 32 lines only.

ARTIGES

Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 11 May 2006

DECLARATION OF ACCESS (to be filled in by the certificate holder under their own responsibility)

SOUTH PACIFIC SERA LIMITED, as holder of the certificate of suitability
R1-CEP 2000-341-Rev 00 for DONOR BOVINE SERUM

hereby authorises
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature *(of the CEP holder):*

Postal Address: 226 Avenue de Colmar (entrance rue Schantz) B.P. 907 -- F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30.30 - Fax 03.88.41.27.71 - Web site: <http://www.pheur.org>

CAIF SA
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Dra. María Bernarda Belay
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DNI 23076025





NEW ZEALAND FOOD SAFETY AUTHORITY
Ministry of Agriculture and Forestry

Certificate number / Referentienummer van het certificaat NZL2007/HYCLONE1/7238

Animal Health Certificate¹ / Diergezondheidscertificaat¹

16.1 Processed blood and blood products for pharmaceutical or technical use - cattle sheep, goats, pigs

Name and address of consignor / Naam en adres van de afzender: HYCLONE1 Hyclone Aktiebolag Omokoroa Farm 441 Old Highway TAURANGA NEW ZEALAND		Exporting country / Land van verzending NEW ZEALAND Competent authority / Bevoegde instantie FOOD SAFETY AUTHORITY	
Name and address of consignee / Naam en adres van degene voor wie de zending is bestemd: Perbio Science NV Industriezone 111 Industrielaan 27 9320 Erembodegem - Aalst BELGIUM		Place and Country of Destination / Plaats en land van bestemming: Brussels, Belgium	Departure Date / Verschepingsdatum: 11-Jan-2007
		Means of transport / Per vervoermiddel: Air, Cathay Pacific, CX108	Place of Loading / plaats van lading: Auckland, New Zealand
		Port of Inspection / Inspectiehaven: Zaventem [VBR]	Port of Discharge / Ontschepinghaven: Zaventem [VBR]

Item / Eenheid	Number and kind of packages / Aantal en soort verpakkingen	Description of product / Productomschrijving	Net weight / Nettogewicht
1	4 Bottles	Frozen Filtered New Zealand Donor Bovine Serum, 500mL bottles, SH3A1248.02, DRK0265	2 ltr
2	6 Bottles	Frozen Filtered New Zealand New Born Calf Serum EMEA, 3000mL bottles, SH30560.03, DRD0244	18 ltr
3	12 Bottles	Frozen Filtered New Zealand Foetal Bovine Serum, 1000mL bottles, SH30406.03, DQL0229	12 ltr
22 Packages In Total / Pakketten in totaal		Total Weight / Totaal gewicht:	32 ltr

Species / Diersoort (1-3) Bovine	Identification Marks / Marktekens ter identificatie Not Applicable	Container (& Seal) Numbers / Container & (Zegel) nummers: Not Applicable
Processing Premises / Verwerkingsplaatsen: (1-3) BBP7 Hyclone Aktiebolag, TAURANGA, NEW ZEALAND		
Production Date(s) / Productiedatum/a: (1) 26-Oct-2006 (2) 5-Apr-2006 (3) 23-Nov-2005		

Health Attestation / Gezondheidsverklaring

- a. The animal products herein described, comply with the relevant New Zealand animal health standards and requirements which have been recognised as equivalent to the European Community standards and requirements as prescribed in Council Decision 97/132/EC. Specifically in accordance with the Animal Products Act 1999. / Die hierin beschreven dierlijke producten voldoen aan de desbetreffende normen en voorschriften van Nieuw-Zeeland op het gebied van de diergezondheid die als gelijkwaardig zijn erkend aan de normen en voorschriften van de Europese Gemeenschap die zijn vastgesteld in Besluit 97/132/EG van de Raad. Zij moeten met name voldoen aan de Animal Products Act Van 1999
- b. This product does not contain and is not derived from bovine, ovine and caprine materials other than those derived from animals born, continuously reared and slaughtered in New Zealand / Dit product bevat geen materiaal zoals hieronder omschreven en is daar niet van afkomstig materiaal afkomstig van runderen, schapen en geiten, die niet geboren, ononderbroken gehouden en geslacht zijn in de volgende landen New Zealand

1. This health certificate is for veterinary purposes only. The official health certificate must accompany the consignment until it reaches the border inspection post or when the official certificate is issued upon departure of the consignment. It must be available in the border inspection post at arrival and the eligibility document statement must be completed. / Dit gezondheidscertificaat is uitsluitend bestemd voor veterinaire doeleinden. Het certificaat gezondheidsverklaring moet de zending vergezellen tot in de grensinspectiepost of mee, wanneer het wordt afgegeven nadat de zending reeds is vertrokken, beschikbaar zijn in de grensinspectiepost bij aankomst van de zending en het geval moet Eligibility Document verduidelijking zijn ingevuld

Done at / Gedaan te
MT. MAUNGANUI, New Zealand

On / op
10-Jan-2007

AP039.4



Signature of official veterinarian, New Zealand Government /
Handtekening ambtelijke veterinaris van de Nieuw-Zeelandse regering

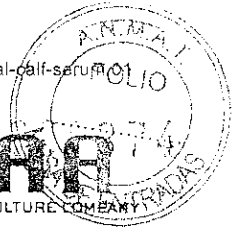
Dra. Bernarda Belay

Name, title and qualifications / Naam, titel en kwalificaties

Co-Ordinadora Técnica
Compania Argentina de Investigaciones Farmacéuticas S.A.
Dra. Bernarda Belay
Inscrita en el Registro de Médicos Nº 12.050
DNI 29376943



PAA
THE CELL CULTURE COMPANY



REVISED-CERTIFICATE OF ANALYSIS
FETAL BOVINE SERUM-GAMMA IRRADIATED

LOT NO.	A70106-7019	CATALOGUE #	A15-701
DATE OF MANUFACTURE	Aug 01, 2006	EXPIRY DATE	Aug 2011
		VOLUME	440.0 L
TEST	TEST METHOD	SPECIFICATION	RESULT
Sterility	USP <71>	No evidence of microbial growth	No evidence of microbial growth
Mycoplasma	Large Volume Direct Culture	Not detected	Not detected
Mycoplasma	FDA Points to consider 1993	Not detected	Not detected
BVD	9 CFR 113.53	Not detected	Not detected
HA	9CFR 113.53	Not detected	Not detected
CPE	9CFR 113.53	Not detected	Not detected
Bovine Parvo	9CFR 113.53	Not detected	Not detected
Bovine Adeno 3	9CFR 113.53	Not detected	Not detected
Bovine Adeno 5	9CFR 113.53	Not detected	Not detected
BRSV	9CFR 113.53	Not detected	Not detected
REO Virus	9CFR 113.53	Not detected	Not detected
Rabies	9CFR 113.53	Not detected	Not detected
Blue Tongue	9CFR 113.53	Not detected	Not detected
BVD Interference	EMEA	≤ 1.0 log	- 0.6log
BLV	ELISA	Not detected	Not detected
Endotoxin	USP <85> Gel clot	< 10.0 EU/ml	0.1 EU/ml
Total Protein	Biuret	≤ 45 g/L	35 g/L
Albumin	Gel Electrophoresis	As reported	15.5 g/L
Globulins	Gel Electrophoresis	As reported	19.5 g/L
Bilirubin	Diazo	As reported	2.5 µmol/L
ALT	International Federation of Clinical Chemistry	As reported	4 U/L
AST	International Federation of Clinical Chemistry	As reported	26 U/L
LDH	Gay's Lactate	As reported	368 U/L
Cholesterol	Cholesterol esterase/cholesterol oxidase/peroxidase	As reported	0.70 mmol/L
Glucose	Glucose oxidase/Peroxidase	As reported	4.9 mmol/L
Urea	Urease/glutamate dehydrogenase	As reported	5.3 mmol/L
Creatinine	Alkaline Picric Acid	As reported	215 µmol/L
Sodium	Ion Selective Electrode	As reported	133 mmol/L
Potassium	Ion Selective Electrode	As reported	13.2 mmol/L
Calcium	Cresolphthalein Complexone	As reported	3.62 mmol/L
Phosphorus	Ammonium Molybdate	As reported	3.3 mmol/L
Osmolality	Freezing Point Depression	As reported	303 mmol/L
Serum Identity	Ouchterlony	Bovine	Bovine
Hemoglobin	Spectrophotometric	≤ 25.0 mg/dL	18.8 mg/dL
pH	Digital pH Meter	6.80 -- 8.20	7.31
Specific Gravity	Refractometer	> 1.020 g/mL	1.026 g/mL
Plating Efficiency	Diploid Cell Line	Pass	Pass
Population Doublings	Diploid Cell Line	Pass	Pass
Cell Toxicity	Diploid Cell Line	None	None
Growth Promotion	Diploid Cell Line	≥ 80% of in-house control	91.7 %
Appearance	Visual	Clear yellow-amber	Clear yellow-amber

