REVIEWED
By S47F [redacted] at 10:54 am, May 22, 2017

LOT RELEASE PROTOCOL

RABIPUR®

Lot No. 616011A-Z

Manufacturer: GSK Vaccines GmbH
Emil-von-Behring-Str. 76
35041 Marburg – Germany

TABLE OF CONTENT LRP page number

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Managed Document No 310384, Version 05, Effective Date 03 11 2015

CERTIFICATION

I herewith certify that Rabipur® batch no. 616011A-Z was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Directive 2001/83/EC and amending Directives 2003/63/EC and 2004/27/EC.

In addition the OMCL performing OCABR has been notified of all relevant approved variations that have an impact on product specification or on data supplied in this protocol as described in the EU administrative procedure for OCABR.

Manufacturer: GSK Vaccines GmbH
Emil-von-Behring-Str. 76
35041 Marburg – Germany

05.04.2016
Date

s47F
Qualified Person
s47F
Name and Signature Qualified Person

s47F
Digitally signed by s47F
DN: SERIALNUMBER=899896 +
CN= [redacted] OU=CR,
OU=people, DC=novartis, DC=com
Reason: I am approving this document.
Date: 2016.04.13 12:48:51 +02:00
Confirmatory Electronic Signature

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OVERVIEW

Identity Number		516
Lot Numbers		
	Semi-Finished Lot	516 616011 ✔
	Final Bulk	516 616010 ✔
Manufacturer Name and Address		GSK Vaccines GmbH Emil-von-Behring-Str. 76 35041 Marburg – Germany
Marketing Authorisation Number issued by EU		60a/84
Site of Manufacture		Marburg
Trade Name		Rabipur®
International Non-Proprietary Name (INN)/ Ph. Eur. name		Inactivated Rabies Virus (Flury LEP)/ Rabies Vaccine for Human use Prepared in Cell Cultures
Volume of Single Human Dose / Type Of Container		1 mL / Vial
Total Number of Containers		48036
Date of Manufacture (Blending)		22.01.2016 ✔
Start of Shelf Life		18.02.2016
Expiry Date Semi-Finished Product (Filling Lot)		18.02.2020
Storage Temperature		+2 °C to +8 °C

Composition of Single Human Dose:

- Inactivated Rabies Virus (Flury LEP) Potency	≥ 2,5 IU	- TRIS (hydroxymethyl)-aminomethan	max 4,0 mg
- Polygelin	max 12 mg	- Potassium-L-Glutamate	max 1,0 mg
- Disodium Edetate	max 0,3 mg	- Sodium Chloride	max 5,0 mg
- Sucrose	max 100,0 mg		

Human Albumin used in the Production:

- Lot Number Human Albumin	2436950017, 2436950020, 2876560005, 2876560006
- Manufacturer of Human Albumin	Baxter, CSL
- Date of Release by Manufacturer	25.08.2010, 02.08.2011, 30.10.2013, 25.02.2014
- OMCL Certificate, see to attachment:	OMCL Certificate Human Albumin
- Stage(s) in the manufacturing process in which lot(s) is(are) used	Cell Culture, Cell Controls, Virus Suspension
Quality Control Procedure	SOP 274261
Manufacturing Procedure	SOP 274404

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MANUFACTURING FLOW

Product Name	Product No.	Lot No.
Cell Cultures and Cell Controls	OR2D005	593D T192_1 593D T192_2 593D T192_3 593D T192_4 593D T233_1 593D T233_2 593D T233_3 593D T233_4 593D T235_1 593D T235_2 593D T235_3 593D T235_4 ✔
Virus Suspension	OR2C005	593C T192-1 593C T233-1 593C T235-1
Inactivated Virus Suspension	OR2B005	593B T192-1 593B T233-1 593B T235-1 ✔
Antigen Concentrate	OR2A005	593A T192-1B 593A T233-1A 593A T233-1B 593A T235-1A ✔
Final Bulk	OMGZ005	516 616010 ✔
Semi-Finished Product	OMGZ925	516 616011 ✔

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SEMI-FINISHED PRODUCT (Filling Lot)

Production Details for Semi-Finished Product, Lot No. 516 616011 (Doc. No. 226797)

Date of Filling	22.01.2016
Date of Lyophilization	22.01.2016
Type of Container	Vial
Number of Containers before Visual Inspection	48242
Number of Containers after Visual Inspection	48036
Filling Volume	1 mL
Recommended Reconstitution Volume	1 mL

Test Details for Semi-Finished Product, Lot No. 516 616011

Dissolution Time and Organoleptic Properties (SOP No. 103207)

Method	Resuspension of the lyophilized material according to leaflet and visual control
Requirement	Max. 1 min for solubilization; clear, colorless solution. Equal to pass.

Date	Result
18.02.2016	Pass

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: Number of final containers according to Ph. Eur.
Media	Thioglycollate Medium Soy Peptone / Casein Peptone Medium
Requirement	No growth of microorganisms during and after incubation. Equal to pass.

Date		Result
On	Off	
01.03.2016	15.03.2016	Pass

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Potency and Identity (SOP No. 103208)

Method		NIH Potency Test in Mice according to Ph. Eur.		
Requirement		Two independent experiments At least 2,5 IU/dose (geometric mean value of two independent test) Confidence limits (P=0,95) 25% - 400%		
Date		Potency	Lower Confidence Limit	Upper Confidence Limit
On	Off			
18.02.2016	17.03.2016	5,9 IU/dose	2,7 IU/dose	12,8 IU/dose
02.03.2016	30.03.2016	4,7 IU/dose	1,7 IU/dose	13,1 IU/dose
Geometric Mean				
31.03.2016		5,4 IU/dose	2,9 IU/dose	10,1 IU/dose
Identity: The potency test serves as proof of identity. Specification: identical			Result	Pass

For details see attachment: Potency Test in vivo for Rabipur Lot 616011

Further Tests

Test	Method	Requirement	Result	Date
Residual Water (SOP No. 225207)	Karl Fischer method according to Ph. Eur.	max 3,0%	1,3 %	09.02.2016
pH Value (SOP No. 102723)	Potentiometric determination according to Ph. Eur.	pH 7,3 – 8,3	pH 7,7	05.02.2016
Bacterial Endotoxins (SOP No. 103220)	LAL-Test according to Ph. Eur.	Less than 25 IU per single dose	< 1 IU/mL	05.02.2016
Bovine Serum Albumin (SOP No. 103104)	Immunochemical method according to Ph. Eur. (ELISA)	max. 50 ng per single dose	5 ng/Ds	10.02.2016
Glycoprotein Content (SOP No. 100376)	Rabies glycoprotein (ELISA)	None (results are collected for potential later correlation with the respective potency test)	22,47 IU/mL	10.02.2016

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(FINAL BULK)

Production Details for Final Bulk, Lot No. 516 616010 (Doc. No. 236027)

Date of Formulation	22.01.2016		
Volume	Storage Temperature	Storage Time	Approved Storage Period
50,288 L	+2 °C to +8 °C	0 days	≤ 6 days

Test Details for Final Bulk, Lot No. 516 616010

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 20 mL / Medium	
Media	Thioglycollate Medium Soy Peptone / Casein Peptone Medium	
Requirement	No growth of microorganisms during and after incubation. Equal to pass.	
Before Sterile Filtration		
Date		Result
On	Off	
11.02.2016	25.02.2016	Pass ✓
After Sterile Filtration		
Date		Result
On	Off	
11.02.2016	25.02.2016	Pass ✓

Glycoprotein content (SOP No. 100376)

Method	ELISA
Requirement	10,4 – 20,8 IU/ml
Date	Result
02.02.2016	17,6 IU/mL ✓

COMMENTS

N/A

ATTACHMENTS

Details on Potency Test
Statement Human Albumin
OMCL Certificate Human Albumin

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RABIES ANTIGEN CONCENTRATE, Lot No. 593A T192-1B

1. VIRUS SUSPENSION

1.1. Production Details for Virus Suspension, Lot No. 593C T192 (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	07.04.2015
Date of Harvest of Sub-Batches	13.04.2015
Volume of Harvest	287 L
Storage Temperature	+2°C to +8°C
Storage Time	00 h 03 min
Approved Storage Time	≤ 24 hours

1.2. Test Details for Virus Suspension, Lot No. 593C T192

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 25 mL / medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth of microorganisms during and after incubation. Equal to pass.	
Date		Result
On	Off	
16.04.2015	30.04.2015	Pass ✓

Mycoplasma (SOP No. 102833)

Method	Culture Method according to Ph. Eur. Random Sample Volume: 20,4 mL	
Media	Fluid Mycoplasma Medium 2, Fluid Mycoplasma Medium 3, Mycoplasma Agar 2, Mycoplasma Agar 3, Frey Bouillon, Friis Bouillon, Frey Agar, Friis Agar	
Requirement	No mycoplasma detectable. Equal to pass.	
Date		Result
On	Off	
14.04.2015	12.05.2015	Pass ✓

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Virus Concentration and Identity (SOP No. 103025)

Method	Virus Titration in Chicken Fibroblast Cell Culture Determination of Identity with Specific Antibodies
Requirement	Virus Titre: $10^{6.0}$ $TCID_{50}$/mL - 10^{8} $TCID_{50}$/mL Identity: Identical to Rabies Virus. Equal to pass.

