s47F

Certificate of Compliance

Issued by:
GSK Vaccines GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Manufacturing License No:
DE_HE_01_MIA_2018_0021

Product Name:	RABIPUR VIAL +AMP +1N AU
Dosage Form:	Vial
Package Size:	1
Material:	704138
Batch:	657011A
Quantity:	18925
Expiry Date:	29-FEB-2020
Storage Condition:	+2°C to +8°C
Release to:	Australia
License Number:	AUST R 100582

Certification

I hereby certify that the above information is authentic and accurate. This batch of product has been manufactured, including quality control and where applicable packaging/labeling in full compliance with the GMP requirements of the local Regulatory Authority and with the specifications in the Marketing Authorization of the importing country. The batch processing, analysis and where applicable packaging records were reviewed and found to be in compliance with GMP. 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 following amendments.

Certificate Comment

Manufacturing Procedure: 9000048565
Quality Control Procedure: 9000054667

Authorized by: s47F

Qualified Person

Date / Signature: 07.05.2018 s47F

Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

Paul-Ehrlich-Institut Postfach D-63207 Langen

GSK Vaccines GmbH
Emil-von-Behring-Straße 76
35041 Marburg

Administrative Code: N2.01.01.0245
Certificate number: 4135/17
Date of issue: 21.12.2017

EC/EEA OFFICIAL CONTROL AUTHORITY BATCH RELEASE TESTING CERTIFICATE FOR IMMUNOLOGICAL PRODUCTS

Examined under Article 114 of Directive 2001/83/EC as amended by Directive 2004/27/EC (Immunological Medicinal Products) and in accordance with the Administrative Procedure for Official Control Authority Batch Release.

Trade name:	Rabipur
INN / Ph. Eur. name / common name:	Rabies vaccine inactivated
Batch numbers and other identification numbers associated with this batch:	657011A-Z
Type of container:	Vial
Total number of containers in this batch:	43.631
Number of doses per container:	1 dose
Date of start of period of validity:	12 October 2017
Expiry date:	11 October 2021
Marketing authorisation number:	PEI.H.11793.01.1 and 60a/84
Name and address of manufacturer:	GSK Vaccines GmbH Emil-von-Behring-Str. 76 35041 Marburg Germany
Name and address of marketing authorisation holder if different:	

This batch has been examined using documented testing procedures that form part of a quality management system. This examination is based on either:

- the relevant Note for Guidance for this product, or, in the absence of the latter,
- the review of the manufacturer's protocol and the appropriate control laboratory tests as indicated in the marketing authorisation.

This batch is in compliance with the approved specifications laid down in the relevant European Pharmacopoeia monographs and the above marketing authorisation.

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Section: Viral Vaccines

PAUL-EHRLICH-INSTITUT LANGEN

Issued by :
GSK Vaccines GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Certificate of Analysis

Rabipur 1 Ds.

Batch Number:	657011A	**Material Code:**	704138
Date of Manufacturing:	08.09.2017	**Expiry Date:**	29.02.2020
Start of Shelf Life:	12.10.2017	**Storage Condition:**	+ 2°C to + 8°C

Test	Specification	Result
Rabies glycoprotein	-	15,64 IU/mL
pH - value	7,3 <= Result <= 8,3	7,6
Sterility	Equal to PASS (= PASS)	PASS
Bovine serum albumine	Result <= 50 ng/Ds	2 ng/Ds
Dissolution time and organoleptic properties		
Organoleptic properties	Equal to PASS (= PASS) (= clear, colourless solution)	PASS
Dissolution time	Result <= 1 min	< 1 min
Potency test = identity	Equal to PASS (= PASS)	PASS
Potency test (geometric mean)		
Lower fiducial limit (>= 25 %)	-	3,0 IU/Ds
Estimated potency	Result >= 2,5 IU/Ds	6,2 IU/Ds
Upper fiducial limit (<= 400 %)	-	12,9 IU/Ds
Endotoxin	Result < 25 IU/Ds	< 1 IU/Ds
Residual moisture	Result <= 3,0 %	1,4 %

Product Specification Reference: 274261 corresponds to 9000054667

Approved By: s47F

Qualified Person

Date: 07.05.2018

LOT RELEASE PROTOCOL

RABIPUR®

Lot No. 657011A-Z

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

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CERTIFICATION

I herewith certify that Rabipur® batch no. 657011A-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

Date	Name and Signature Qualified Person
19.12.2017	s47F Sachkundige Person/ Qualified Person s47F