STATEMENT OF ORIGIN

THIS SERUM HAS BEEN DERIVED FROM BLOOD ASEPTICALLY COLLECTED IN APPROVED ABATOIRS. THE SERUM WAS ASEPTICALLY PROCESSED AND FILTER STERILIZED IN CANADA, IN A FACILITY REGISTERED WITH MEDICAL DEVICES (U.S.) AND FOLLOWING GUIDELINES OF F.D.A. (U.S.) AND H.P.B. (CANADA). THE COUNTRY OF ORIGIN OF THE CRUDE BLOOD IS CANADA.

PAA Laboratories Inc.
145 Bethridge Road
Elbicoke, Ontario
M9W 1N4
Canada

Tel: 416 744 8996
Fax: 416 744 8401
Toll Free: 1 800 470 8277
USInfo@paa.com
www.paa.com

Kiran Gill
Kiran Gill, Quality Assurance Date
SOP CTQC14 VERSION 4 ATTACHMENT 1

February 21, 2007

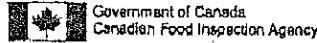
Dra. Bernarda Belay
Dra. Bernarda Belay
Co-Directora Tecnica
M.N. 15.148

Page 1 of 8
Compania Argentina de
Investigaciones Farmaceuticas S.A.
Dra. Maria Bernarda Belay
Acreditada
DNI 29376225



Rx datum/tijd 20-FEB-2007(DIN) 12:56 66
 20-FEB-2007 13:11 FROM BODINCO ALKMAAR TO 00302250610
 3.2.S.2.3 Monovalent pools of inactivated poliomyelitis vaccine, NVI

MWCB-7-fetal-calf-serum.01
 RBF#: TMAM-2007-6/0



VETERINARY CERTIFICATE

FOR PRODUCTS TO BE USED FOR TECHNICAL PURPOSES INCLUDING PHARMACEUTICALS,
 IN VITRO DIAGNOSIS AND LABORATORY REAGENTS, BUT EXCLUDING SERUM OF EQUIDAE,
 INTENDED FOR DISPATCH TO THE EUROPEAN COMMUNITY

Note for the Importer: This certificate is only for veterinary purposes and has to accompany the consignment until it reaches the border inspection post.

1. CONSIGNOR (NAME AND FULL ADDRESS) PAA LABORATORIES INC. 145 BETHRIDGE ROAD ETOBICOKE ONTARIO CANADA M9W 1N4	2. VETERINARY CERTIFICATE NO. (1) TMAM-2007- 6/0 ORIGINAL
2. CONSIGNEE (NAME AND FULL ADDRESS) BODINCO C/O N.V. I 3721 MA BILTHOVEN / HOLLAND	3. ORIGIN OF THE BLOOD PRODUCTS 3.1 COUNTRY: CANADA 3.2 CODE OF TERRITORY: CA-01
3. DESTINATION OF THE BLOOD PRODUCTS 5.1 EU MEMBER STATE: HOLLAND 6.2 NAME AND ADDRESS OF THE DESTINATION: AS CONSIGNEE ABOVE	4. COMPETENT AUTHORITY CANADIAN FOOD INSPECTION AGENCY GOVERNMENT OF CANADA
7. MEANS OF TRANSPORT AND CONSIGNMENT IDENTIFICATION	6. PLACE OF LOADING 145 BETHRIDGE ROAD ETOBICOKE ONTARIO CANADA
7.1 LORRY, RAIL, SHIP OR AIRCRAFT (1) 7.2 NUMBER OF SEAL (IF APPLICABLE): 7.3 REGISTRATION NUMBER, SHIP NAME OR FLIGHT NUMBER N/A	7.4 NATURE OF PACKAGING: PLASTIC BOTTLES 7.5 NUMBER OF PACKAGES: 200 X 1L 7.6 NET WEIGHT: 240 KG 7.7 LOT/BATCH PRODUCTION REFERENCE NUMBER: A70106-7019
8. IDENTIFICATION OF THE BLOOD PRODUCTS	
8.1 NATURE OF THE BLOOD PRODUCTS: STERILE FETAL BOVINE SERUM GAMMA IRRADIATED	
8.2 SPECIES OF ANIMALS FROM WHICH THE BLOOD PRODUCTS DERIVE: BOVINE	
8.3 ADDRESS AND REGISTRATION NUMBER OF THE APPROVED ESTABLISHMENT: PAA LABORATORIES INC. 145 BETHRIDGE ROAD, ETOBICOKE ONTARIO CANADA M9W 1N4 REGISTRATION NUMBER: BPT-02	

16



PAGE 1 OF 3

HAZ110 (JUNE 10, 2004)

Canada

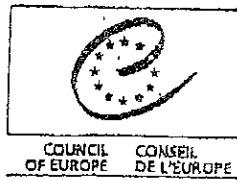
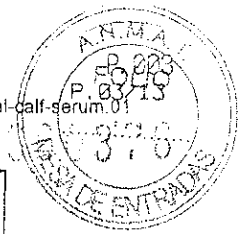
CAIF SA
 Dra. Bernarda Belay
 Co-Directora Tecnica
 M.N. 15.148

27/02/2007

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 Investigaciones Farmacéuticas S.A.
 Dra. María Bernarda Belay
 Apoderada
 DNI 20278921

Page 2 of 8





edom

European Directorate for the Quality of Medicines
Certification Unit

Certificate of suitability
No. R1-CEP 2000-093-Rev 01

- 1 *Name of the substance:*
- 2 **FOETAL BOVINE SERUM**
- 3 *Name of holder:*
- 4 **PAA LABORATORIES INC.**
- 5 **145 Bethridge Road**
- 6 **CDN - M9W 1N4 Etobicoke, Ontario**
- 7 *Sites of production:*
- 8 **PAA LABORATORIES INC.**
- 9 **145 Bethridge Road**
- 10 **CDN - M9W 1N4 Etobicoke, Ontario**
- 11 **PAA LABORATORIES PTY. LTD.**
- 12 **66 Riverside Place**
- 13 **Brisbane Facility Unit 2**
- 14 **AUS - GBA-4170 Morningside, Queensland**
- 15 **PAA LABORATORIES PTY. LTD.**
- 16 **46 Steel Place**
- 17 **AUS - GBA-4170 Morningside, Queensland**

18 **THIS CERTIFICATE SUPERSEDES THE PREVIOUS CERTIFICATE**
19 **R1-CEP 2000-093-REV 00**

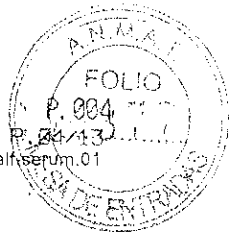
20 After examination of the information provided on the origin of raw material(s) and type of
21 tissue(s) used and on the manufacturing process for this substance on the sites of production
22 mentioned above, CDN - M9W 1N4 Etobicoke, Ontario and AUS - GBA-4170 Morningside,
23 Queensland, we certify that the substance **FOETAL BOVINE SERUM** meets the criteria described
24 in the current version of the monograph Products with risk of transmitting agents of animal
25 spongiform encephalopathies no. 1483 of the European Pharmacopoeia, current edition including
26 supplements.