Date		Result	
On	Off	Concentration	Identity
16.04.2015	20.04.2015	7,7 Log $TCID_{50}$/mL ✔	Pass ✔

1.3. Production Details for Filtered Virus Suspension Lot No. 593C T192 (SOP No. 274054)

Date of Filtration	13.04.2015

1.4. Test Details for Filtered Virus Suspension, 593C T192

Total Nitrogen (SOP No. 103347)

Method	Nitrogen Determination (High Temperature Analyzer) Sample Volume: 30 mL
Requirement	0,8 – 1,2 mg/mL

Date		Result
On	Off	
14.04.2015	15.04.2015	1,1 mg/mL

Beta-Propriolactone (SOP No. 243472)

Method	Gas Chromatographic Determination Sample Volume: 3 mL
Requirement	257 – 357 µg/mL

Date	Result
05.05.2015	314 µg/mL

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pH Value (SOP No. 102723)

Method	Potentiometric Determination according to Ph. Eur. Sample Volume: 40 mL
Requirement	pH 7.2 – 7.8

Date	Result
13.04.2015	pH 7.3

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593B T192 (Doc. No. 274054)

Date of inactivation	On	Off
	13.04.2015 ✓	14.04.2015 ✓
Method of inactivation	Beta-Propiolactone, 24 hours at +3°C (± 1°C), followed by 2 hours at +37°C (± 1°C)	
Storage	≤ 4 days at +2°C to +8°C	

2.2. Test Details for Inactivated Virus Suspension, Lot No. 593B T192

Residual Infectious Virus (SOP No. 103173)

Method	Test in Chicken Fibroblast Cell Culture; Fluorescence Microscopy	
Sample	Equivalent to min. 25 Doses of the Vaccine	
Requirement	No live virus detectable. Equal to pass.	
Date		Result
On	Off	
23.04.2015	18.05.2015	Pass ✓

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
21.04.2015	1.95 IU/mL ✓

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3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593A T192-1B (Doc. No. 274056)

Date of Purification and Concentration	15.04.2015
Method of Purification and Concentration	Density Gradient Centrifugation, 9 h, 35000 rpm
Storage	≤ -70 °C, max. 24 months
Volume	1272 mL

3.2. Test Details for Antigen Concentrate, Lot No. 593A T192-1B

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 10 mL / Medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth of microorganisms during and after incubation. Equal to pass.	
Date		Result
On	Off	
20.04.2015	04.05.2015	Pass ✓

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
21.04.2015	169 IU/mL ✓

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

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RABIES ANTIGEN CONCENTRATE, Lot No. 593A T233-1A

1. VIRUS SUSPENSION

1.1. Production Details for Virus Suspension, Lot No. 593C T233 (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	10.07.2015
Date of Harvest of Sub-Batches	16.07.2015
Volume of Harvest	283 L
Storage Temperature	+2°C to +8°C
Storage Time	18 h 29 min
Approved Storage Time	≤ 24 hours

1.2. Test Details for Virus Suspension, Lot No. 593C T233

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 25 mL / medium
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium
Requirement	No growth of microorganisms during and after incubation. Equal to pass.

Date		Result
On	Off	
22.07.2015	05.08.2015	Pass ✔

Mycoplasma (SOP No. 102833)

Method	Culture Method according to Ph. Eur. Random Sample Volume: 20,4 mL
Media	Fluid Mycoplasma Medium 2, Fluid Mycoplasma Medium 3, Mycoplasma Agar 2, Mycoplasma Agar 3, Frey Bouillon, Friis Bouillon, Frey Agar, Friis Agar
Requirement	No mycoplasma detectable. Equal to pass.

Date		Result
On	Off	
28.07.2015	25.08.2015	Pass ✔

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Virus Concentration and Identity (SOP No. 103025)

Method	Virus Titration in Chicken Fibroblast Cell Culture Determination of Identity with Specific Antibodies
Requirement	Virus Titre: $10^{6.0}$ $TCID_{50}$/mL - 10^{8} $TCID_{50}$/mL Identity: Identical to Rabies Virus. Equal to pass.

Date		Result	
On	Off	Concentration	Identity
23.07.2015	27.07.2015	7.4 Log $TCID_{50}$/mL ✓	Pass ✓

1.3. Production Details for Filtered Virus Suspension Lot No. 593C T233 (SOP No. 274054)

Date of Filtration	17.07.2015

1.4. Test Details for Filtered Virus Suspension, 593C T233

Total Nitrogen (SOP No. 103347)

Method	Nitrogen Determination (High Temperature Analyzer) Sample Volume: 30 mL	
Requirement	0,8 – 1,2 mg/mL	
Date		Result
On	Off	
21.07.2015	22.07.2015	1,1 mg/mL

Beta-Propriolactone (SOP No. 243472)

Method	Gas Chromatographic Determination Sample Volume: 3 mL
Requirement	257 – 357 µg/mL

Date	Result
07.08.2015	309 µg/mL

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pH Value (SOP No. 102723)

Method	Potentiometric Determination according to Ph. Eur. Sample Volume: 40 mL
Requirement	pH 7.2 – 7.8

Date	Result
17.07.2015	pH 7.3

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593B T233 (Doc. No. 274054)

Date of inactivation	On	Off
	17.07.2015 ✓	18.07.2015 ✓
Method of inactivation	Beta-Propiolactone, 24 hours at +3°C (± 1°C), followed by 2 hours at +37°C (± 1°C)	
Storage	≤ 4 days at +2°C to +8°C	

2.2. Test Details for Inactivated Virus Suspension, Lot No. 593B T233

Residual Infectious Virus (SOP No. 103173)

Method	Test in Chicken Fibroblast Cell Culture; Fluorescence Microscopy
Sample	Equivalent to min. 25 Doses of the Vaccine
Requirement	No live virus detectable. Equal to pass.

Date		Result
On	Off	
30.07.2015	24.08.2015	Pass ✓

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
28.07.2015	2.27 IU/mL ✓

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3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593A T233-1A (Doc. No. 274056)

Date of Purification and Concentration	21.07.2015
Method of Purification and Concentration	Density Gradient Centrifugation, 9 h, 35000 rpm
Storage	≤ -70 °C, max. 24 months
Volume	1274 mL

3.2. Test Details for Antigen Concentrate, Lot No. 593A T233-1A

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 10 mL / Medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth of microorganisms during and after incubation. Equal to pass.	
Date		Result
On	Off	
23.07.2015	06.08.2015	Pass ✔

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
28.07.2015	177 IU/mL ✔

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

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RABIES ANTIGEN CONCENTRATE, Lot No. 593A T233-1B

1. VIRUS SUSPENSION

1.1. Production Details for Virus Suspension, Lot No. 593C T233 (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	10.07.2015
Date of Harvest of Sub-Batches	16.07.2015
Volume of Harvest	283 L
Storage Temperature	+2°C to +8°C
Storage Time	18 h 29 min
Approved Storage Time	≤ 24 hours

1.2. Test Details for Virus Suspension, Lot No. 593C T233

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 25 mL / medium
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium
Requirement	No growth of microorganisms during and after incubation. Equal to pass.

Date		Result
On	Off	
22.07.2015	05.08.2015	Pass ✓

Mycoplasma (SOP No. 102833)

Method	Culture Method according to Ph. Eur. Random Sample Volume: 20,4 mL
Media	Fluid Mycoplasma Medium 2, Fluid Mycoplasma Medium 3, Mycoplasma Agar 2, Mycoplasma Agar 3, Frey Bouillon, Friis Bouillon, Frey Agar, Friis Agar
Requirement	No mycoplasma detectable. Equal to pass.

Date		Result
On	Off	
28.07.2015	25.08.2015	Pass ✓

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Virus Concentration and Identity (SOP No. 103025)

Method	Virus Titration in Chicken Fibroblast Cell Culture Determination of Identity with Specific Antibodies
Requirement	Virus Titre: $10^{6.0}$ $TCID_{50}$/mL - 10^{8} $TCID_{50}$/mL Identity: Identical to Rabies Virus. Equal to pass.

Date		Result	
On	Off	Concentration	Identity
23.07.2015	27.07.2015	7.4 Log $TCID_{50}$/mL	Pass

1.3. Production Details for Filtered Virus Suspension Lot No. 593C T233 (SOP No. 274054)

Date of Filtration	17.07.2015

1.4. Test Details for Filtered Virus Suspension, 593C T233

Total Nitrogen (SOP No. 103347)

Method	Nitrogen Determination (High Temperature Analyzer) Sample Volume: 30 mL	
Requirement	0,8 – 1,2 mg/mL	
Date		Result
On	Off	
21.07.2015	22.07.2015	1,1 mg/mL

Beta-Propriolactone (SOP No. 243472)

Method	Gas Chromatographic Determination Sample Volume: 3 mL
Requirement	257 – 357 µg/mL

Date	Result
07.08.2015	309 µg/mL

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pH Value (SOP No. 102723)

Method	Potentiometric Determination according to Ph. Eur. Sample Volume: 40 mL
Requirement	pH 7.2 – 7.8

Date	Result
17.07.2015	pH 7.3

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593B T233 (Doc. No. 274054)

	On	Off
Date of inactivation	17.07.2015	18.07.2015
Method of inactivation	Beta-Propiolactone, 24 hours at +3°C (± 1°C), followed by 2 hours at +37°C (± 1°C)	
Storage	≤ 4 days at +2°C to +8°C	

2.2. Test Details for Inactivated Virus Suspension, Lot No. 593B T233

Residual Infectious Virus (SOP No. 103173)

Method	Test in Chicken Fibroblast Cell Culture; Fluorescence Microscopy
Sample	Equivalent to min. 25 Doses of the Vaccine
Requirement	No live virus detectable. Equal to pass.

Date		Result
On	Off	
30.07.2015	24.08.2015	Pass ✓

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
28.07.2015	2.27 IU/mL ✓

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3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593A T233-1B (Doc. No. 274056)

Date of Purification and Concentration	21.07.2015
Method of Purification and Concentration	Density Gradient Centrifugation, 9 h, 35000 rpm
Storage	≤ -70 °C, max. 24 months
Volume	1274 mL

3.2. Test Details for Antigen Concentrate, Lot No. 593A T233-1B

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 10 mL / Medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth of microorganisms during and after incubation. Equal to pass.	
Date		Result
On	Off	
23.07.2015	06.08.2015	Pass ✓

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL

Date	Result
28.07.2015	184 IU/mL ✓

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

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RABIES ANTIGEN CONCENTRATE, Lot No. 593A T235-1A

1. VIRUS SUSPENSION

1.1. Production Details for Virus Suspension, Lot No. 593C T235 (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	15.07.2015
Date of Harvest of Sub-Batches	20.07.2015
Volume of Harvest	257 L
Storage Temperature	+2°C to +8°C
Storage Time	14 h 14 min
Approved Storage Time	≤ 24 hours

1.2. Test Details for Virus Suspension, Lot No. 593C T235

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 25 mL / medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth of microorganisms during and after incubation. Equal to pass.	
Date		Result
On	Off	
23.07.2015	06.08.2015	Pass ✓

Mycoplasma (SOP No. 102833)

Method	Culture Method according to Ph. Eur. Random Sample Volume: 20,4 mL	
Media	Fluid Mycoplasma Medium 2, Fluid Mycoplasma Medium 3, Mycoplasma Agar 2, Mycoplasma Agar 3, Frey Bouillon, Friis Bouillon, Frey Agar, Friis Agar	
Requirement	No mycoplasma detectable. Equal to pass.	
Date		Result
On	Off	
28.07.2015	25.08.2015	Pass ✓

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Managed Document No. 310360, Version 05, Effective Date 19 02 2016

Virus Concentration and Identity (SOP No. 103025)

Method	Virus Titration in Chicken Fibroblast Cell Culture Determination of Identity with Specific Antibodies
Requirement	Virus Titre: $10^{6.0}$ $TCID_{50}$/mL - 10^{8} $TCID_{50}$/mL Identity: Identical to Rabies Virus. Equal to pass.