OVERVIEW

Identity Number		516
Lot Numbers		
	Semi-Finished Lot	516 657011
	Final Bulk	516 657010
Manufacturer Name and Address		GSK Vaccines GmbH Emil-von-Behring-Str. 76 35041 Marburg – Germany
Marketing Authorisation Number issued by EU		PEI.H.11793.01.1 and 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		43631
Date of Manufacture (Blending)		08.09.2017
Start of Shelf Life		12.10.2017
Expiry Date Semi-Finished Product (Filling Lot)		11.10.2021
Storage Temperature		+2 ºC to +8 ºC

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	2876560007
- Manufacturer of Human Albumin	CSL
- Date of Release by Manufacturer	20.05.2011
- 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	LSOP 9000054667
Manufacturing Procedure	LSOP 9000048565

MANUFACTURING FLOW

Product Name	Lot No.
Cell Cultures and Cell Controls 593D	T324_1 T324_2 T324_3 T324_4 T325_1 T325_2 T325_3 T325_4 T327_1 T327_2 T327_3 T327_4
Virus Suspension 593C Inactivated Virus Suspension 593B	T324-1 T325-1 T327-1
Antigen Concentrate 593A	T324-1A T325-1A T327-1B
Final Bulk	516 657010
Semi-Finished Product	516 657011

SEMI-FINISHED PRODUCT (Filling Lot)

Production Details for Semi-Finished Product, Lot No. 516 657011 (Doc. No. 9000046070)

Date of Filling	11.09.2017
Date of Lyophilization	11.09.2017
Type of Container	Vial
Number of Containers before Visual Inspection	43768
Number of Containers after Visual Inspection	43631
Filling Volume	1 mL
Recommended Reconstitution Volume	1 mL

Test Details for Semi-Finished Product, Lot No. 516 657011

Dissolution Time and Organoleptic Properties (LSOP 9000054768)

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
12.10.2017	Pass

Sterility (LSOP 9000056366)

Method	Membrane Filter Method according Ph. Eur. and USP 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	
05.10.2017	19.10.2017	Pass

Potency and Identity (LSOP 9000054770)

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			
12.10.2017	09.11.2017	11,6 IU/dose	4,2 IU/dose	35,0 IU/dose
20.10.2017	17.11.2017	3,6 IU/dose	1,3 IU/dose	9,6 IU/dose
Geometric Mean				
21.11.2017		6,2 IU/dose	3,0 IU/dose	12,9 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 657011

Further Tests

Test	Method	Requirement	Result	Date
Residual Water (LSOP 9000053147)	Karl Fischer method according to Ph. Eur.	max 3,0%	1,4 %	04.10.2017
pH Value (LSOP 9000047122)	Potentiometric determination according to Ph. Eur.	pH 7,3 – 8,3	pH 7,6	28.09.2017
Bacterial Endotoxins (LSOP 9000054775)	LAL-Test according to Ph. Eur.	Less than 25 IU per single dose	< 1 IU/mL	02.10.2017
Bovine Serum Albumin (LSOP 9000054759)	Immunochemical method according to Ph. Eur. (ELISA)	max. 50 ng per single dose	2 ng/Ds	05.10.2017
Glycoprotein Content (LSOP 9000055019)	Rabies glycoprotein (ELISA)	None (results are collected for potential later correlation with the respective potency test)	15,64 IU/mL	29.09.2017

FINAL BULK

Production Details for Final Bulk, Lot No. 516 657010 (Doc. No. 9000046037)

Date of Formulation	08.09.2017		
Volume	Storage Temperature	Storage Time	Approved Storage Period
46,50 kg	+2 ºC to +8 ºC	3 days	≤ 6 days

Test Details for Final Bulk, Lot No. 516 657010

Bioburden (LSOP 9000053339)

Method	Membrane Filter Method according Ph. Eur. Sample Volume: 100 mL / Medium	
Media	Tryptic Soy Agar	
Requirement	≤ 10 CFU / 100mL	
Before Sterile Filtration		
Date		Result
On	Off	
08.09.2017	13.09.2017	0 CFU

Sterility (LSOP 9000056366)

Method	Membrane Filter Method according Ph. Eur. and USP 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.	
After Sterile Filtration		
Date		Result
On	Off	
13.09.2017	27.09.2017	Pass

Glycoprotein content (LSOP 9000055019)

Method	ELISA
Requirement	10,4 – 20,8 IU/ml

Date	Result
14.09.2017	17,1 IU/mL

COMMENTS

N/A

ATTACHMENTS

Details on Potency Test
Statement Human Albumin
OMCL Certificate Human Albumin

RABIES ANTIGEN CONCENTRATE, Lot No. 593AT324-1A

1. VIRUS SUSPENSION

1.1. Production Details for Virus Suspension, Lot No. 593CT324 (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	16.03.2016
Date of Harvest of Sub-Batches	21.03.2016
Storage Temperature	+2°C to +8°C
Storage Time	11 h 15 min
Approved Storage Time	≤ 24 hours