- 27 — countries of origin of source materials: **United States of America, Australia and**
- 28 **Canada.**
- 29 — nature of animal tissues used in manufacture: **Foetal bovine blood.**

30 The submitted dossier must be updated after any significant change that may alter the quality,
31 safety or efficacy of the substance, or that may alter the risk of transmitting animal spongiform
32 encephalopathy agents.

Postal Address: 228 Avenue de Colmar (entrance rue Schertz) B.P. 907 — F 67029 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 - E-mail: certification@phaux.org

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Dra. Bernarda
Co-Directora Técnica
M.N. 15.148
27 Feb 2007
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Dra. María Bernarda
Avenida
DNI 29.576.845



3.2.S.2.3

- 35 Manufacture of the substance shall take place in accordance with a suitable quality assurance system such as GMP, and in accordance with the dossier submitted.
- 36 Failure to comply with these provisions will render this certificate void.
- 37 The certificate is valid provided that there has been no deterioration in the TSE status of the country(ies) of origin of the source material.
- 38 This certificate is renewed from 24 August 2005 according to the provisions of Resolution AP-CSR/04/05, amended, and of Directive 2001/83/EC and Directive 2001/82/EC and any subsequent amendment, and the related guidelines.
- 40
- 41 This certificate has 41 lines only.

Artiges

Dr. A. ARTIGES
Director of the Quality of Medicines

Strasbourg, 6 March 2006

DECLARATION OF ACCESS (to be filled in by the certificate holder under their own responsibility)

FAA LABORATORIES INC., as holder of the certificate of suitability
R1-CEP 2000-893-Rev 01 for FOETAL BOVINE SERUM

hereby authorizes N. V. I.
(name of the pharmaceutical company)

to use the above-mentioned certificate of suitability in support of their application(s) for the following Marketing Authorisation(s): *(name of product(s) and marketing number(s), if known)*

The holder also certifies that no significant changes to the operations as described in the CEP dossier have been made since the granting of this version of the certificate.

Date and Signature (of the CEP holder): Feb 13/07

Postal Address: 228 Avenue de Colmar (entrance rue Schertz) B.P. 607 - F 67028 Strasbourg Cedex 1
Telephone: 03.88.41.30 30 - Fax 03.88.41.27.71 - E-mail: certification@pheur.org

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Dra. Bernarda Belaj
Co-Directora Técnica
M.N. 15.148

22 Feb 2007

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Dra. María Bernarda Belaj
Asociada

Page 4 of 4
ONI 200.0025





CANSERA INTERNATIONAL INC.
1634 BETHRODGE ROAD, REEDALE ONTARIO, CANADA, M9W 1M4

CERTIFICATE OF ORIGIN

LOT # A70106-7019

STERILE FETAL BOVINE SERUM

ORIGIN: CANADA

THE UNDERSIGNED HAS EXAMINED THE MANUFACTURER'S INVOICE OR SHIPPER'S AFFIDAVIT CONCERNING THE ORIGIN OF THE MERCHANDISE AND DEMS IT TO BE TRUE AND CORRECT TO THE BEST OF HIS/HER KNOWLEDGE AND BELIEF.

VIVIAN BAO, a Commissioner, etc.
City of Toronto, for Cansera International Inc.
Expires January 26, 2010

U. Kes

CAIF SA
Dra. Bernarda Belay
Directora Técnica
M.N. 19.142

Page 5 of 8
2007-13-09 FROM BDDINCO ALKMAR
2007 FEB-2007(DIN) 12:56
Investigación
Dra. Mariana Belay
Aprobado:
DNI 2527692

66 TO 00302250610

P.007
P.07/24



9. HEALTH ATTESTATION

I, the undersigned official veterinarian, declare that I have read and understood Regulation (EC) No 1774/2002⁶ and certify that the blood products described above:

- 9.1 consist of blood products that satisfy the health requirements below;
- 9.2 consist exclusively of blood products not intended for human or animal consumption;
- 9.3 have been prepared exclusively with the following animal by-products:

- ^M either blood of slaughtered animals, which is fit for human consumption in accordance with community legislation, but is not intended for human consumption for commercial reasons;
- ^M and/or blood of slaughtered animals, which is rejected as unfit for human consumption but is not affected by any signs of diseases communicable to human or animals, derived from carcasses that are fit for human consumption in accordance with Community legislation;
- ^M and/or blood obtained from animals other than ruminants that are slaughtered in a slaughterhouse, after undergoing ante-mortem inspection, and were fit, as a result of such inspection, for slaughter for human consumption in accordance with Community legislation;
- ^M and/or blood and blood products derived from the production of products intended for human consumption;
- ^M and/or blood and blood products originating from animals that did not show clinical signs of any disease communicable through that product to humans or animals;

9.4 ⁽¹⁾ either - In the case of blood products derived from ruminant animals they originate in a third country or regions where:

- ^M either the animals and products come from a region where no case of foot and mouth disease, vesicular stomatitis, rinderpest, peste des petits ruminants, Rift Valley fever and bluetongue⁽¹⁾ has been recorded for 12 months and in which vaccination has not been carried out against those diseases for at least 12 months and from which imports of ruminant animals are authorized pursuant to community legislation. The blood from which such products are manufactured must have been collected:
 - ^{M1} either in a slaughterhouse approved in accordance with Community legislation;
 - ^{M2} or from live animals in facilities approved in accordance with community legislation;
 - ^{M3} or in slaughterhouses approved and supervised by the competent authority of the third country. In this case the Commission and Member States must be notified of the address and approval number of such slaughterhouse and the certificate shall indicate this information.

Address: _____
Approval number: _____

^M or the products have undergone one of the following treatments, guaranteeing the absence of pathogens of the ruminant diseases foot and mouth disease, vesicular stomatitis, rinderpest, peste des petits ruminants, Rift Valley fever and bluetongue⁽¹⁾

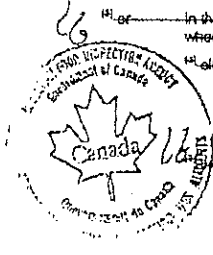
- ^M either heat treatment of a temperature of 65°C for at least three hours, followed by an effectiveness check;
- ^M or irradiation at 2,5 megarads or by gamma rays, followed by an effectiveness check;
- ^M or change in pH to pH 5 for two hours, followed by an effectiveness check;
- ^M or heat treatment of at least 80°C throughout their cubetance, followed by an effectiveness check;

^M or core-positive bluetongue animals are present, and the blood and blood products are intended for technical purposes including pharmaceuticals, in-vitro diagnostic and laboratory reagents, to be processed in the approved plants (approval number) _____ in (Member State) _____⁽¹⁾

^M or in the case of blood products derived from animals excluding ruminants they originate in a third country or regions where:

^M either the animals and the products come from a region where no case of foot and mouth disease, swine vesicular disease, classical swine fever, African swine fever, Newcastle disease or avian influenza has been recorded for 12 months in the susceptible species and in which vaccination has not been carried out against these diseases for at least 12 months. The health certificate shall follow the model according to the species of animal from which the blood products are derived;

^M either the products have undergone a heat treatment of a temperature of 65°C for at least three hours, followed by an effectiveness check, guaranteeing the absence of pathogens of the following diseases: Foot and mouth disease, swine vesicular disease, classical swine fever, African swine fever, Newcastle disease or avian influenza in the susceptible species;



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Dra. Bernarda Beiry
Co-Directora Técnica
M.N. 15.148

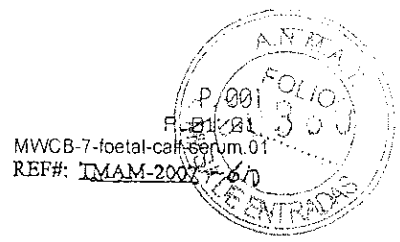
CAIF
Compañía Argentina de
Investigaciones Farmacológicas S.A.
Dra. María Beronzi
Asesora
DNI 29379925

Page 6 of 8
ANEXO P. 13

22/2/2007

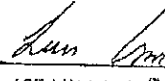


Rx datum/tijd 20-FEB-2007(DIN) 13:02 66
20-FEB-2007 13:13 FROM BODINCO ALKMAAR TO 00302250610
3.2.S.2.3 Monovalent pools of inactivated poliomyelitis vaccine, NVI



- 8.6 the end product was:
 - (a) either - packed in new or sterilized bags,
 - (b) transported in bulk in containers or other means of transport that were thoroughly cleaned and disinfected with a disinfectant approved by the competent authority before use, and which bears labels indicating "NOT FOR HUMAN OR ANIMAL CONSUMPTION";
- 8.8 the end product was stored in enclosed storage;
- 8.7 the product has undergone all precautions to avoid contamination with pathogenic agents after treatment.