Date		Result	
On	Off	Concentration	Identity
23.07.2015	27.07.2015	8.0 Log $TCID_{50}$/mL ✔	Pass ✔

1.3. Production Details for Filtered Virus Suspension Lot No. 593C T235 (SOP No. 274054)

Date of Filtration	21.07.2015

1.4. Test Details for Filtered Virus Suspension, 593C T235

Total Nitrogen (SOP No. 103347)

Method	Nitrogen Determination (High Temperature Analyzer) Sample Volume: 30 mL	
Requirement	0,8 – 1,2 mg/mL	
Date		Result
On	Off	
28.07.2015	29.07.2015	1,1 mg/mL

Beta-Propriolactone (SOP No. 243472)

Method	Gas Chromatographic Determination Sample Volume: 3 mL
Requirement	257 – 357 µg/mL

Date	Result
07.08.2015	322 µg/mL

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pH Value (SOP No. 102723)

Method	Potentiometric Determination according to Ph. Eur. Sample Volume: 40 mL
Requirement	pH 7.2 – 7.8

Date	Result
21.07.2015	pH 7.3

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593B T235 (Doc. No. 274054)

	On	Off
Date of inactivation	21.07.2015	22.07.2015
Method of inactivation	Beta-Propiolactone, 24 hours at +3°C (± 1°C), followed by 2 hours at +37°C (± 1°C)	
Storage	≤ 4 days at +2°C to +8°C	

2.2. Test Details for Inactivated Virus Suspension, Lot No. 593B T235

Residual Infectious Virus (SOP No. 103173)

Method	Test in Chicken Fibroblast Cell Culture; Fluorescence Microscopy
Sample	Equivalent to min. 25 Doses of the Vaccine
Requirement	No live virus detectable. Equal to pass.

Date		Result
On	Off	
30.07.2015	24.08.2015	Pass ✔

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
28.07.2015	2.23 IU/mL ✔

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Managed Document No. 310360, Version 05, Effective Date 19 02 2016

3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593A T235-1A (Doc. No. 274056)

Date of Purification and Concentration	23.07.2015
Method of Purification and Concentration	Density Gradient Centrifugation, 9 h, 35000 rpm
Storage	≤ -70 °C, max. 24 months
Volume	1274 mL

3.2. Test Details for Antigen Concentrate, Lot No. 593A T235-1A

Sterility (SOP No. 102858)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 10 mL / Medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth of microorganisms during and after incubation. Equal to pass.	
Date		Result
On	Off	
27.07.2015	10.08.2015	Pass ✔

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
28.07.2015	191 IU/mL ✔

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

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Managed Document No. 310360, Version 05, Effective Date 19 02 2016

1. STARTING MATERIALS for ANTIGEN CONCENTRATE Lot 593A T 192

1.1. Master Seed

Virus Strain used to prepare licensed Rabies Vaccine	Rabies Master Seed Virus Flury LEP
Lot No. of Master Seed	C25/83
Preparation Date of Master Seed Lot	1983
No. of Passages between two seeds mentioned above	187
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. Monographs and with the Marketing Authorization	29.01.1985
WHO Reference	Annex 2 of the WHO Technical Report Series 658, 1981, page 54 - 88

1.2. Working Seed (Doc. No. 101508)

	Sub-Batch 1	Sub-Batch 2	Sub-Batch 3	Sub-Batch 4
Lot No. of Working Seed	C26/11D-04	C26/11D-04	C26/11D-04	C26/11D-04
Preparation Date of Working Seed Lot	24.07.2014	24.07.2014	24.07.2014	24.07.2014
Passage Level from Master Seed Lot	1	1	1	1
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. Monographs and with the Marketing Authorization	24.09.2014	24.09.2014	24.09.2014	24.09.2014

WSL C26/11D approved 20/01/2015, PM-2014-04464

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Managed Document No 310362, Version 07, Effective Date 14102015

2. CELL SUBSTRATE FOR VIRUS PROPAGATION (Doc. No. 274048)

Cell Culture System	Chicken Fibroblast Cell Cultures			
Flock Number	10306			
Delivery Date of incubated Eggs	06.04.2015			
Manufacturing Date of Cell Culture	07.04.2015			
Population doubling level (PDL) of produced cells when inoculated with virus seed	2,2 / 2,4 / 2,4 / 2,6 Cells x 10^6/mL			
Nature and concentration of antibiotics used in production of cell culture maintenance medium	Aureomycin (4,6 mg/mL) Amphotericin B (0,46 µg/mL) Neomycine Sulfate (229 µg/mL)			
Starting Material	Identification and source of starting materials used in preparing production cells including excipients and preservatives			
	Sub-Batch 1	Sub-Batch 2	Sub-Batch 3	Sub-Batch 4
PBS (pH7,2) SOP271810	022	022	022	022
Trypsinization Medium SOP275550	042/01	042/01	042/01	042/01
FCS SOP222018	0037	0037	0037	0037
Medium 3 + $NaHCO_3$ SOP271811	016/04	016/04	016/04	016/04
Medium 3 + HSA SOP300719	030/08	030/08	030/09	030/09
Size of Sub-Batch	71L	71L	71L	71L
For details see attachment: Details on SPF Eggs to 593D T 192				

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Managed Document No 310362, Version 07, Effective Date 14102015

3. CONTROL CELL CULTURES, Lot No. 593D T 192

3.1. Production Details for Control Cell Cultures, (Doc. No. 274048)

Ratio or Proportion of Control to Production Cell Culture	1 L of pooled 284L (4x71L) Cell Culture	
Period of Observation of Cultures	On (Date of Sampling)	Off (Date Control Cells handed to QC)
	07.04.2015	08.04.2015

3.2. Test Details for Control Cell Cultures, LotNo.593DT 192

Cytopathic Degenerations (SOP No. 104212)

Method	Microscopic Examination according to Ph. Eur. Random Sample: At least 500 mL of the control cells used for vaccine manufacturing	
Requirement	No cytopathic effect detectable. Equal to pass.	
Date		Result
On	Off	
08.04.2015	24.04.2015	Pass ✓

Hemadsorbing Viruses (SOP No. 103210)

Method	Test according to Ph. Eur. with Guinea Pig Erythrocytes (rbc) Sample Volume: At least 25% of the control cells after incubation for at least 14 days	
Storage Time and Temperature of rbc (SOP No. 104540)	≤ 7 days after blood withdrawal at +2 to +8°C	
Incubation	30-60 min at +2 °C to +8 °C 30-60 min at +20 °C to +25 °C	
Requirement	No haemadsorbing viruses detectable. Equal to pass.	
Date		Result
On	Off	
24.04.2015	24.04.2015	Pass ✓

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Managed Document No 310362, Version 07, Effective Date 14102015

Extraneous Agents – Chicken Fibroblast Cells (SOP No. 104681)

Method	Inoculation of Chicken Fibroblast Cells Random sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days
Incubation	+36 °C (±1 °C) and +34 °C (±2 °C)
Requirement	No signs of extraneous agents. Equal to pass.

Date		Result
On	Off	
24.04.2015	08.05.2015	Pass ✓

Extraneous Agents – Vero Cells (SOP No. 104682)

Method	Inoculation of Vero Cells Random Sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days
Incubation	+36 °C (± 1 °C)
Requirement	No signs of extraneous agents. Equal to pass.

Date		Result
On	Off	
24.04.2015	08.05.2015	Pass ✓

Extraneous Agents – Human Amnion Cells Line AV3 (SOP No. 104683)

Method	Inoculation of Human Amnion Cells Line AV3 Random Sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days
Incubation	+36 °C (± 1 °C)
Requirement	No signs of extraneous agents. Equal to pass.

Date		Result
On	Off	
24.04.2015	08.05.2015	Pass ✓

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Managed Document No 310362, Version 07, Effective Date 14102015

Avian Leukosis Viruses (SOP No. 244413, 227575)

Method	Culture Method according to Ph. Eur. Random Sample Volume: 5 mL supernatant after incubation for at least 14 days
Requirement	No avian leukosis viruses detectable. Equal to pass.