1.2. Test Details for Virus Suspension, Lot No. 593CT324

Sterility (SOP No. 102858)

Method	Membrane Filtration according Ph. Eur. and USP Random Sample: 25 mL / medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth. Equal to pass.	
Date		Result
Start	End	
01.04.2016	15.04.2016	Pass

Mycoplasma (SOP No. 102833)

Method	Cultivation Method according to Ph. Eur. Random Sample: 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
Start	End	
08.04.2016	06.05.2016	Pass

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 with Rabies Virus. Equal to pass.

Date		Result	
Start	End	Concentration	Identity
24.03.2016	29.03.2016	8.2 Log $TCID_{50}$/mL	Pass

1.3. Production Details for Filtered Virus Suspension Lot No. 593CT324 (SOP No. 274054)

Date of Filtration	22.03.2016

1.4. Test Details for Filtered Virus Suspension, 593CT324

Total Nitrogen (SOP No. 103347)

Method	High Temperature Analyzer Random Sample: 30 mL	
Requirement	0.8 – 1.2 mg/mL	
Date		Result
Start	End	
29.03.2016	29.03.2016	1.1 mg/mL

Beta-Propriolactone (SOP No. 243472)

Method	Gas Chromatography Random Sample: 3 mL
Requirement	257 – 357 µg/mL

Date	Result
13.04.2016	307 µg/mL

pH Value (SOP No. 102723)

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

Date	Result
22.03.2016	pH 7.3

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593BT324 (Doc. No. 274054)

Date of inactivation	Start	End
	22.03.2016	23.03.2016
Method of inactivation	Beta-Propiolactone, 24 hours at +3ºC (± 1ºC), followed by 2 hours at +37ºC (± 1ºC)	
Storage	≤ 4 days at +2°C to +8°C	
Volume of Harvest	288 L	

2.2. Test Details for Inactivated Virus Suspension, Lot No. 593BT324

Residual Infectious Virus (SOP No. 103173)

Method	Test in Chicken Fibroblast Cell Culture; Fluorescence Microscopy
Random Sample	Min. 25 Doses of vaccine
Requirement	No viable (live) virus detectable. Equal to pass.

Date		Result
Start	End	
31.03.2016	25.04.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
29.03.2016	2.62 IU/mL

3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593AT324-1A (Doc. No. 274056)

Date of Purification and Concentration	24.03.2016
Method of Purification and Concentration	Density Gradient Centrifugation
Storage	max. 24 months at ≤ -70°C
Volume	1271 mL

3.2. Test Details for Antigen Concentrate, Lot No. 593AT324-1A

Sterility (SOP No. 102858

Method	Membrane Filtration according to Ph. Eur. and USP Random Sample: 10 mL / Medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth. Equal to pass.	
Date		Result
Start	End	
31.03.2016	14.04.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
29.03.2016	223 IU/mL

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

RABIES ANTIGEN CONCENTRATE, Lot No. 593AT325-1A

1. VIRUS SUSPENSION

1.1. **Production Details for Virus Suspension, Lot No. 593CT325** (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	18.03.2016
Date of Harvest of Sub-Batches	24.03.2016
Storage Temperature	+2°C to +8°C
Storage Time	21 h 03 min
Approved Storage Time	≤ 24 hours

1.2. Test Details for Virus Suspension, Lot No. 593CT325

Sterility (SOP No. 102858)

Method	Membrane Filtration according Ph. Eur. and USP Random Sample: 25 mL / medium		
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium		
Requirement	No growth. Equal to pass.		
Date		Result	
Start	End		
01.04.2016	15.04.2016	Pass	

Mycoplasma (SOP No. 102833)

Method	Cultivation Method according to Ph. Eur. Random Sample: 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	
Start	End		
08.04.2016	06.05.2016	Pass	

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 with Rabies Virus. Equal to pass.