Done at MARKHAM on February 15th, 2007


Signature of Official Veterinarian⁽¹⁾
Canadian Food Inspection Agency
Government of Canada

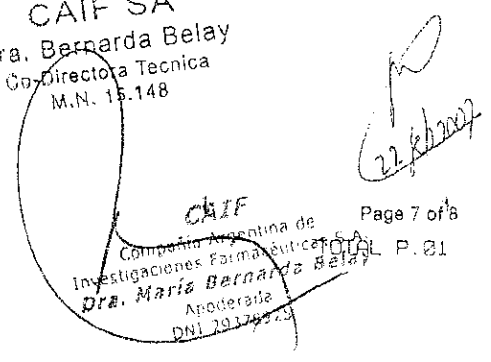


LUCIAN GROSS D.V.M
CANADIAN FOOD INSPECTION AGENCY
145 RENFREW DR. UNIT # 180
MARKHAM ONT.
L3R 9R8 905-613-2880
(Name, qualification and title, in capital letters)

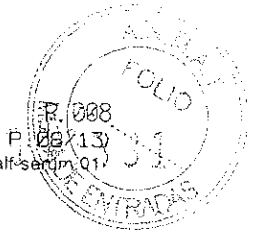
- (1) Issued by the competent authority.
- (2) For goods vehicles, the registration number should be given. For bulk containers, the container number and the seal number (if applicable) should be included.
- (3) Delete as appropriate.
- (4) OJ L 273, 10.10.2002, p. 1.
- (5) In the case of countries in which bluetongue zero-positive ruminant animals are present, blood products have been treated or the animals have been tested seronegative.
- (6) This must be the same Member State of first entry of the product into the Community.
- (7) The signature and stamp must be in colour different to that of the printing.



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Acreditada
DNI 20174823
Page 7 of 8
P. 81



STERIS



CERTIFICATE OF PROCESSING

CUSTOMER PAA Laboratories Inc.	IRRADIATION LOT NUMBER 1432	PO NUMBER N/A
PRODUCT CODE NUMBER Fetal Bovine Serum	PRODUCT LOT NUMBER A70106-7019	NUMBER OF CASES 17

P A A	
Q.C. MANAGER	<i>[Signature]</i>
DATE	FEB 15 2007
APPROVED	

TOTAL MINIMUM DOSE DELIVERED: 30.5 kGy
 TOTAL MAXIMUM DOSE DELIVERED: 37.9 kGy

IRRADIATION START TIME & DATE: 1918 2/14/2007
 IRRADIATION FINISH TIME & DATE: 2116 2/14/2007

REMARKS: There was no process interruption time logged for this run.

MINIMUM SPECIFIED DOSE:	25.0 kGy	MINIMUM DELIVERED DOSE:	30.5 kGy
MAXIMUM SPECIFIED DOSE:	N/A kGy	MAXIMUM DELIVERED DOSE:	N/A kGy

Q.A. APPROVED	TITLE	DATE
<i>[Signature]</i> L. Samson	QS/RC Technician	February 15, 2007

Isomedix Corporation • 184 Crown Court • Whitby • Ontario • L1N 7B1
 Isomedix Corporation operates under a quality system that is in compliance with the ISO 13485:2003 quality standard.
 Isomedix Corporation adheres to requirements provided through ANSQA/AMISO 11137 and EN 552

Form #00087.1
 Revision: 1
 Effective Jan, 01A, 02

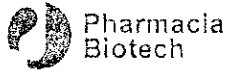
CAIF SA
 Dra. Bernarda Belay
 Co-Directora Técnica
 M/N. 15.48

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 Investigaciones Farmacéuticas S.A.
 Dra. María Bernarda Belay
 DNI 2837892





3.2.S.2.3 Control of Materials
Certificate of analysis for Sepharose CL-6B



CERTIFICATE of ANALYSIS

Product: Sepharose® CL-6B Code Number: 17-0160-05

Lot No: 243329

Analysis:	Limits:	Results:
Selectivity; K_{av} test with dextran fractions Mp = 200 000 50 000 10 000	0.19-0.37 0.39-0.55 0.66-0.78	0.30 0.49 0.72
Flow rate at $\Delta p/L=15$ cm per hour	100-200	155
Particle size distribution volume share within 45-165 μm ; %	min. 95	99
Determination of cationic interactions μg Cytochrome C per mL gel bed	max. 8	1
Microbial contamination microorganism per mL suspension	max. 100	0

Analysis and limits according to: AS 45-6000-42 Ed.:AM Date of approval: 1996-08-28

Pharmacia Biotech AB
Quality Assurance

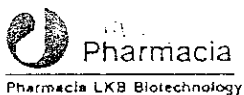
Gen Pelletton

Issued by

CAIF SA
Dra. Bernarda Beley
Co-Directora Técnica
M.N. 15.148

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Compañía Argentina
Investigaciones Farmacéuticas S.A.
Dra. María Bernarda Beley
Acreditada
OM 42.159/95





AS No. 042:10
 Effective; 1988-05-06
 Supersedes AS FC 042:9

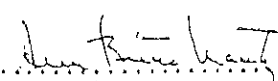
ANALYTICAL SPECIFICATIONS

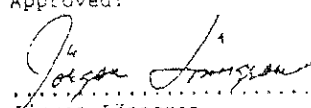
SEPHAROSE^R CL-6B

Item No: 17-0160-00

Description: Bead formed cross-linked agarose gel. For gel filtration and affinity chromatography. Supplied as a suspension in ethanol, 20 vol %

Test	Tolerance limits	Test method
Flow rate at $\Delta p/L = 15$ Column: 5 cm i.d. Bed height 10 cm	100-200 cm per hour	30284
Particle size distribution	≥80 vol % within 45-165 μm	30441 31064
Function	To pass test	30100
Porosity, dextran	Mw Kav	
	181 000 0,23 - 0,41	
	40 700 0,42 - 0,58	
	9 300 0,68 - 0,81	
Unspecific adsorption mg Cytochrome C per 100 mL gel bed	≤ 0,8	
Microbial contamination	max. 10^2 microorganisms per mL suspension	30460

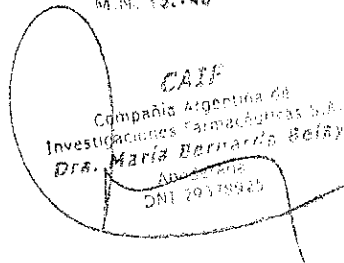
Checked:

 Anna-Britta Krantz
 Manager Quality Documentation

Approved:

 Jørgen Lönngren
 Vice President
 Research and Development

Sepharose is a registered trademark of Pharmacia AB

BRA 4/88

CAIF SA
 Dra. Bernarda Belay
 Subdirectora Técnica
 M.N. 15.146





Appendix 2: Tumorigenicity of the WHO Vero cell bank

Report of in vivo tumorigenicity
testing of the W.H.O. Vero cell
Master Seed lot

RIVM

Bilthoven, April 1989

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Dra. Bernarda Belay
Co-Directora Técnica
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Dra. ~~Maria Bernarda Belay~~
Apoderada
DNI 20.114.21



Report of in vivo tumorigenicity testing of the W.H.O. Vero cell Master Seed lot

by RIVM

Summary

Samples of the WHO Master Vero cell seed lot were tested for tumorigenicity in antithymocyte globulin-(ATG)-treated new-born rats according to current WHO Requirements (W.H.O. TRS no. 745, 1987 pp.93-107). The cells were received at passage 134 and further cultivated to be tested at passage level 156, i.e. more than 10 population doublings beyond the maximum passage level permitted for production. They were also tested at passage level 139 for comparison. As positive control HeLa cells and as negative control MRC₂ human diploid cells were used.