Amplification in Cells		ELISA		Result
Date		Date		
On	Off	On	Off	
24.04.2015	05.05.2015	11.05.2015	12.05.2015	Pass

4. COMMENTS

N/A

5. ATTACHMENTS

Details on SPF Eggs to 593D T **192**
Seed virus certificate of analysis

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VALO BioMedia	Control Certificate	VALO BioMedia GmbH
		FO-DE-144.01
		Gültig ab 01.10.12
	Formblätter	Seite 1/2

Consignee: Novartis Vaccines and Diagnostics GmbH
Marburg , 35006

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06. APR. 2015 s47F

Date of Delivery: 06.04.2015
SPF Eggs : 4120

Details of the consignment: Latest Sampling Date **23.03.2015**

The following tests were carried out on samples of the above mentioned flock. No test result or clinical observation showed any sign of infection and the SPF status is confirmed to be in accordance with the valid EP:		Testing Method	Result
Avian Adeno Viruses, group 1		AGP	N
Avian Encephalomyelitis Virus		ELISA	N
Avian Infectious Bronchitis Virus		ELISA	N
Avian Infectious Laryngotracheitis Virus		ELISA	N
Avian Leukosis Viruses/antibodies subtypes A,B, J		ELISA	N
Avian Leukosis Viruses – P27 antigen		ELISA	N
Avian Nephritis Virus		ELISA	N
Avian Orthoreoviruses		ELISA	N
Avian Reticuloendotheliosis Virus		ELISA	N
Avibacterium paragallinarum		CO/PM	N
Chicken Anemia Virus (CAV)		ELISA	N
Egg Drop Syndrome Virus		HI	N
Fowlpox Virus		CO/PM	N
Infectious Bursal Disease Virus (IBDV)	Serotype 1	ELISA	N
	Serotype 2	VN	N
Influenza A Virus		AGP	N
Marek's Disease Virus		AGP	N
Mycobacterium avium		CO/PM	N
Mycoplasma gallisepticum		SPA	N
Mycoplasma synoviae		SPA	N
Newcastle Disease Virus		HI	N
Salmonella pullorum		SPA	N
Salmonella spp.		BE	N
Turkey Rhinotracheitis Virus		ELISA	N

Keys of signs:

N	= negative	SPA	= Serum Plate Agglutination	PM	= Post Mortem
HI	= Hemagglutination-Inhibition Test	BE	= Bacteriological Examination	VN	= Virus Neutralization Test
AGP	= Agar-Gel-Precipitation Test	P	= positive	ELISA	= Enzyme Linked Immunosorbent Assay, commercial test kit
EP	= European Pharmacopoeia	CO	= Clinical Observation		

We hereby confirm that all VALO SPF flocks from which we have supplied SPF eggs during the last four weeks are still in accordance with the requirements of the valid EP. Any change of the status of the flocks will be reported to all related customers immediately. The eggs of this delivery have been collected within 7 days prior to the date of departure from our farm. The origin of the eggs is the Federal Republic of Germany.

Anlage 7 zum BPR 593-01
der Charge 593DT192
Seite 1 von 2
06. APR. 2015 s47F

Osterholz-Scharmbeck, 01.04.2015

s47F

Signature of VALO BioMedia GmbH

ROH 279051 0300
06. APR. 2015 s47F

Consignee: Novartis Vaccines and Diagnostics GmbH
Marburg , 35006

Date of Delivery: 06.04.2015
SPF Eggs : 4120

Flock	Hatch Date	Age of Flock	Laying Date	number of eggs
10306	18.08.2014	31	23 -25.03 2015	4570
Start of incubation	Start of candling	No. of eggs discarded	% fertility	No. of eggs delivered
29.03.2015 1100	06.04.2015 600	264	5,8	4306
Incubation humidity	Frequency of turning	Incubation temperature	Date of delivery	Flock to be used until 4 weeks before slaughtering
85° ± 30% Fahrenheit	Every 60 minutes	100° ± 5% Fahrenheit	06.04.2015 14:00 Uhr	02.11.2015

ROH 279051 0300
06. APR. 2015 s47F [redacted]

Anlage 7 zum BPR 593-01
der Charge 593 DT 192
Seite 2 von 2
06. APR. 2015 s47F [redacted]

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06. APR. 2015 s47F [redacted]

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Master Seed Virus und Working Seed Virus (Flury LEP)

Batch Number:	C26/11D	**Material Code:**	OKGU004 / OKGU00S
Date of Manufacturing:	20.01.2012	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Cell Controls

Test	Specification	Result
Cytopathic effects		
Cytopathic degenerations	Equal to PASS (= no cytopathic effect detectable)	PASS
Haemadsorption		
Haemadsorbing viruses	Equal to PASS (= no haemadsorbing viruses detectable)	PASS
Avian leucosis viruses		
Avian leucosis viruses	Equal to PASS (= no avian leucosis viruses detectable)	PASS
Extraneous agents		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS

Issued by: s47F [redacted]

System: LIMS

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Master Seed Virus und Working Seed Virus (Flury LEP)

Batch Number:	C26/11D	**Material Code:**	OKGU004 / OKGU005
Date of Manufacturing:	20.01.2012	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Virus Suspension

Test	Specification	Result
Virus titer and identity		
Virus titer	>= 6,0 Log GKID50/ml	7,3 Log $GKID_{50}$/ml
Identity	Equal to PASS (= identical to rabies virus)	PASS
Sterility		
Sterility	Equal to PASS	PASS
Mycoplasma		
Culture method	Equal to PASS (= no mycoplasma detectable)	PASS
Indicator cell culture method	Equal to PASS (= no mycoplasma detectable)	PASS
Mycobacteria		
Mycobacteria	Equal to PASS (= no mycobacteria detectable)	PASS

Neutralized Virus Suspension

Test	Specification	Result
Extraneous agents		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS

Issued by: s47F [redacted]

System: LIMS

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Master Seed Virus und Working Seed Virus (Flury LEP)

Batch Number:	C26/11D	**Material Code:**	OKGU004 / OKGU00S
Date of Manufacturing:	20.01.2012	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Test	Specification	Result
Test in adult mice		
Test in adult mice	Equal to PASS (= no signs of infection)	PASS
Test in suckling mice		
Test in suckling mice	Equal to PASS (= no signs of infection)	PASS
Test in guinea pigs		
Test in guinea pigs	Equal to PASS (= no signs of infection)	PASS
Passage of organ suspension in cell culture:		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS
Avian viruses		
Absence of avian viruses	Equal to PASS (= no avian viruses detectable in the allantoic and yolk sac liquid)	PASS
Neutralisation of Rabies-Seed Virus		
Neutralisation of Rabies-Seed Virus	Equal to PASS	PASS

Product Specification Reference: 100778

Approval By: [redacted] (Qualified [redacted] **Date:** 20.02.2014

Issued by: [redacted] System: LIMS

1. STARTING MATERIALS for ANTIGEN CONCENTRATE Lot 593A T 233

1.1. Master Seed

Virus Strain used to prepare licensed Rabies Vaccine	Rabies Master Seed Virus Flury LEP
Lot No. of Master Seed	C25/83
Preparation Date of Master Seed Lot	1983
No. of Passages between two seeds mentioned above	187
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. Monographs and with the Marketing Authorization	29.01.1985
WHO Reference	Annex 2 of the WHO Technical Report Series 658, 1981, page 54 - 88

1.2. Working Seed (Doc. No. 101508)

	Sub-Batch 1	Sub-Batch 2	Sub-Batch 3	Sub-Batch 4
Lot No. of Working Seed	C26/13B-04	C26/13B-04	C26/13B-04	C26/13B-04
Preparation Date of Working Seed Lot	10.03.2015	10.03.2015	10.03.2015	10.03.2015
Passage Level from Master Seed Lot	1	1	1	1
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. Monographs and with the Marketing Authorization	04.05.2015	04.05.2015	04.05.2015	04.05.2015

WSL C26/13B approved 20/01/2015, PM-2014-04464

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Managed Document No 310362, Version 07, Effective Date 14 10 2015

2. CELL SUBSTRATE FOR VIRUS PROPAGATION (Doc. No. 274048)

Cell Culture System	Chicken Fibroblast Cell Cultures			
Flock Number	10407			
Delivery Date of incubated Eggs	09.07.2015			
Manufacturing Date of Cell Culture	10.07.2015			
Population doubling level (PDL) of produced cells when inoculated with virus seed	2,6 / 2,4 / 2,5 / 3,0 Cells x 10^6/mL			
Nature and concentration of antibiotics used in production of cell culture maintenance medium	Aureomycin (4,6 mg/mL) Amphotericin B (0,46 µg/mL) Neomycine Sulfate (229 µg/mL)			
Starting Material	Identification and source of starting materials used in preparing production cells including excipients and preservatives			
	Sub-Batch 1	Sub-Batch 2	Sub-Batch 3	Sub-Batch 4
PBS (pH7,2) SOP271810	024	024	024	024
Trypsinization Medium SOP275550	049/02	049/02	049/02	049/02
FCS SOP222018	0038	0038	0038	0038
Medium 3 + $NaHCO_3$ SOP271811	017/08	017/08	017/08	017/08
Medium 3 + HSA SOP300719	039/09	039/09	039/10	039/10
Size of Sub-Batch	71L	71L	71L	71L
For details see attachment: Details on SPF Eggs to 593D **T 233**				

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3. CONTROL CELL CULTURES, Lot No. 593D T 233

3.1. Production Details for Control Cell Cultures, (Doc. No. 274048)

Ratio or Proportion of Control to Production Cell Culture	1 L of pooled 284L (4x71L) Cell Culture	
Period of Observation of Cultures	On (Date of Sampling)	Off (Date Control Cells handed to QC)
	10.07.2015	10.07.2015

3.2. Test Details for Control Cell Cultures, LotNo.593DT 233

Cytopathic Degenerations (SOP No. 104212)

Method	Microscopic Examination according to Ph. Eur. Random Sample: At least 500 mL of the control cells used for vaccine manufacturing	
Requirement	No cytopathic effect detectable. Equal to pass.	
Date		Result
On	Off	
10.07.2015	24.07.2015	Pass ✔

Hemadsorbing Viruses (SOP No. 103210)

Method	Test according to Ph. Eur. with Guinea Pig Erythrocytes (rbc) Sample Volume: At least 25% of the control cells after incubation for at least 14 days	
Storage Time and Temperature of rbc (SOP No. 104540)	≤ 7 days after blood withdrawal at +2 to +8°C	
Incubation	30-60 min at +2 °C to +8 °C 30-60 min at +20 °C to +25 °C	
Requirement	No haemadsorbing viruses detectable. Equal to pass.	
Date		Result
On	Off	
24.07.2015	24.07.2015	Pass ✔

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Managed Document No. 310362, Version 07, Effective Date 14 10 2015

Extraneous Agents – Chicken Fibroblast Cells (SOP No. 104681)

Method	Inoculation of Chicken Fibroblast Cells Random sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days	
Incubation	+36 °C (±1 °C) and +34 °C (±2 °C)	
Requirement	No signs of extraneous agents. Equal to pass.	
Date		Result
On	Off	
24.07.2015	07.08.2015	Pass

Extraneous Agents – Vero Cells (SOP No. 104682)

Method	Inoculation of Vero Cells Random Sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days	
Incubation	+36 °C (± 1 °C)	
Requirement	No signs of extraneous agents. Equal to pass.	
Date		Result
On	Off	
24.07.2015	07.08.2015	Pass

Extraneous Agents – Human Amnion Cells Line AV3 (SOP No. 104683)

Method	Inoculation of Human Amnion Cells Line AV3 Random Sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days	
Incubation	+36 °C (± 1 °C)	
Requirement	No signs of extraneous agents. Equal to pass.	
Date		Result
On	Off	
24.07.2015	07.08.2015	Pass

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Avian Leukosis Viruses (SOP No. 244413, 227575)

Method	Culture Method according to Ph. Eur. Random Sample Volume: 5 mL supernatant after incubation for at least 14 days
Requirement	No avian leukosis viruses detectable. Equal to pass.