Date		Result	
Start	End	Concentration	Identity
07.04.2016	11.04.2016	8.2 Log $TCID_{50}$/mL	Pass

1.3. Production Details for Filtered Virus Suspension Lot No. 593CT325 (SOP No. 274054)

Date of Filtration	25.03.2016

1.4. Test Details for Filtered Virus Suspension, 593CT325

Total Nitrogen (SOP No. 103347)

Method	High Temperature Analyzer Random Sample: 30 mL
Requirement	0.8 – 1.2 mg/mL

Date		Result
Start	End	
29.03.2016	29.03.2016	1.1 mg/mL

Beta-Propriolactone (SOP No. 243472)

Method	Gas Chromatography Random Sample: 3 mL
Requirement	257 – 357 µg/mL

Date	Result
13.04.2016	313 µg/mL

pH Value (SOP No. 102723)

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

Date	Result
25.03.2016	pH 7.4

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593BT325 (Doc. No. 274054)

Date of inactivation	Start	End
	25.03.2016	26.03.2016
Method of inactivation	Beta-Propiolactone, 24 hours at +3ºC (± 1ºC), followed by 2 hours at +37ºC (± 1ºC)	
Storage	≤ 4 days at +2°C to +8°C	
Volume of Harvest	289 L	

2.2. Test Details for Inactivated Virus Suspension, Lot No. 593BT325

Residual Infectious Virus (SOP No. 103173)

Method	Test in Chicken Fibroblast Cell Culture; Fluorescence Microscopy
Random Sample	Min. 25 Doses of vaccine
Requirement	No viable (live) virus detectable. Equal to pass.

Date		Result
Start	End	
07.04.2016	02.05.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
05.04.2016	2.92 IU/mL

3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593AT325-1A (Doc. No. 274056)

Date of Purification and Concentration	29.03.2016
Method of Purification and Concentration	Density Gradient Centrifugation
Storage	max. 24 months at ≤ -70°C
Volume	1271 mL

3.2. Test Details for Antigen Concentrate, Lot No. 593AT325-1A

Sterility (SOP No. 102858

Method	Membrane Filtration according to Ph. Eur. and USP Random Sample: 10 mL / Medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth. Equal to pass.	
Date		Result
Start	End	
04.04.2016	18.04.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
05.04.2016	217 IU/mL

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

RABIES ANTIGEN CONCENTRATE, Lot No. 593AT327-1B

1. VIRUS SUSPENSION

1.1. Production Details for Virus Suspension, Lot No. 593CT327 (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	23.03.2016
Date of Harvest of Sub-Batches	28.03.2016
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. 593CT327

Sterility (SOP No. 102858)

Method	Membrane Filtration according Ph. Eur. and USP Random Sample: 25 mL / medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth. Equal to pass.	
Date		Result
Start	End	
05.04.2016	19.04.2016	Pass

Mycoplasma (SOP No. 102833)

Method	Cultivation Method according to Ph. Eur. Random Sample: 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
Start	End	
08.04.2016	06.05.2016	Pass

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 with Rabies Virus. Equal to pass.

Date		Result	
Start	End	Concentration	Identity
07.04.2016	11.04.2016	8.2 Log $TCID_{50}$/mL	Pass

1.3. Production Details for Filtered Virus Suspension Lot No. 593CT327 (SOP No. 274054)

Date of Filtration	29.03.2016

1.4. Test Details for Filtered Virus Suspension, 593CT327

Total Nitrogen (SOP No. 103347)

Method	High Temperature Analyzer Random Sample: 30 mL
Requirement	0.8 – 1.2 mg/mL

Date		Result
Start	End	
05.04.2016	06.04.2016	1.1 mg/mL

Beta-Propriolactone (SOP No. 243472)

Method	Gas Chromatography Random Sample: 3 mL
Requirement	257 – 357 µg/mL

Date	Result
13.04.2016	311 µg/mL

pH Value (SOP No. 102723)

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

Date	Result
29.03.2016	pH 7.3

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593BT327 (Doc. No. 274054)

Date of inactivation	Start	End
	29.03.2016	30.03.2016
Method of inactivation	Beta-Propiolactone, 24 hours at +3ºC (± 1ºC), followed by 2 hours at +37ºC (± 1ºC)	
Storage	≤ 4 days at +2°C to +8°C	
Volume of Harvest	287 L	

2.2. Test Details for Inactivated Virus Suspension, Lot No. 593BT327

Residual Infectious Virus (SOP No. 103173)

Method	Test in Chicken Fibroblast Cell Culture; Fluorescence Microscopy
Random Sample	Min. 25 Doses of vaccine
Requirement	No viable (live) virus detectable. Equal to pass.