Vero cells at passage level 156 induced small non-progressively growing nodules at the injection site. These nodules, consisting of accumulations of Vero cells and stroma, were still grossly visible at the end of the three-week observation period. No metastasis was observed in lymph-nodes, lungs, kidneys, liver, brain and other tissues of rats inoculated with Vero cells at this passage level. Vero cells at passage level 139 induced small nodules at the site of injection that regressed after the first week. Histologically morphologic structures resembling those observed at the injection site in rats inoculated with passage 156 cells were however present in all rats inoculated with passage 139 cells. Signs of metastasis were not observed in rats inoculated with passage 139 cells.

HeLa cells, used as positive control, in contrast with Vero cells, induced Vero cells, progressively growing tumors at the site of injection in all inoculated animals, and extensive metastasis in lungs and some other tissues.

MRC₂ cells induced no grossly visible nodules but histologically at least one animal showed an accumulation of cells at the site of injection, which probably represented proliferated MRC₂ cells. Signs of metastasis were not observed.

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DNI 2937852



Introduction

At the request of WHO the W.H.O. Vero cell Master Seed lot was examined for tumorigenicity. In the letter from the Institut Merieux, accompanying the samples (Annex 1) it was stated that the cells were at the 134th passage and that the maximum passage level permitted for production is the 150th. According to WHO Requirements (W.H.O. TRS no. 745, 1987 pp.100), the testing has to be carried out at least ten population doublings beyond the maximum passage level used for production. As the Vero cells could be passaged at weekly intervals using a 1:4 split a cell doubling number of 10 beyond the 150 th passage would be reached at the 155th passage. It was therefore decided to perform the test at the 156th passage i.e. approximately 12 cell doublings beyond the 150 passage. In addition to the required positive control, for which HeLa cells were used, it was thought desirable to compare the 156th passage level also with the same Vero cells but at a lower passage level and with a negative control, i.e. a non-tumorigenic diploid cell line. MRC₅ cells were employed as such. At passage 139 sufficient cells (i.e. 10×10^7) would be obtained to perform the test.

For technical reasons the testing had to be done in two parts with testing on the 156th Vero cell passage (and HeLa cells) first, followed some weeks later by a test on the 139th passage in combination with MRC₅ cells, also including HeLa cells as control.

Materials and Methods

Cell lines

Vero cells of the cell bank described as "Vero Cells - W.H.O. Seed 134th passage - Oct. 1987" were received from Institut Merieux. The sample consisted of three ampoules marked 1866, 1869 and 1889 as indicated in the accompanying letter (Annex 1). The cells were cultured in Eagles Minimal Essential Medium with non-essential aminoacids and glutamine (MEM), supplemented with 10% fetal bovine serum (FBS). Ampoule 1866 was thawed and seeded on April 28, 1988. On April 29 it was noticed that very few cells had attached. On April 29 ampoule 1869 was started using a smaller tissue culture vessel. A confluent monolayer was reached after 11 days. The cells could from then on be subcultured at weekly intervals using a 1:4 split until the 156th passage was reached. Rats were inoculated with this passage

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Investigaciones Farmacéuticas S.A.
Dra. ~~Maria Bernarda Belay~~
Apoderada
DNI 29178925





on October 10, 1988, together with HeLa cells as positive control. Ampoule 1888 was seeded on October 12, 1988 and after four passages as passage 139 inoculated into rats on November 11, with MRC₅ (p.d.l. 32) cells as negative control and HeLa cells as positive control.

HeLa cells were from the frozen RIVM stock passage 174 of proven tumorigenic potential.

MRC₅ cells were obtained at p.d.l. 15 from Dr. J.P.Jacobs, NIBSC, South Mimms, Potters Bar, England and passaged at weekly intervals in MEM with 10% FBS applying a 1:2 split until p.d.l. 32.

Cells were subcultured by removing medium from the culture and adding 0.25% trypsin and 0.025% EDTA in phosphat buffered saline, without calcium and magnesium. The culture was then incubated at 37°C until cells were detached. Countings of viable cells were made with trypan blue and cell concentration was adjusted to 10⁷ living cells per 0.2 ml for tumorigenicity testing

Rats

Outbred Wistar (RIV-TOX) rats were from the SPF breeding unit of the RIVM.

Tumorigenicity testing

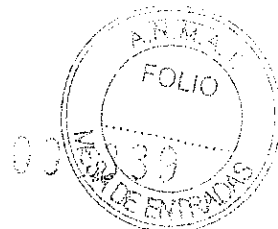
The testing was carried according to WHO Requirements (W.H.O. TRS nr. 745, 1987, pp.93-107) and essentially as described previously (Annex 2). The cells were suspended in MEM and inoculated subcutaneously (s.c.) in the abdominal (umbilical) region in volumes of 0.2 ml, containing 10⁷ cells, per rat on day 0. The new-born rats were inoculated s.c. with 0.1 ml ATG on days 0, 2, 7 and 14 and were observed for three weeks. Developing nodules were measured weekly at the two largest perpendicular diameters. At the end of the three-week observation period the animals were sacrificed and examined for gross lesions, especially metastatic tumors. Organs, including lung, kidney, liver, axillary lymph-nodes if they could be found, site of injection as required and, in addition, brain and on occasion other tissues were fixed in formalin and prepared for histological examination. Tissue sections were stained with hematoxylin and eosin.

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HeLa cells : Tumor development in rats inoculated with 10^7 HeLa cells, used as positive controls in comparison with passage 156 Vero cells, is summarized in Table 4. All ten animals injected with HeLa cells developed gross nodules at the injection site, that, in contrast to nodules in animals injected with Vero cells, grew clearly three-dimensionally and progressively during the three-week observation period. When sacrificed at the end of the three-week observation period all ten animals showed numerous metastatic processes in the lungs (in some animals to the extent that hardly any normal lung tissue remained) and five of the ten animals also in the regional (axillary) lymph nodes. Histological examination there were no signs of metastasis in liver, kidneys, spleen, (or heart, as far as examined) but some of the animals showed metastatic brain lesions. Tumors at sites of injection and metastatic tumors consisted of densely packed epithelial type cells and showed numerous mitoses. In some tumors there was more or less extensive necrosis, others showed formation of bone or cartilage.

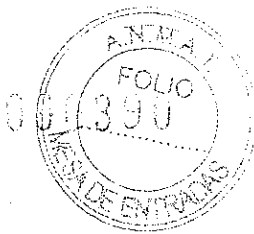
All rats inoculated with HeLa cells, used as positive controls in the test for tumorigenicity of the WHO Vero cell seed at passage level 139 and MRC_5 cells, developed progressively growing tumors at the injection site (Table 5). Lung metastasis was observed in two animals and lymph node metastasis in three. Two of the animals died during the third week of the test.

MRC₅ cells : Only one of the 10 rats, inoculated with 10^7 MRC_5 cells, used as negative control substrate, showed an indication of a possible nodule at the end of the first week of the test (Table 6). There were no indications of nodule formation at the end of the second or third week. Histological examination of the injection sites showed a small circumscribed nodule, possibly of originating in the injection MRC_5 cells in one animal and in one other animal (no.5) a more extensive accumulation of cells rather of uniform type. These cells sometimes appeared to infiltrate between muscle fibers at the injection site. The cells most probably originated from the injected MRC_5 cells. Mitotic figures were very rare. No signs of metastasis were observed histologically or macroscopically in any of the tissues examined, including lung, liver, kidney, spleen, brain or other tissues examined.