Amplification in Cells		ELISA		Result
Date		Date		
On	Off	On	Off	
24.07.2015	03.08.2015	05.08.2015	06.08.2015	Pass

4. COMMENTS

N/A

5. ATTACHMENTS

Details on SPF Eggs to 593D T 233
Seed virus certificate of analysis

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	Control Certificate	VALO BioMedia GmbH
		FO-DE-144.01
		Gültig ab 01.10.12
	Formblätter	Seite 1/2

Consignee: Novartis Vaccines and Diagnostics GmbH
Marburg , 35006

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09. JULI 2015 S47F

Date of Delivery: 09.07.2015
SPF Eggs : 4120

Details of the consignment: Latest Sampling Date **22.06.2015**

The following tests were carried out on samples of the above mentioned flock. No test result or clinical observation showed any sign of infection and the SPF status is confirmed to be in accordance with the valid EP:		Testing Method	Result
Avian Adeno Viruses, group 1		AGP	N
Avian Encephalomyelitis Virus		ELISA	N
Avian Infectious Bronchitis Virus		ELISA	N
Avian Infectious Laryngotracheitis Virus		ELISA	N
Avian Leukosis Viruses/antibodies subtypes A,B, J		ELISA	N
Avian Leukosis Viruses – P27 antigen		ELISA	N
Avian Nephritis Virus		ELISA	N
Avian Orthoreoviruses		ELISA	N
Avian Reticuloendotheliosis Virus		ELISA	N
Avibacterium paragallinarum		CO/PM	N
Chicken Anemia Virus (CAV)		ELISA	N
Egg Drop Syndrome Virus		HI	N
Fowlpox Virus		CO/PM	N
Infectious Bursal Disease Virus (IBDV)	Serotype 1	ELISA	N
	Serotype 2	VN	N
Influenza A Virus		AGP	N
Marek's Disease Virus		AGP	N
Mycobacterium avium		CO/PM	N
Mycoplasma gallisepticum		SPA	N
Mycoplasma synoviae		SPA	N
Newcastle Disease Virus		HI	N
Salmonella pullorum		SPA	N
Salmonella spp.		BE	N
Turkey Rhinotracheitis Virus		ELISA	N

Anlage 7 zum BPR 593-01
der Charge 593DT 233
Seite 1 von 2
09. JULI 2015 S47F

Keys of signs:
N = negative; HI = Hemagglutination-Inhibition Test; AGP = Agar-Gel-Precipitation Test; EP = European Pharmacopoeia; SPA = Serum Plate Agglutination; BE = Bacteriological Examination; P = positive; CO = Clinical Observation; PM = Post Mortem; VN = Virus Neutralization Test; ELISA = Enzyme Linked Immunosorbent Assay commercial test kit

We hereby confirm that all VALO SPF flocks from which we have supplied SPF eggs during the last four weeks are still in accordance with the requirements of the valid EP. Any change of the status of the flocks will be reported to all related customers immediately. The eggs of this delivery have been collected within 7 days prior to the date of departure from our farm. The origin of the eggs is the Federal Republic of Germany.

Osterholz-Scharmbeck, 01.07.2015

ROH 279051 0355
09. JULI 2015
S47F

S47F
Signature of VALO BioMedia GmbH

GXP COPY
09. JULI 2015 S47F

Consignee: Novartis Vaccines and Diagnostics GmbH
Marburg , 35006

Date of Delivery: 09.07.2015
SPF Eggs : 4120

Anlage 7 zum BPR 593-01
der Charge 593DT 233
Seite 2 von 2
09. JULI 2015 S47F

Flock	Hatch Date	Age of Flock	Laying Date	number of eggs
10407	28.07.2014	47	23./24.06.2015	4780
Start of incubation	Start of candling	No. of eggs discarded	% fertility	No. of eggs delivered
01.07.2015 6⁰⁰	09.07.2015 3¹⁰	371	7,8	4409
Incubation humidity	Frequency of turning	Incubation temperature	Date of delivery	Flock to be used until 4 weeks before slaughtering
85° ± 30% Fahrenheit	Every 60 minutes	100° ±5% Fahrenheit	09.07.2015 14:00 Uhr	05.10.2015

ROH 279051 0355
09. JULI 2015 S47F

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Rabies Seed Virus with HSA

Batch Number:	C26/13B	**Material Code:**	OKGU004 / OHGU005
Date of Manufacturing:	08.04.2013	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Cell Controls

Test	Specification	Result
Cytopathic effects		
Cytopathic degenerations	Equal to PASS (= no cytopathic effect detectable)	PASS
Haemadsorption		
Haemadsorbing viruses	Equal to PASS (= no haemadsorbing viruses detectable)	PASS
Avian leucosis viruses		
Avian leucosis viruses	Equal to PASS (= no avian leucosis viruses detectable)	PASS
Extraneous agents		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS

Issued by: s47F [redacted]

System: LIMS

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Rabies Seed Virus with HSA

Batch Number:	C26/13B	**Material Code:**	OKGU004 / OHGU005
Date of Manufacturing:	08.04.2013	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Virus Suspension

Test	Specification	Result
Virus titer and identity		
Virus titer	>= 6,0 Log GKIDS0/ml	7,0 Log $GKID_{50}$/ml
Identity	Equal to PASS (= identical to rabies virus)	PASS
Sterility		
Sterility	PASS	PASS
Mycoplasma		
Mycoplasma	Equal to PASS (= no mycoplasma detectable)	PASS
Mycobacteria		
Mycobacteria	Equal to PASS (= no mycobacteria detectable)	PASS

Neutralized Virus Suspension

Test	Specification	Result
Extraneous agents		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS

Issued by: 547F [redacted]

System: LIMS

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Rabies Seed Virus with HSA

Batch Number:	C26/13B	**Material Code:**	OKGU004 / OHGU005
Date of Manufacturing:	08.04.2013	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Test	Specification	Result
Test in adult mice		
Test in adult mice	Equal to PASS (= no signs of infection)	PASS
Test in suckling mice		
Test in suckling mice	Equal to PASS (= no signs of infection)	PASS
Test in guinea pigs		
Test in guinea pigs	Equal to PASS (= no signs of infection)	PASS
Passage of organ suspension in cell culture:		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS
Avian viruses		
Absence of avian viruses	Equal to PASS (= no avian viruses detectable in the allantoic and yolk sac liquid)	PASS
Neutralisation of Rabies-Seed Virus		
Neutralisation of Rabies-Seed Virus	Equal to PASS	PASS

Product Specification Reference: 100778

Approval By: s47F [redacted] **Date:** 10.07.14

Issued by: s47F [redacted] System: LIMS

1. STARTING MATERIALS for ANTIGEN CONCENTRATE Lot 593A T 235

1.1. Master Seed

Virus Strain used to prepare licensed Rabies Vaccine	Rabies Master Seed Virus Flury LEP
Lot No. of Master Seed	C25/83
Preparation Date of Master Seed Lot	1983
No. of Passages between two seeds mentioned above	187
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. Monographs and with the Marketing Authorization	29.01.1985
WHO Reference	Annex 2 of the WHO Technical Report Series 658, 1981, page 54 - 88

1.2. Working Seed (Doc. No. 101508)

	Sub-Batch 1	Sub-Batch 2	Sub-Batch 3	Sub-Batch 4
Lot No. of Working Seed	C26/13B-04	C26/13B-04	C26/13B-04	C26/13B-04
Preparation Date of Working Seed Lot	10.03.2015	10.03.2015	10.03.2015	10.03.2015
Passage Level from Master Seed Lot	1	1	1	1
Date of approval of protocols indicating compliance with the requirements of the relevant Ph. Eur. Monographs and with the Marketing Authorization	04.05.2015	04.05.2015	04.05.2015	04.05.2015

WSL C26/13B approved 20/01/2015, PM-2014-04464

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Managed Document No 310362, Version 07, Effective Date 14102015

2. CELL SUBSTRATE FOR VIRUS PROPAGATION (Doc. No. 274048)

Cell Culture System	Chicken Fibroblast Cell Cultures			
Flock Number	10306			
Delivery Date of incubated Eggs	14.07.2015			
Manufacturing Date of Cell Culture	15.07.2015			
Population doubling level (PDL) of produced cells when inoculated with virus seed	3,0 / 2,4 / 2,9 / 2,5 Cells x 10^6/mL			
Nature and concentration of antibiotics used in production of cell culture maintenance medium	Aureomycin (4,6 mg/mL) Amphotericin B (0,46 µg/mL) Neomycine Sulfate (229 µg/mL)			
Starting Material	Identification and source of starting materials used in preparing production cells including excipients and preservatives			
	Sub-Batch 1	Sub-Batch 2	Sub-Batch 3	Sub-Batch 4
PBS (pH7,2) SOP271810	024	024	024	024
Trypsinization Medium SOP275550	050/01	050/01	050/01	050/01
FCS SOP222018	0038	0038	0038	0038
Medium 3 + $NaHCO_3$ SOP271811	017/06	017/06	017/06	017/06
Medium 3 + HSA SOP300719	038/01	038/01	038/02	038/02
Size of Sub-Batch	71L	71L	71L	71L
For details see attachment: Details on SPF Eggs to 593D T 235				

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3. CONTROL CELL CULTURES, Lot No. 593D T 235

3.1. Production Details for Control Cell Cultures, (Doc. No. 274048)

Ratio or Proportion of Control to Production Cell Culture	1 L of pooled 284L (4x71L) Cell Culture	
Period of Observation of Cultures	On (Date of Sampling)	Off (Date Control Cells handed to QC)
	15.07.2015	16.07.2015

3.2. Test Details for Control Cell Cultures, LotNo.593DT 235

Cytopathic Degenerations (SOP No. 104212)

Method	Microscopic Examination according to Ph. Eur. Random Sample: At least 500 mL of the control cells used for vaccine manufacturing	
Requirement	No cytopathic effect detectable. Equal to pass.	
Date		Result
On	Off	
16.07.2015	31.07.2015	Pass ✔

Hemadsorbing Viruses (SOP No. 103210)

Method	Test according to Ph. Eur. with Guinea Pig Erythrocytes (rbc) Sample Volume: At least 25% of the control cells after incubation for at least 14 days	
Storage Time and Temperature of rbc (SOP No. 104540)	≤ 7 days after blood withdrawal at +2 to +8°C	
Incubation	30-60 min at +2 °C to +8 °C 30-60 min at +20 °C to +25 °C	
Requirement	No haemadsorbing viruses detectable. Equal to pass.	
Date		Result
On	Off	
31.07.2015	31.07.2015	Pass ✔

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Extraneous Agents – Chicken Fibroblast Cells (SOP No. 104681)

Method	Inoculation of Chicken Fibroblast Cells Random sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days
Incubation	+36 °C (±1 °C) and +34 °C (±2 °C)
Requirement	No signs of extraneous agents. Equal to pass.