Date		Result
Start	End	
07.04.2016	02.05.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
05.04.2016	2.26 IU/mL

3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593AT327-1B (Doc. No. 274056)

Date of Purification and Concentration	31.03.2016
Method of Purification and Concentration	Density Gradient Centrifugation
Storage	max. 24 months at ≤ -70°C
Volume	1271 mL

3.2. Test Details for Antigen Concentrate, Lot No. 593AT327-1B

Sterility (SOP No. 102858

Method	Membrane Filtration according to Ph. Eur. and USP Random Sample: 10 mL / Medium	
Media	Thioglycollate Medium Soy Peptone/Casein Peptone Medium	
Requirement	No growth. Equal to pass.	
Date		Result
Start	End	
06.04.2016	20.04.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
05.04.2016	219 IU/mL

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

1. STARTING MATERIALS for Lot 593DT324

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	23.01.1985
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

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

Cell Culture System	Chicken Fibroblast Cell Cultures			
Flock Number	20402			
Delivery Date of incubated Eggs	15.03.2016			
Manufacturing Date of Cell Culture	16.03.2016			
Nature and concentration of antibiotics used in production of cell culture maintenance medium	Aureomycin (4.8 µg/mL) Amphotericin B (0.5 µg/mL) Neomycin Sulphate (242.2 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	029	029	029	029
Trypsinization Medium SOP275550	073/03	073/03 073/04	073/04	073/04
FCS SOP222018	2220180040	2220180040	2220180040	2220180040
Medium 3 + NaHCO3 SOP271811	022/04	022/04	022/04	022/04
Medium 3 + HSA SOP300719	053/11	053/11	053/12	053/12
Size of Sub-Batch	71 L	71 L	71 L	71 L
Population doubling level (PDL) of produced cells when inoculated with virus seed	2.3 Cells x 10^6/mL	2.3 Cells x 10^6/mL	2.3 Cells x 10^6/mL	2.3 Cells x 10^6/mL
For details see attachment: Details on SPF Eggs to 593DT324				

3. CONTROL CELL CULTURES, Lot No. 593DT324

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

Ratio or Proportion of Control to Production Cell Culture	5.7 mL sample volume out of 1.6 L cell concentrate per sub batch	
Period of Observation of Cultures	Start (Date of Sampling)	End (Date Control Cells handed to QC)
	16.03.2016	17.03.2016

3.2. Test Details for Control Cell Cultures, Lot No. 593DT324

Cytopathic Degenerations (SOP No. 104212)

Method	Microscopic Examination according to Ph. Eur. Random Sample: ≥ 500 mL of the cultures used for manufacture of the vaccine	
Requirement	No cytopathic degenerations or cytopathic effects detectable. Equal to pass.	
Date		Result
Start	End	
17.03.2016	01.04.2016	Pass

Hemadsorbing Viruses (SOP No. 103210)

Method	Test according to Ph. Eur. with Guinea Pig Erythrocytes Random Sample: ≥ 25% of the control cells after ≥ 14 days of incubation	
Storage Time and Temperature of erythrocytes (SOP No. 104540)	≤ 7 days after blood draw at +2°C to +8°C	
Incubation	30-60 min at +2°C to +8°C 30-60 min at +20°C to +25°C	
Requirement	No evidence of hemadsorbing agents. Equal to pass.	
Date		Result
Start	End	
01.04.2016	01.04.2016	Pass

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

Method	Inoculation of Chicken Fibroblast according to Ph. Eur. Random sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C) and +34°C (± 2°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
01.04.2016	15.04.2016	Pass

Extraneous Agents – Vero Cells (SOP No. 104682)

Method	Inoculation of Vero Cells according to Ph. Eur. Random Sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
01.04.2016	15.04.2016	Pass

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

Method	Inoculation of Human Amnion Cells Line AV3according to Ph. Eur. Random Sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
01.04.2016	15.04.2016	Pass

Avian Leukosis Viruses (SOP No. 244413, 227575)

Method	Culture Method according to Ph. Eur. Random Sample: 5 mL culture supernatant from the control cells after ≥ 14 days of incubation; sample is incubated for 9-12 days before testing for avian leukosis virus.
Requirement	No avian leukosis viruses detectable. Equal to pass.

Amplification in Cells		ELISA		Result
Date		Date		
Start	End	Start	End	
01.04.2016	12.04.2016	20.04.2016	21.04.2016	Pass

4. COMMENTS

N/A

5. ATTACHMENTS

Details on SPF Eggs to 593DT324
Seed Virus Certificate of Analysis

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

Consignee: GSK Vaccines Gmbh
Marburg , 35006

ROH 279051 0477

15. MRZ 2016

s47F

Date of Delivery: 15.03.2016
SPF Eggs : 4120

Details of the consignment:

Latest Sampling Date	**29.02.2016**

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.