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Comment

The results of in the present study on Vero cell tumorigenicity were in general similar to those reported in earlier studies (Van Steenis en Van Wezel, Develop. Biol. Standard. 50, pp.37, 46, 1982, and Levinbook et al., J. Biol. Standard. 12, 391-398, 1984). Vero cell passage 156 induced in the present study nodules that remained grossly visible during the three-week test period whereas the nodules induced by passage 139 regressed after the first week of observation. Nodule formation has been noted to vary from experiment to experiment and it cannot be excluded that the observed difference is related to variations in the test system. Levinbook and coworkers also noted a similar difference between Vero cells of passage 140 and Vero cells of passage 149 and higher however. They ascribed this difference to an increasing tendency towards tumorigenicity at higher Vero cell passages, although, as in the present study, these authors noted no differences in histomorphologic appearance between Vero cell accumulations of lower and higher passage at the site of injection. The differences observed in the present study could therefore reflect changes in behaviour of Vero cells with increasing passage as suggested by Levinbook et al.

In conclusion:

Vero cells of the W.H.O. Vero Cell Master seed lot at passage level 156 did meet requirements of non-progressive growth and absence of metastasis in antithymocyte-treated new-born rats.

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Table 1
 Summary of results of in vivo tumorigenicity testing of the WHO Vero cell Master-cell seed in ATG-treated new-born rats in comparison with HeLa cells and MRC₅ cells

Cell type	Mean nodule dimensions (mm)			Metastasis frequency ²⁾
	at site of injection			
	Week 1	Week 2	Week 3	
Vero passage 156 (10-14-88) ¹⁾	3.1 x 2.1	5.1 x 3.6	5.0 x 3.9	0/10
Vero passage 139 (11-11-88)	2.0 x 1.6			0/7
HeLa 174 (10-14-88)	6 x 2.6	10.8 x 7.5	13.3 x 11.7	10/10
HeLa 174 (11-11-88)	9.1 x 6.4	11.9 x 8.5	16.2 x 11.9	4/8
MRC ₅ (11-11-88)				0/10

¹⁾ Date of inoculation
²⁾ Number of animals with metastases / number surviving at end of 21-day observation period

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Table 2
Tumor development in ARIG-treated newborn rats following the subcutaneous injection of
 1×10^7 Vero cells of (Vero cell seed passage 156) per animal

Cell type	Rat no.	Nodular dimensions (mm) at site of injection at end of each week	Metastasis (macroscopic and/or histol.) present/absent (+/-)														
			Week 1	Week 2	Week 3	Node 1	Node 2	Lung	Liver	Kidney	Spleen	Brain	Heart	Pancreas	Thymus		
Vero 156	1	4 x 2	4 x 3	3 x 3	+	-	-	-	-	-	-	-	-	-	-	-	-
*	2	6 x 3	2 x 2	2 x 3	- ¹⁾	-	-	-	-	-	-	-	-	-	-	-	-
*	3	3 x 2	6 x 6	5 x 3	- ¹⁾	-	-	-	-	-	-	-	-	-	-	-	-
*	4	3 x 2	2 x 2	5 x 5	+	-	-	-	-	-	-	-	-	-	-	-	-
*	5	2 x 1	4 x 6	2 x 2	+	-	-	-	-	-	-	-	-	-	-	-	-
*	6	1 x 1	8 x 5	10 x 3	- ¹⁾	-	-	-	-	-	-	-	-	-	-	-	-
*	7	3 x 2	7 x 6	6 x 4	+	-	-	-	-	-	-	-	-	-	-	-	-
*	8	2 x 1	8 x 5	6 x 5	+	-	-	-	-	-	-	-	-	-	-	-	-
*	9	2 x 2	4 x 3	5 x 5	+	-	-	-	-	-	-	-	-	-	-	-	-
*	10	5 x 5	6 x 6	8 x 6	+	-	-	-	-	-	-	-	-	-	-	-	-
Mean dimensions		3.1x2.1	5.1x3.6	5.0x3.9													

¹⁾ Injection site not present in histological section
²⁾ Examined only macroscopically

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Table 3
Tumor development in AR10-treated new-born rats following the subcutaneous injection of 1×10^7 Vero cells (WHO cell seed passage 139) per animal

Cell type	Rat no.	Nodule dimensions (mm) at site of injection at end of each week	Metastasis (histol. and/or macrosc.) present/absent (+/-)											
			Week 1	Week 2	Week 3	L. node	Lung	Liver	Kidney	Spleen	Brain	Heart	Pancreas	Thymus
Vero 139	1	2 x 2	-	+	+	-	-	-	-	-	-	-	-	-
"	2	4 x 2	-	+	+	-	-	-	-	-	-	-	-	-
"	3	2 x 2	-	+	+	-	-	-	-	-	-	-	-	-
"	4	3 x 1	-	+	+	-	-	-	-	-	-	-	-	-
"	5	3 x 2	-	+	+	-	-	-	-	-	-	-	-	-
"	6	1)	-	+	+	-	-	-	-	-	-	-	-	-
"	7	2	-	+	+	-	-	-	-	-	-	-	-	-

Mean dimensions 2.0x1.6

1) = indication of nodules

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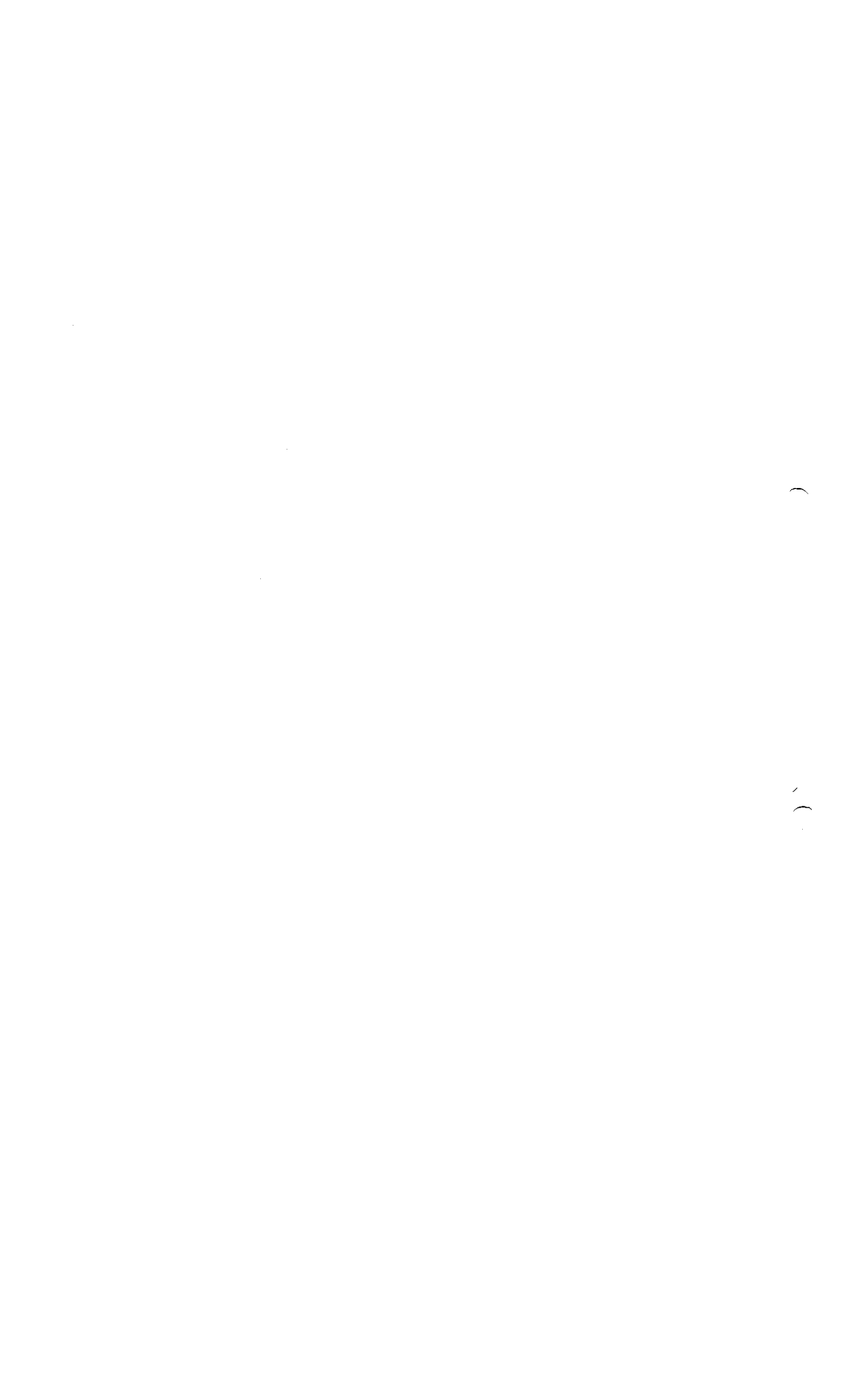
Table 4
Tumor development in ARIC-treated newborn rats following the subcutaneous injection of 1×10^7 Meta cells per animal