Date		Result
On	Off	
31.07.2015	14.08.2015	Pass ✔

Extraneous Agents – Vero Cells (SOP No. 104682)

Method	Inoculation of Vero Cells Random Sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days
Incubation	+36 °C (± 1 °C)
Requirement	No signs of extraneous agents. Equal to pass.

Date		Result
On	Off	
31.07.2015	14.08.2015	Pass ✔

Extraneous Agents – Human Amnion Cells Line AV3 (SOP No. 104683)

Method	Inoculation of Human Amnion Cells Line AV3 Random Sample: 2 x 5 mL of control cells supernatant incubated for at least 14 days
Incubation	+36 °C (± 1 °C)
Requirement	No signs of extraneous agents. Equal to pass.

Date		Result
On	Off	
31.07.2015	14.08.2015	Pass ✔

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Managed Document No 310362, Version 07, Effective Date 14102015

Avian Leukosis Viruses (SOP No. 244413, 227575)

Method	Culture Method according to Ph. Eur. Random Sample Volume: 5 mL supernatant after incubation for at least 14 days
Requirement	No avian leukosis viruses detectable. Equal to pass.

Amplification in Cells		ELISA		Result
Date		Date		
On	Off	On	Off	
31.07.2015	10.08.2015	18.08.2015	18.08.2015	Pass

4. COMMENTS

N/A

5. ATTACHMENTS

Details on SPF Eggs to 593D T 235
Seed virus certificate of analysis

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VALO BioMedia	Control Certificate	VALO BioMedia GmbH
		FO-DE-144.01
		Gültig ab 01.10.12
	Formblätter	Seite 1/2

Consignee: Novartis Vaccines and Diagnostics GmbH
Marburg , 35006

GXP COPY

Date of Delivery: 14.07.2015
SPF Eggs : 4120

14. JULI 2015 [redacted]

Details of the consignment:

Latest Sampling Date	29.06.2015

The following tests were carried out on samples of the above mentioned flock. No test result or clinical observation showed any sign of infection and the SPF status is confirmed to be in accordance with the valid EP:		Testing Method	Result
Avian Adeno Viruses, group 1		AGP	N
Avian Encephalomyelitis Virus		ELISA	N
Avian Infectious Bronchitis Virus		ELISA	N
Avian Infectious Laryngotracheitis Virus		ELISA	N
Avian Leukosis Viruses/antibodies subtypes A,B, J		ELISA	N
Avian Leukosis Viruses – P27 antigen		ELISA	N
Avian Nephritis Virus		ELISA	N
Avian Orthoreoviruses		ELISA	N
Avian Reticuloendotheliosis Virus		ELISA	N
Avibacterium paragallinarum		CO/PM	N
Chicken Anemia Virus (CAV)		ELISA	N
Egg Drop Syndrome Virus		HI	N
Fowlpox Virus		CO/PM	N
Infectious Bursal Disease Virus (IBDV)	Serotype 1	ELISA	N
	Serotype 2	VN	N
Influenza A Virus		AGP	N
Marek's Disease Virus		AGP	N
Mycobacterium avium		CO/PM	N
Mycoplasma gallisepticum		SPA	N
Mycoplasma synoviae		SPA	N
Newcastle Disease Virus		HI	N
Salmonella pullorum		SPA	N
Salmonella spp.		BE	N
Turkey Rhinotracheitis Virus		ELISA	N

Keys of signs:

N	= negative	SPA	= Serum Plate Agglutination	PM	= Post Mortem
HI	= Hemagglutination-Inhibition Test	BE	= Bacteriological Examination	VN	= Virus Neutralization Test
AGP	= Agar-Gel-Precipitation Test	P	= positive	ELISA	= Enzyme Linked Immunosorbent Assay, commercial test kit
EP	= European Pharmacopoela	CO	= Clinical Observation		

We hereby confirm that all VALO SPF flocks from which we have supplied SPF eggs during the last four weeks are still in accordance with the requirements of the valid EP. Any change of the status of the flocks will be reported to all related customers immediately. The eggs of this delivery have been collected within 7 days prior to the date of departure from our farm. The origin of the eggs is the Federal Republic of Germany.

Osterholz-Scharmbeck, 08.07.2015

ROH 279051 0357
4. JULI 2015 [redacted]

[redacted]
Signature of VALO BioMedia GmbH

Anlage 7 zum BPR 593-01
der Charge 593DT 235
Seite 1 von 2
14. JULI 2015 [redacted]

Consignee: Novartis Vaccines and Diagnostics GmbH
Marburg , 35006

Date of Delivery: 14.07.2015
SPF Eggs : 4120

Flock	Hatch Date	Age of Flock	Laying Date	number of eggs
10306	18.08.2014	45	[illegible]	[illegible]
Start of incubation	Start of candling	No. of eggs discarded	% fertility	No. of eggs delivered
06.07.2015	615	346	6,1	4254
Incubation humidity	Frequency of turning	Incubation temperature	Date of delivery	Flock to be used until 4 weeks before slaughtering
85° ± 30% Fahrenheit	Every 60 minutes	100° ± 5% Fahrenheit	14.07.2015 14:00 Uhr	02.11.2015

Anlage 7 zum BPR 593-01
der Charge 593DT 235
Seite 2 von 2
14. JULI 2015 s47F

ROH 279051 0357
14. JULI 2015 s47F

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14. JULI 2015 s47F

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Rabies Seed Virus with HSA

Batch Number:	C26/13B	**Material Code:**	OKGU004 / OHGU005
Date of Manufacturing:	08.04.2013	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Cell Controls

Test	Specification	Result
Cytopathic effects		
Cytopathic degenerations	Equal to PASS (= no cytopathic effect detectable)	PASS
Haemadsorption		
Haemadsorbing viruses	Equal to PASS (= no haemadsorbing viruses detectable)	PASS
Avian leucosis viruses		
Avian leucosis viruses	Equal to PASS (= no avian leucosis viruses detectable)	PASS
Extraneous agents		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS

Issued by: s47F [redacted]

System: LIMS

NOVARTIS
VACCINES AND
DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Rabies Seed Virus with HSA

Batch Number:	C26/13B	**Material Code:**	OKGU004 / OHGU005
Date of Manufacturing:	08.04.2013	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Virus Suspension

Test	Specification	Result
Virus titer and identity		
Virus titer	>= 6,0 Log GKIDS0/ml	7,0 Log $GKID_{50}$/ml
Identity	Equal to PASS (= identical to rabies virus)	PASS
Sterility		
Sterility	PASS	PASS
Mycoplasma		
Mycoplasma	Equal to PASS (= no mycoplasma detectable)	PASS
Mycobacteria		
Mycobacteria	Equal to PASS (= no mycobacteria detectable)	PASS

Neutralized Virus Suspension

Test	Specification	Result
Extraneous agents		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS

Issued by: [redacted]

System: LIMS

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Rabies Seed Virus with HSA

Batch Number:	C26/13B	**Material Code:**	OKGU004 / OHGU005
Date of Manufacturing:	08.04.2013	**Expiry Date:**	N/A
Start of Shelf Life:	N/A	**Storage Condition:**	≤ - 70°C

Test	Specification	Result
Test in adult mice		
Test in adult mice	Equal to PASS (= no signs of infection)	PASS
Test in suckling mice		
Test in suckling mice	Equal to PASS (= no signs of infection)	PASS
Test in guinea pigs		
Test in guinea pigs	Equal to PASS (= no signs of infection)	PASS
Passage of organ suspension in cell culture:		
Chicken fibroblast cells	Equal to PASS (= no signs of extraneous agents)	PASS
Vero cells	Equal to PASS (= no signs of extraneous agents)	PASS
Human amnion cell line AV3	Equal to PASS (= no signs of extraneous agents)	PASS
Avian viruses		
Absence of avian viruses	Equal to PASS (= no avian viruses detectable in the allantoic and yolk sac liquid)	PASS
Neutralisation of Rabies-Seed Virus		
Neutralisation of Rabies-Seed Virus	Equal to PASS	PASS

Product Specification Reference: 100778

Approval By: s47F [redacted] **Date:** 10.07.14

Issued by: s47F [redacted] System: LIMS

GSK Vaccines		**Wirksamkeitsprüfung:**	**Tollwut-Impfstoffprüfung**
Qualitätskontrolle		**SOP Nr.:**	**103208-09**
Probit-Programm		**Vorgangs-Nr.:**	**10114**

Testnummer: 6

Standardsubstanz: WF-3
Sollwert: 10,77 I.E./ml

Prüfpräparat: Rabies
Ch. B.: 616 011
Lag./Temp.:
Bemerkung (LIMS-ID): 4479286
Impfdosis: 1,00 ml

Infektiöses Agens:: Tollwut-Challengevirus
Ch. B.: 080212
LD 50 / Tier: 100

Probanden: Mäuse:NMRI (CR-Sulzfeld)
Immunisierungsdosis: 2 x 0,5 ml i.p.
Belastungsdosis: 0,03 ml i.c.