Osterholz-Scharmbeck, 09.03.2016

Anlage 5 zum BPR 593-01
der Charge 593DT 324
Seite 2 von 3

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Signature of VALO BioMedia GmbH

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15. MRZ. 2016

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Consignee: GSK Vaccines Gmbh
Marburg , 35006

Date of Delivery: 15.03.2016
SPF Eggs : 4120

Flock	Hatch Date	Age of Flock	Laying Date	number of eggs
20402	25.05.2015	40	02.-03.03 2016	4570
Start of incubation	Start of candling	No. of eggs discarded	% fertility	No. of eggs delivered
07.03.2016 570	15.03.2016 600	161	3,5	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	15.03.2016 14:00 Uhr	08.08.2016

ROH 279051 0477

15. MRZ. 2016

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Anlage 5 zum BPR 593-01
der Charge 593DT 324
Seite 3 von 3

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15. MRZ. 2016

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NOVARTIS
VACCINES AND
DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-BehringStr. 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: 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

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 Person) s47F **Date:** 10.07.14

Issued by: s47F [redacted] System: LIMS

1. STARTING MATERIALS for Lot 593DT325

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	23.01.1985
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

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

Cell Culture System	Chicken Fibroblast Cell Cultures			
Flock Number	10506			
Delivery Date of incubated Eggs	17.03.2016			
Manufacturing Date of Cell Culture	18.03.2016			
Nature and concentration of antibiotics used in production of cell culture maintenance medium	Aureomycin (4.8 µg/mL) Amphotericin B (0.5 µg/mL) Neomycin Sulphate (242.2 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	029	029	029	029
Trypsinization Medium SOP275550	073/03	073/03	073/03	073/03
FCS SOP222018	2220180040	2220180040	2220180040	2220180040
Medium 3 + NaHCO3 SOP271811	022/05	022/05	022/05	022/05
Medium 3 + HSA SOP300719	054/01	054/01	054/02	054/02
Size of Sub-Batch	71 L	71 L	71 L	71 L
Population doubling level (PDL) of produced cells when inoculated with virus seed	1.9 Cells x 10^6/mL	2.2 Cells x 10^6/mL	2.0 Cells x 10^6/mL	2.0 Cells x 10^6/mL
For details see attachment: Details on SPF Eggs to 593DT325				

3. CONTROL CELL CULTURES, Lot No. 593DT325

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

Ratio or Proportion of Control to Production Cell Culture	5.7 mL sample volume out of 1.6 L cell concentrate per sub batch	
Period of Observation of Cultures	Start (Date of Sampling)	End (Date Control Cells handed to QC)
	18.03.2016	18.03.2016

3.2. Test Details for Control Cell Cultures, Lot No. 593DT325

Cytopathic Degenerations (SOP No. 104212)

Method	Microscopic Examination according to Ph. Eur. Random Sample: ≥ 500 mL of the cultures used for manufacture of the vaccine	
Requirement	No cytopathic degenerations or cytopathic effects detectable. Equal to pass.	
Date		Result
Start	End	
18.03.2016	01.04.2016	Pass

Hemadsorbing Viruses (SOP No. 103210)

Method	Test according to Ph. Eur. with Guinea Pig Erythrocytes Random Sample: ≥ 25% of the control cells after ≥ 14 days of incubation	
Storage Time and Temperature of erythrocytes (SOP No. 104540)	≤ 7 days after blood draw at +2°C to +8°C	
Incubation	30-60 min at +2°C to +8°C 30-60 min at +20°C to +25°C	
Requirement	No evidence of hemadsorbing agents. Equal to pass.	
Date		Result
Start	End	
01.04.2016	01.04.2016	Pass

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

Method	Inoculation of Chicken Fibroblast according to Ph. Eur. Random sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C) and +34°C (± 2°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
01.04.2016	15.04.2016	Pass

Extraneous Agents – Vero Cells (SOP No. 104682)

Method	Inoculation of Vero Cells according to Ph. Eur. Random Sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
01.04.2016	15.04.2016	Pass

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

Method	Inoculation of Human Amnion Cells Line AV3according to Ph. Eur. Random Sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
01.04.2016	15.04.2016	Pass

Avian Leukosis Viruses (SOP No. 244413, 227575)

Method	Culture Method according to Ph. Eur. Random Sample: 5 mL culture supernatant from the control cells after ≥ 14 days of incubation; sample is incubated for 9-12 days before testing for avian leukosis virus.
Requirement	No avian leukosis viruses detectable. Equal to pass.