Meta 174	Cell type	Rat no.	Node dimensions (mm) at site of injection at end of each week			Metastasis (necros. and/or histol.) present/absent (Y/N)									
			Week 1	Week 2	Week 3	L. node									
						Long	Liver	Kidney	Spleen	Brain	Heart	Pancreas			
*		1	3 x 1	9 x 9	16 x 15	+	+	-	-	-	-	-	-	-	-
*		2	6 x 6	13 x 10	11 x 9	+	+	-	-	-	-	-	-	-	-
*		3	7 x 6	11 x 8	12 x 14	-	+	-	-	-	-	-	-	-	-
*		4	9 x 3	11 x 9	17 x 14	+	+	-	-	-	-	-	-	-	-
*		5	6 x 3	10 x 6	10 x 10	-	+	-	-	-	-	-	-	-	-
*		6	5 x 3	5 x 5	18 x 18	-	+	-	-	-	-	-	-	-	-
*		7	8 x 3	10 x 7	20 x 15	-	+	-	-	-	-	-	-	-	-
*		8	+	9 x 5	8 x 8	+	+	-	-	-	-	-	-	-	-
*		9	6 x 2	14 x 8	7 x 7	+	+	-	-	-	-	-	-	-	-
*		10	10 x 3	16 x 7	14 x 6	-	+	-	-	-	-	-	-	-	-
Mean dimensions			6 x 2.6	10.87 x 5	13.26 x 11.7										

* Examined only microscopically

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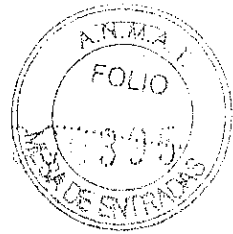


table 5

Tumor development in ARTG-treated new-born rats following the subcutaneous injection of 1×10^7 Hela cells per animal (Experiment 2)

Cell type	Rat no.	Nodule dimensions (mm) at site of injection at end of each week			Metastasis (macrosc.) present	
		Week 1	Week 2	Week 3	L.node	Lung
Hela 174	1	6 x 6	8 x 8	5 x 5	+	-
"	2	5 x 5	10 x 10	12 x 8	+	-
"	3	10 x 8	14 x 8	27 x 17	-	-
"	4	8 x 8	11 x 9	14 x 9	-	+
"	5	7 x 5	15 x 8	22 x 14	+	-
"	6	6 x 5	16 x 9	14 x 9	-	+
"	7	14 x 6	8 x 8	8 x 8	-	-
"	8	17 x 8	13 x 8	28 x 25	-	-
Mean dimensions		9.1x6.4	11.9x8.5	16.2x11.9		

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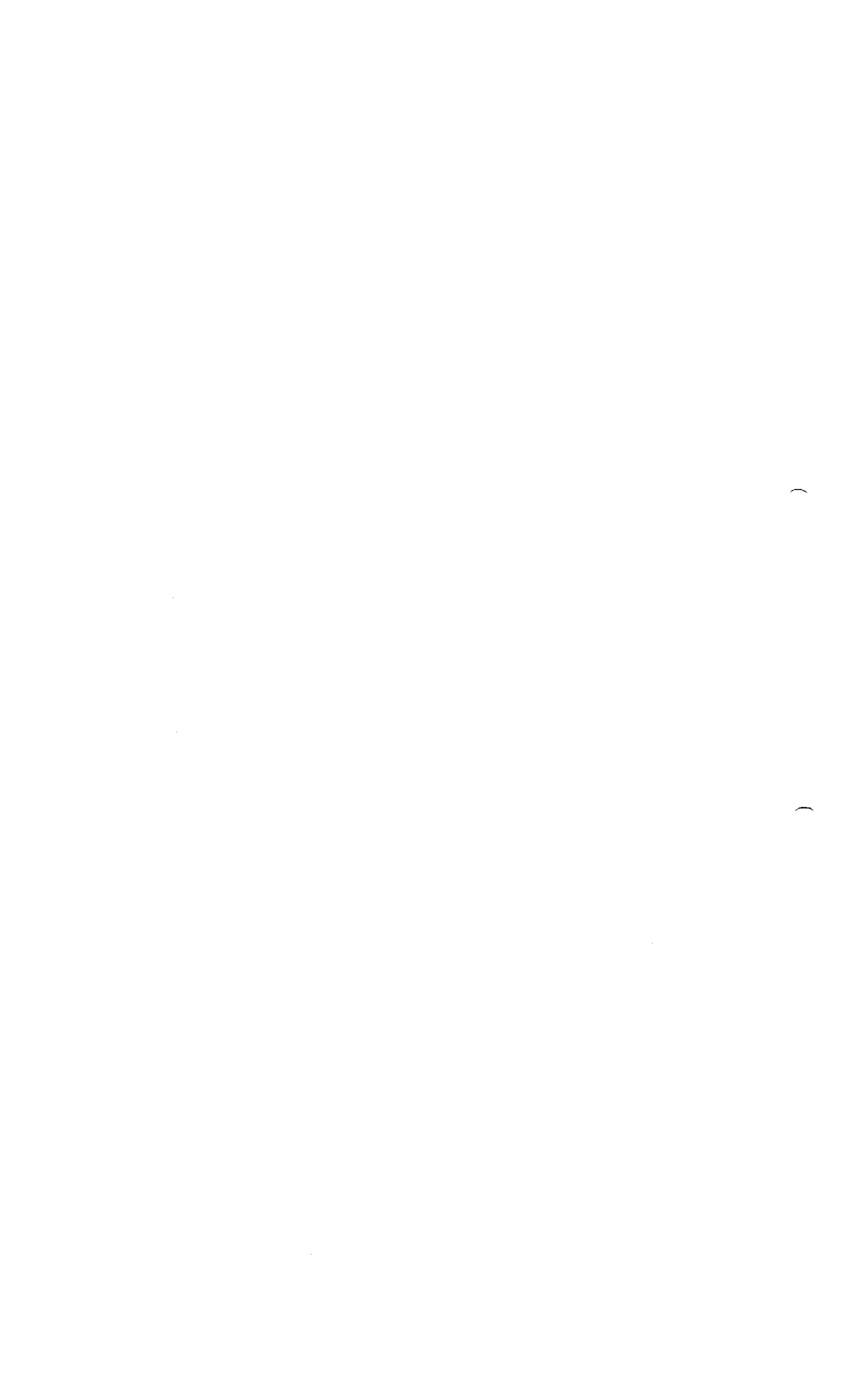




Table 6
Tumor development in AKR/J-treated newborn rats following the subcutaneous injection of 1×10^7 MMS cells (passage 32) per animal