Testdaten:
Testbeginn (Immunisierung): 18.02.2016 / 25.02.2016
Belastung: 03.03.2016
Testende: 17.03.2016

Dateineingabe: Graf

Standardsubstanz: WF-3

PD50: 8,2915

Dosis	Reagenten	Probanden
100.0000 µl	17	18
20.0000 µl	16	20
4.0000 µl	5	20
0.8000 µl	1	19

Prüfpräparat: Rabies Ch. B. 616 011

PD50: 15,2197

Dosis	Reagenten	Probanden
100.0000 µl	16	20
20.0000 µl	11	20
4.0000 µl	7	20
0.8000 µl	0	20

Ergebnis zu Vorgangsnummer 10114

Spezifikation (laut Prüfungsvorschrift):

Wirkungsquotient x Sollwert:		**5,87 I.E./ml**	**5,9 I.E./Dosis**
95 % Konfidenzintervall:	Untere Vertrauens-Grenze:	2,69 I.E./ml	2,7 I.E./Dosis
	Obere Vertrauens-Grenze:	12,80 I.E./ml	12,8 I.E./Dosis

Validitätskriterien (PD50, Vertrauensgrenzen, LD50, Linearität/Parallelität) - entsprechen / ~~entsprechen nicht~~ - den Anforderungen und die Rohdaten aus dem LTR (Reagenten/Probanden) wurden auf Richtigkeit überprüft.

Marburg, den 21.03.16

S47F

Unters eiter Labor Bioassays)

~~**Prüfpräparat - entspricht / entspricht nicht - den Anforderungen**~~ entfällt / 30.03.16 S47F

Marburg, den 30.03.16

S47F

Unterschrift (Labormanager bzw. Vertreter)

GSK Vaccines		**Wirksamkeitsprüfung:**	**Tollwut-Impfstoffprüfung**
Qualitätskontrolle		**SOP Nr.:**	**103208-09**
Probit-Programm		**Vorgangs-Nr.:**	**10131**

Testnummer: **7**

Standardsubstanz: **WF-3**
Sollwert: 10,77 I.E./ ml

Prüfpräparat: **Rabies**
Ch. B.: 616 011
Lag./Temp.:
Bemerkung (LIMS-ID): 4479287
Impfdosis: 1,00 ml

Infektiöses Agens:: Tollwut-Challengevirus
Ch. B.: 080212
LD 50 / Tier: 121

Probanden: Mäuse:NMRI (CR-Sulzfeld)
Immunisierungsdosis: 2 x 0,5 ml i.p.
Belastungsdosis: 0,03 ml i.c.

Testdaten:
Testbeginn (Immunisierung): 02.03.2016 / 0903.2016
Belastung: 16.03.2016
Testende: 30.03.2016

Dateineingabe: **Graf**

Standardsubstanz: WF-3

PD50: 1,8237

Dosis	Reagenten	Probanden
100. 0000µl	20	20
20.0000 µl	16	20
4.0000 µl	11	20
0.8000 µl	9	20

Prüfpräparat: Rabies Ch. B. 616 011

PD50: 4,2025

Dosis	Reagenten	Probanden
100.0000 µl	19	20
20.0000 µl	14	19
4.0000 µl	9	20
0.8000 µl	5	20

Ergebnis zu Vorgangsnummer 10131

Spezifikation (laut Prüfungsvorschrift):

Wirkungsquotient x Sollwert:		**4,67**	**I.E./ml**	**4,7**	**I.E./Dosis**
95 % Konfidenzintervall:	Untere Vertrauens-Grenze:	1,66	I.E./ml	1,7	I.E./Dosis
	Obere Vertrauens-Grenze:	13,15	I.E./ml	13,1	I.E./Dosis

Validitätskriterien (PD50, Vertrauensgrenzen, LD50, Linearität/Parallelität) - entsprechen / ~~entsprechen nicht~~ - den Anforderungen und die Rohdaten aus dem LTR (Reagenten/Probanden) wurden auf Richtigkeit überprüft.

Marburg, den 31.03.16 s47F

Unterschr[redacted]iter Labor Bioassays)

~~**Prüfpräparat - entspricht / entspricht nicht - den Anforderungen**~~ auftaTF 01.04.16 s47F

Marburg, den 01. APR. 2016 s47F

U[redacted]bzw. Vertreter)

GSK Vaccines	Berechnung der gewichteten mittleren Aktivität gem. Ph.Eur. und Vorgehen bei OOS-Resultaten bei Aktivitätsbestimmungen	Laboratory Test Record
LTR-Nr.: LTR-225189-06	*Calculation of weighted mean activity according to Ph.Eur. and procedure in case of OOS-results in activity assays*	Seite 1 von 2
SOP-Nr.: SOP-225189-06	**Laufende Test-Nr.:** 9	225189-00000174
Labor / Bereich: Bioassays		

1 Probe(n) *(Sample (s))*

Präparat: Rabies *Product*	**Ch.B.:** 616 011 *Batch-No.:*
LIMS-ID: 4479289 *LIMS-ID*	**Lfd.-Nr.:** 6268057 *Running-No.:*

2 Prüfung/Test *(Assay:/Test)*

Berechnung der Aktivität *(calculation of activity)*

Durchgeführte Prüfung: *Assay performed:*	Tollwut-Wirksamkeitsprüfung
Nach SOP Nr.: *Acc SOP no.:*	103208-09

	Kombination der Ergebnisse aus V-Nr: *Mean of result of test no.:*	**Probit-Vorgangs-Nr:** *Probit calculation no.:*
1.	6	10114
2.	7	10131
3.	/	/

Ergebnis: *Result*	5,4 IE/Dosis	2,9 IE/Dosis	10,1 IE/Dosis
	Wirksamkeit *Activity*	**Unteres Konfidenzintervall** *Lower confidence limit*	**Oberes Konfidenzintervall** *Upper confidence limit*

Berechnung durchgeführt *Calculation done by:*	**Datum** *Date*	31.03.2016	**Unterschrift** *Signature*	S47F [redacted]

Bemerkungen:

Weitergabe sowie Vervielfältigung dieser Unterlage, Verwertung und Mitteilung ihres Inhalts nicht gestattet, soweit nicht ausdrücklich zugestanden. Zuwiderhandlungen verpflichten zu Schadenersatz. Alle Rechte fur den Fall der Patenterteilung oder Gebrauchsmuster-Eintragung vorbehalten.

LIMS Reportname 225189-00000174 User: GRAFHA1 Druckdatum: 10:06 31.03.2016

3 Ergebnis *(Result)*

Präparat *Product*	Ch.Bez. *Batch-No.*	LIMS-ID *LIMS-ID*	LIMS-Eintrag *LIMS-Entry*	Bewertung *Assessment*	Beurteilung *Validation*
Rabies	616 011	4479289	Ja *yes* / ~~Nein~~ *no*	Pass / ~~Fail~~	valid / ~~invalid~~

Protokoll richtig ausgefüllt und geprüft *The record is correctly filled out and checked*	31.03.16 Datum *Date*	s47F Unterschrift *Signature*
	Verantwortlicher Mitarbeiter/Supervisor *Responsible operator / Supervisor*	
Ergebnistabelle und Bewertung geprüft, sofern zutreffend im LIMS eingetragen *Summary table and assessment are checked, if applicable entered in LIMS* **(siehe Tabelle)** *(See table)*	31.03.16 Datum *Date*	s47F Unterschrift *Signature*
	Verantwortlicher Mitarbeiter/Supervisor *Responsible operator / Supervisor*	
Der Test ist valide *Test is valid* **(siehe Tabelle)** *(See table)*	01. APR. 2016 Datum *Date*	s47F
	Laborleiter/Supervisor *Head of laboratory / Supervisor*	
AM erstellt *Deviation is initiated* **Ja** *Yes* ☐ **Nein** *No* ☒ **AM Nr.** *(DR No)*	31.03.16 Datum *date*	s47F Unterschrift *Signature*
	Verantwortlicher Mitarbeiter *Responsible operator*	

Bemerkungen:

Weitergabe sowie Vervielfältigung dieser Unterlage, Verwertung und Mitteilung ihres Inhalts nicht gestattet, soweit nicht ausdrücklich zugestanden. Zuwiderhandlungen verpflichten zu Schadenersatz. Alle Rechte für den Fall der Patenterteilung oder Gebrauchsmuster-Eintragung vorbehalten.

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Rabies 616 011

Mittelwertberechnung SOP 225189-06

	A	B	C	D	E	F	G	H	I	J
1	**EuPharm 6.2**	**Test 6**	**Test 7**							
2										
3	Activity (IE / Dose)	5,8700	4,6700							
4	Lower limit	2,6900	1,6600							
5	Upper limit	12,8000	13,1500							
6										
7	M	1,7699	1,5412				1,6555	2	0,0131	
8	Lower limit (M)	0,9895	0,5068							
9	Upper limit (M)	2,5494	2,5764							
10	df	0	0	0	0	0	0			
11	t	1,9600	1,9600	1,9600	1,9600	1,9600	1,9600			
12	L (length of CI)	1,5599	2,0696							
13										
14	Weight (6.2.3)	6,3148	3,5874				9,9022	0,3178		
15	M (weighted 6.2.3)	11,1763	5,5288				1,6870	1,0642	2,3098	
16	Activity with CI						5,4033	2,8984	10,0729	
17										
18	Chisq (6.2.2)	0,0433	0,0763				0,1197	0,7294	**homogeneous**	
19										
20	Intra-assay	0,1584	0,2788							
21	Inter-assay	0,0131	0,0131							
22	Weight (6.2.4)	5,8332	3,4267				9,2599	0,3286		
23	M (weighted 6.2.4)	10,3239	5,2811				1,6852	1,0280	2,3425	
24	Activity with CI						5,3937	2,7954	10,4069	
25										
26	**Final (IE / Dose)**						**5,4033**	**2,8984**	**10,0729**	**3,4753**

gerechnet: 31.03.16

geprüft: 01.04.16

[redacted]

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P.O. Box 1630, 35006 Marburg, Germany
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05.04.2016

Statement

Human Albumin used in the production of Rabipur® batch **616011A-Z**

Herewith I confirm that the Human Albumin lots listed in the table below were used for production of Rabipur Lot 616011A-Z. The internal GSK Vaccines lot number and the respective supplier lot number including OCABR certificate reference are indicated.