Amplification in Cells		ELISA		Result
Date		Date		
Start	End	Start	End	
01.04.2016	12.04.2016	20.04.2016	21.04.2016	Pass

4. COMMENTS

5. ATTACHMENTS

Details on SPF Eggs to 593DT325
Seed Virus Certificate of Analysis

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

Consignee: GSK Vaccines Gmbh
Marburg , 35006

ROH 279051 0479

17. MRZ. 2016 s47F

Date of Delivery: 17.03.2016
SPF Eggs : 4120

Details of the consignment:

Latest Sampling Date	29.02.2016

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		E LIS A	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 colected within 7 days prior to the date of departure from our farm. The origin of the eggs is the Federal Republic of Germany.

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Osterholz-Scharmbeck, 09.03.2016

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Signature of VALO BioMedia GmbH

Anlage 5 zum BPR 593-01
der Charge 593DT 325
Seite 2 von 3
17. MRZ 2016

Seite geprüft von (QASF)
29. März 2016
Kürzel: s47F

Consignee: GSK Vaccines Gmbh
Marburg , 35006

Date of Delivery: 17.03.2016
SPF Eggs : 4120

ROH 279051 0479
17. MRZ. 2016
s47F

Flock	Hatch Date	Age of Flock	Laying Date	number of eggs
10506	20.04.2015	45	04.-06.07 2016	4770
Start of incubation	Start of candling	No. of eggs discarded	% fertility	No. of eggs delivered
09.03.2016 345	[illegible]	650	43,6	[illegible]
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	17.03.2016 14:00 Uhr	27.06.2016

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Anlage 5 zum BPR 593-01
der Charge 593DT 325
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Seite geprüft von (QASF)
29. März 2016
Kürzel: s47F

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-BehringStr. 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: 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

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 Person) s47F **Date:** 10.07.14

Issued by: s47F [redacted] System: LIMS

1. STARTING MATERIALS for Lot 593DT327

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	23.01.1985
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

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

Cell Culture System	Chicken Fibroblast Cell Cultures			
Flock Number	20402			
Delivery Date of incubated Eggs	22.03.2016			
Manufacturing Date of Cell Culture	23.03.2016			
Nature and concentration of antibiotics used in production of cell culture maintenance medium	Aureomycin (4.8 µg/mL) Amphotericin B (0.5 µg/mL) Neomycin Sulphate (242.2 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	029	029	029	029
Trypsinization Medium SOP275550	073/03 074/01	074/01	074/01	074/01
FCS SOP222018	2220180040	2220180040	2220180040	2220180040
Medium 3 + NaHCO3 SOP271811	022/05 022/06	022/05	022/06	022/06
Medium 3 + HSA SOP300719	054/05	054/05	054/06	054/06
Size of Sub-Batch	71 L	71 L	71 L	71 L
Population doubling level (PDL) of produced cells when inoculated with virus seed	2.6 Cells x 10^6/mL	2.5 Cells x 10^6/mL	2.6 Cells x 10^6/mL	2.1 Cells x 10^6/mL
For details see attachment: Details on SPF Eggs to 593DT327				

3. CONTROL CELL CULTURES, Lot No. 593DT327

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

Ratio or Proportion of Control to Production Cell Culture	5.7 mL sample volume out of 1.6 L cell concentrate per sub batch	
Period of Observation of Cultures	Start (Date of Sampling)	End (Date Control Cells handed to QC)
	23.03.2016	24.03.2016

3.2. Test Details for Control Cell Cultures, Lot No. 593DT327

Cytopathic Degenerations (SOP No. 104212)

Method	Microscopic Examination according to Ph. Eur. Random Sample: ≥ 500 mL of the cultures used for manufacture of the vaccine	
Requirement	No cytopathic degenerations or cytopathic effects detectable. Equal to pass.	
Date		Result
Start	End	
24.03.2016	08.04.2016	Pass

Hemadsorbing Viruses (SOP No. 103210)

Method	Test according to Ph. Eur. with Guinea Pig Erythrocytes Random Sample: ≥ 25% of the control cells after ≥ 14 days of incubation	
Storage Time and Temperature of erythrocytes (SOP No. 104540)	≤ 7 days after blood draw at +2°C to +8°C	
Incubation	30-60 min at +2°C to +8°C 30-60 min at +20°C to +25°C	
Requirement	No evidence of hemadsorbing agents. Equal to pass.	
Date		Result
Start	End	
08.04.2016	08.04.2016	Pass

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

Method	Inoculation of Chicken Fibroblast according to Ph. Eur. Random sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C) and +34°C (± 2°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
08.04.2016	22.04.2016	Pass

Extraneous Agents – Vero Cells (SOP No. 104682)

Method	Inoculation of Vero Cells according to Ph. Eur. Random Sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
08.04.2016	22.04.2016	Pass