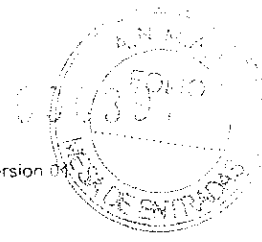
Cell type	Rat no.	Nodule dimensions (mm) at site of injection at end of each week	Metastasis (macro- and/or histo-) present/absent (Y/N)														
			Week 1	Week 2	Week 3	Histol. (week 3)	Lymph Node	Lung	Liver	Kidney	Spleen	Brain	Heart	Pancreas	Thymus		
MMS	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	2	1)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
"	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1) Pelletarian of node
2) Examined only macroscopically

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Appendix 1: Preparation of the WHO Vero cell bank



FACSIMILE TRANSMISSION

To: Dr Tiny van der Velden
RIVM

From: Dr Bryan Bolton
ECACC

Fax No: 0031302742971
Priority: Normal

No of Pages: 4
Date: 21 June, 1999
Ref.:

IF FAX ILLEGIBLE OR INCOMPLETE PLEASE TELEPHONE +44 1980 612511

Dear Dr Velden

Enclosed are copies of the results of the testing carried out on the WHO Vero Cell Bank. The copy of one of the test sheets is very poor but it's the best I can find.

Please let me know if that is the information require.

Yours sincerely

Dr Bryan Bolton
Marketing Manager

European Collection of Cell Cultures, Centre for Applied Microbiology & Research
Salisbury, Wiltshire SP4 0JG, UK.
Tel: +44 1980 612512 Fax: +44 1980 611315



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PACTEUR MÉRIEUX Sérums et Vaccins

1541 Avenue Marcel Méteux
89280 MARCY L'ÉTOILE FRANCE
tel. 76.87.32.32

**CERTIFICAT DE CONTROLE
QUALITY CONTROL RELEASE**

PRODUIT : VERO CELLS - WHO WORKING CELL BANK

LOT : 87-10

EPREUVE : LABORATORY TESTING

RESULTAT : RESULT

Tests in eggs

. Allantoic cavity : SATISFACTORY
. Chorio allantoic membrane : SATISFACTORY
. Yolk sac : SATISFACTORY

Tests on cell cultures

Intact cells coculture with :
. Human diploid cells : SATISFACTORY
. Primary monkey kidney cells : SATISFACTORY

Disrupted cells coculture with :
. Human diploid cells : SATISFACTORY
. Primary monkey kidney cells : SATISFACTORY

Tests for Tumorigenicity

Test in vivo (Newborn rat immunodepressed) : SATISFACTORY
Test in vitro (3T3 assay system) : SATISFACTORY

Electron microscopy examination : In progress

Tests for endogenous virus oncornavirus and retrovirus (electron microscopy examination after BUOR induction) : SATISFACTORY

Tests for retrovirus (Viral reverse transcriptase after BUOR induction) : SATISFACTORY

DATE : 06 JUNE 1990

SIGNATURE : Dr L. PEYRON
Directeur des Services
de Contrôles

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89280 MARSY L'ÉTOILE FRANCE
tél. 78.873232

**CERTIFICAT DE CONTROLE
QUALITY CONTROL RELEASE**

PRODUIT : VERO CELLS - WHO WORKING CELL BANK
PRODUCT

LOT : 87-10

EPREUVE : LABORATORY TESTING

RESULTAT : RESULT

CONTROL AT THE LEVEL OF THE W.C.B. (137e passage)

Control of cells

Test for haemadsorbing viruses	: SATISFACTORY
Identity test (Isoenzyme analysis)	: SATISFACTORY - Conform
Test for sterility	: SATISFACTORY
Test for cultivable mycoplasma	: SATISFACTORY
Electron microscopy examination	: In progress

Control of supernatant

Tests on cell cultures :	
. Vero cells	: SATISFACTORY
. Human diploid cells	: SATISFACTORY
. Primary monkey kidney cells	: SATISFACTORY
Test for cultivable mycoplasma	: SATISFACTORY
Test for mycoplasma Hyorhinis	: SATISFACTORY

CONTROL TO PDL AFTER THE PRODUCTION LEVEL (# 150e passage)

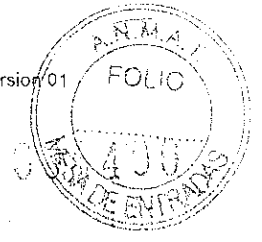
Tests in animals

Intramuscular route inoculation :	
. Suckling mice	: SATISFACTORY
. Mice	: SATISFACTORY
. Guinea-pigs	: SATISFACTORY
. Rabbits	: SATISFACTORY
Intracerebrally route inoculation :	
. Mice	: SATISFACTORY

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THE RESULTS OF TESTING* OF THE WHO VERO CELL MASTER SEED LOT 10-47 (PASSAGE 134)

TEST	LEVEL OF PASSAGE	RESULTS	TESTED BY
Tests for adventitious agents:			
<u>Tests in animals & eggs</u>			
	141 and 136	satisfactory	Dr. S. Saxena, Central Research Institute, India
2 litters of suckling mice	"	"	"
10 adult mice	"	"	"
5 guinea-pigs	"	"	"
5 rabbits	"	"	"
10 embryonated chick eggs	"	"	"
<u>Stability tests</u>			
Mycoplasmas	134, 135, 136, 144	negative	Dr. R. Nectter, Laboratoire National de la Santé, Paris, France
Stability (bacteria and fungi)	134, 135, 136, 144	negative	Dr. J. Forest, Health and Welfare, Canada Dr. M. Wells, Food and Drug Adm., Bethesda, USA
<u>Morphological tests</u>			
	139	negative	Prof. S. G. Oroskov, Institute of Poliomyelitis and Viral Encephalitis, Moscow
<u>Tests on cell cultures</u>			
		negative	Dr. L. Payron, Pasteur Merieux, France
<u>Is for retroviruses</u>			
reverse transcriptase	134	negative	Dr. R. Nectter, Laboratoire National de la Santé, Paris Dr. M. Wells, Food and Drug Adm., Bethesda, USA
<u>Other tests (biochemical)</u>			
Siman Herpes, Papilloma, Adenovirus, CMV, SVV viruses	137	negative	Dr. F. Borrad, Institut Pasteur, France
<u>Test for tumorigenicity in vitro</u>			
Colony forming ability in soft agarose	137	positive, but uncharacteristic of Vero cells	Dr. M. Wells, Food & Drug Adm., Bethesda, USA
Colony forming ability in soft agar	141	141 vero cells formed colonies	Dr. J. Forest, Health and Welfare, Canada
Colony forming ability in soft agar	135, 140, 145, 150	cells which have maintained on MEM with 5% FCS have had phenotypes extremely stable and no progressive increase	Dr. T. Saiga, Kyoto University, Japan
Muscle-organ cultures	135, 140, 145, 150	extremely stable and no progressive increase	
dis-organ cultures	137	positive, but characteristic of Vero cells	
<u>In vivo</u>			
AIG-treated newborn wistar rats	141	adenocarcinoma at the inoculation site in 9 of the 12 animals without metastasis	Dr. J. Forest, Health and Welfare, Canada
Anti-thymocyte globulin Bilkhoven, Netherlands	138	small nodules at the site	Dr. G. van Steenis, NIPHEP Bilkhoven, The Netherlands
AIG-treated new born rats	138	small non-progressively growing nodules at the injection site. No metastasis were observed in lymph-nodes, lungs, kidneys, liver, brain and other tissues of rats	Dr. G. van Steenis, NIPHEP Bilkhoven, The Netherlands
<u>Identity tests</u>			
Characterisation of saccharymes:LDH, GPI, PGD		satisfactory	Dr. R. Nectter, Laboratoire National de la Santé, Paris, France
Specific fingerprint		numerical Vero cells	Dr. F. Borrad, Institut Pasteur, France

* according to WHO TRS no. 713, (1987), Annex 3, pp 83-107

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