Lot Release Protocol to Rabipur Lot 616011A-Z		**OCABR Certification to Human Albumin Lots**
Lot Number Human Albumin (GSK Vaccines)	**Lot Number Human Albumin** (Baxter Bioscience/CSL Behring)	
2436950017	LA09D077AA	OCABR Certificate to filling lot no. LA09D077A
2436950020	LA10D172AA	OCABR Certificate to filling lot no. LA10D172A
2876560005	4362500013	OCABR Certificate to filling lot no. 2096400013
2876560006	4362500015	OCABR Certificate to filling lot no. 2096400015

s47F [redacted]

s47F [redacted]

(Qualified Person)

NIBSC
A centre of the Health Protection Agency

UKAS TESTING
1470

Blanche Lane
South Mimms
Potters Bar
Hertfordshire EN6 3QG
United Kingdom

EC/EEA OFFICIAL CONTROL AUTHORITY BATCH RELEASE CERTIFICATE FOR MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD OR PLASMA –Finished Product

Examined under Article 114 of Directive 2001/83/EC as amended by Directive 2004/27/EC (Medicinal Products Derived from Human Blood or Plasma) and in accordance with the Administrative Procedures for Official Control Authority Batch Release.

NIBSC Release Certificate Number:	10/1 H5230 A

Product trade name:	Albumina 25% P/V, Solucaode Albumina Humana 100ml
International non-proprietary name, Ph.Eur. name or common name:	Human Albumin 25%
Batch/lot or filling batch/lot number:	LAlb0077A
Type of final container as defined by CPMP III/3593/91:	Bottle
Number of final containers in batch/lot:	9289
Nominal dose per container:	1
Date of start of period of validity:	30th May 2009
Date of expiry:	30th April 2012
EC/EEA Marketing Authorization Number: Issued by:	3917184 (PT) INFARMED, Portugal
Name and address of Manufacturer:	Baxter Healthcare Corporation 4501 Colorado Boulevard, Los Angeles, California 90039, U S A
Name and address of EC/EEA Marketing Authorization holder if different from the manufacturer:	Baxter Medico Farmaceutica Lda Sintra Business Park, Zone Industrial da Abrunheira, Edificio No. 10, 2710-089 Sintra, Portugal

This batch has been examined using documented procedures forming part of a quality system accredited to ISO/IEC 17025. All tests may not be accredited. Tests may include those for which accreditation is claimed under the bounds of our flexible scope of accreditation. Accredited tests are shown in the UKAS Schedule of Accreditation.
This examination is based on either:
– The relevant Note for Guidance of this product, or in its absence,
– The review of the manufacturer's protocol and the appropriate control laboratory tests as indicated in the Marketing Authorisation application.

All the constituent plasma pools have been tested by an EU/EEA OMCL for virological markers. Testing not undertaken by NIBSC is outside the scope of our UKAS accredited system.

This batch is in compliance with the approved specifications laid down in the relevant European Pharmacopoeia monographs and the above Marketing Authorization and is released.

Signed: s47F [redacted]

Name: s47F [redacted]

Date of Issue: 25th August 2010

An authorized signatory for the National Institute for Biological Standards and Control

NIBSC
A centre of the Health Protection Agency

UKAS TESTING
1470

Blanche Lane
South Mimms
Potters Bar
Herlfordshire EN6 3QG
United Kingdom

EU/EEA OFFICIAL CONTROL AUTHORITY BATCH RELEASE CERTIFICATE FOR MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD OR PLASMA –Finished Product

Examined under Article 114 of Directive 2001/83/EC as amended by Directive 2004/27/EC (Medicinal Products derived from Human Blood or Plasma) and in accordance with the Administrative Procedures for Official Control Authority Batch Release.

NIBSC Release Certificate Number:	**11/2 H 5189 A**

Product trade name:	**Albumina 25% P/V, Solucao de Albumina Humana 100ml**
International non-proprietary name, Ph.Eur. name or common name:	**Human Albumin 25%**
Batch/lot of filling batch/lot number:	**LA10D172A**
Type of final container:	**Bottle**
Number of final containers in batch/lot:	**8523**
Nominal dose per container:	**1**
Date of start of period of validity:	**9th December 2010**
Date of expiry:	**30th November 2015**
EU/EEA Marketing Authorization Number: Issued by:	**3917184 (PT)** **INFARMED, Portugal**
Name and address of Manufacturer:	**Baxter Healthcare Corporation** **4501 Colorado Boulevard,** **Los Angeles, California 90039, USA**
Name and address of EU/EEA Marketing Authorization holder if different from the manufacturer:	**Baxter Medico Farmaceutica Lda** **Sintra Business Park, Zone Industrial da Abrunheira,** **Edificio No. 10, 2710-089 Sintra, Portugal**

This batch has been examined using documented procedures forming part of a quality system accredited to ISO/IEC 17025. All tests may not be accredited. Tests may include those for which accreditation is claimed under the bounds of our flexible scope of accreditation. Accredited tests are shown in the UKAS Schedule of Accreditation.

This examination is based on either:

- The relevant Note for Guidance of this product, or in its absence.
- The review of the manufacturer's protocol and the appropriate control laboratory tests as indicated in the Marketing Authorisation application.

All the constituent plasma pools have been tested by an EU/EEA OMCL for virological markers. Testing not undertaken by NIBSC is outside the scope of our UKAS accredited system.

This batch is in compliance with the approved specifications laid down in the relevant European Pharmacopoeia monographs and the above Marketing Authorization, and is released.

Signed: s47F [redacted]

Name: s47F [redacted]

Date of Issue: 2nd August 2011

An authorized signatory for the National Institute for Biological Standards and Control.

(Form CRO-B8U version 4 04 Jan 2011)

Page 1 of 1

Swiss Official Control Authority Batch Release Certificate for Medicinal Products Derived from Human Blood or Plasma

According to EU/EEA Guidelines and the MRA Switzerland - EC, Annex 1, Chapter 15

Swiss Agency for Therapeutic Products, Division Laboratories OMCL, CH-3000 Berne 9, Switzerland

OFFICIAL CONTROL AUTHORITY BATCH RELEASE CERTIFICATE - Finished Product

Examined under the Swiss Federal Law on Therapeutic Products of December 15, 2000, in accordance with Article 114 of Directive 2001/83/EC as amended by Directive 2004/27/EC (Medicinal Products derived from Human Blood or Plasma) and the Administrative Procedure for Official Control Authority Batch Release.

Trade name	**Albumin CSL 25%**
International non-proprietary name / Ph. Eur. name / common name:	Human albumin solution
Lot number appearing on package:	as given by manufacturer
Other identification numbers associated with this batch:	2096400013
Type of container:	Bottle
Total number of containers in this batch:	7710
Nominal dose per container:	1
Date of start of period of validity:	21/07/2013
Date of expiry:	20/07/2016
Marketing authorisation number in Switzerland:	52476
Name and address of manufacturer:	CSL Behring AG CH-3014 Bern
Name and address of marketing authorisation holder:	CSL Behring AG CH-3014 Bern

This batch has been examined by the OMCL Biologika using documented procedures which form part of a quality system which is in accordance with the ISO/IEC 17025 standard. This examination is based on the relevant Note for Guidance for this product.
All the constituent plasma pools have been tested by an OMCL for virological markers.
This batch is in compliance with the approved specifications laid down in the relevant European Pharmacopoeia monographs and the above marketing authorisation and is released.

Signed	s47F [redacted]
Name and function of signatory	s47F [redacted] Scientific Expert for Blood Products/OCABR Contact Person
Date of issue	30.10.2013

Certificate number: C-003813

Swiss Official Control Authority Batch Release Certificate for Medicinal Products Derived from Human Blood or Plasma

According to EU/EEA Guidelines and the MRA Switzerland - EC, Annex 1, Chapter 15

Swiss Agency for Therapeutic Products, Division Laboratories OMCL, CH-3000 Berne 9, Switzerland

OFFICIAL CONTROL AUTHORITY BATCH RELEASE CERTIFICATE - Finished Product

Examined under the Swiss Federal Law on Therapeutic Products of December 15, 2000, in accordance with Article 114 of Directive 2001/83/EC as amended by Directive 2004/27/EC (Medicinal Products derived from Human Blood or Plasma) and the Administrative Procedure for Official Control Authority Batch Release.

Trade name	**Albumin CSL 25%**
International non-proprietary name / Ph. Eur. name / common name:	Human albumin solution
Lot number appearing on package:	as given by manufacturer
Other identification numbers associated with this batch:	2096400015
Type of container:	Bottle
Total number of containers in this batch:	7645
Nominal dose per container:	1
Date of start of period of validity:	14/12/2013
Date of expiry:	13/12/2016
Marketing authorisation number in Switzerland:	52476
Name and address of manufacturer:	CSL Behring AG CH-3014 Bern
Name and address of marketing authorisation holder:	CSL Behring AG CH-3014 Bern

This batch has been examined by the OMCL Biologika using documented procedures which form part of a quality system which is in accordance with the ISO/IEC 17025 standard. This examination is based on the relevant Note for Guidance for this product.
All the constituent plasma pools have been tested by an OMCL for virological markers.
This batch is in compliance with the approved specifications laid down in the relevant European Pharmacopoeia monographs and the above marketing authorisation and is released.

Signed	s47F [redacted]
Name and function of signatory	s47F [redacted] Scientific Expert for Blood Products
Date of issue	25.02.2014

Swiss Agency for Therapeutic Products swissmedic

Certificate number: C-004407

Schweizerisches Heilmittelinstitut
Institut suisse des produits thérapeutiques
Istituto svizzero per gli agenti terapeutici
Swiss Agency for Therapeutic Products

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