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

Method	Inoculation of Human Amnion Cells Line AV3according to Ph. Eur. Random Sample: At least 2 x 5 mL culture supernatant from the control cells for each cell culture system after ≥ 14 days of incubation	
Incubation	+36°C (± 1°C)	
Requirement	No signs of the presence of extraneous agents. Equal to pass.	
Date		Result
Start	End	
08.04.2016	22.04.2016	Pass

Avian Leukosis Viruses (SOP No. 244413, 227575)

Method	Culture Method according to Ph. Eur. Random Sample: 5 mL culture supernatant from the control cells after ≥ 14 days of incubation; sample is incubated for 9-12 days before testing for avian leukosis virus.
Requirement	No avian leukosis viruses detectable. Equal to pass.

Amplification in Cells		ELISA		Result
Date		Date		
Start	End	Start	End	
08.04.2016	18.04.2016	20.04.2016	21.04.2016	Pass

4. COMMENTS

N/A

5. ATTACHMENTS

Details on SPF Eggs to 593DT327
Seed Virus Certificate of Analysis

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

Consignee: GSK Vaccines Gmbh
Marburg , 35006

ROH 279051 0 4 B 1

Date of Delivery: 22.03.2016
SPF Eggs : 4120

22. MRZ. 2016 [redacted]

Details of the consignment: Latest Sampling Date 07 .03.2016

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.

Osterholz-Scharmbeck, 16.03.2016

Anlage 5 zum BPR 593-01
der Charge 593DT 327
Seite 2 von 3
22. MRZ. 2016 [redacted]

s47F
Signature of VALO BioMedia GmbH

GXP COPY
22. MRZ. 2016
s47F

Seite geprüft von (QASF)
20. April 2016
Kürzel: s47F

Consignee: GSK Vaccines Gmbh
Marburg , 35006

Date of Delivery: 22.03.2016
SPF Eggs : 4120

Flock	Hatch Date	Age of Flock	Laying Date	number of eggs
20402	25.05.2015	44	08 - 10. 01 2016	4570
Start of incubation	Start of candling	No. of eggs discarded	% fertility	No. of eggs delivered
14.03.2016 341	21.03 Uhr 600	197	4,3 %	4373
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	22.03.2016 14:00 Uhr	08.08.2016

ROH 279051 0481
22. MRZ. 2016
s47F

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22. MRZ. 2016
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22. MRZ. 2016
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Anlage 5 zum BPR 593-01
der Charge 593DT 327
Seite 3 von 3
22. MRZ. 2016
s47F

Seite geprüft von (QASF)
20. April 2016
Kürzel: s47F

NOVARTIS
VACCINES AND DIAGNOSTICS

Novartis Vaccines and Diagnostics GmbH
Emil-von-BehringStr. 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: 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

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 Person) s47F **Date:** 10.07.14

Issued by: s47F [redacted] System: LIMS

Substance	Rabies
Method	9000054770-11
Assay number	14
Technician	s47F
1.+2. Immunisierung	12.10. + 19.10.2017
Challenge	26.10.2017
Testende	09.11.2017
Tierart/Lieferant	Mause/CR

Remarks:Validitätskriterien (PD50, Vertrauengrenzen, LD50, Linearität/Parallelität) entsprechen/~~entsprechen nicht~~ den Anforderungen

19. NOV. 2017 s47F

Standard	
Id.	Referenz-Standard
	WF-3
Ass. pot.	10.77IU/ml
Doses	(1)
0.1ml	12/20
0.02ml	7/20
0.004ml	4/20
0.0008ml	0/20

Sample 1	
Id.	657 011
GLIMS-ID	8990968
Ass. pot.	?IU/ml
Doses	(1)
0.2ml	13/20
0.04ml	13/20
0.008ml	5/20
0.0016ml	0/20

Model: r/n=(phi(x)) where x=c.+b*ln(dose)
Design: Completely randomised
Weight function: w=n/(m*(1-m))
Theoretical variance: 1

Common slope(factor): b = 0.456340 (0.336456 to 0.576225)
Correlation | r |: 0.926932 (Weighted)

Source of variation	Degrees of freedom	Sum of squares	Mean square	Chi-square	Probability
Preparations	1	0.777124	0.777124	0.777124	0.378
Regression	1	39.2018	39.2018	39.2018	0.000 (***)
Non-parallelism	1	0.0352694	0.0352694	0.0352694	0.851
Non-linearity	4	6.51602	1.62900	6.51602	0.164
Standard	2	1.58530	0.792649	1.58530	0.453
Sample 1	2	4.93072	2.46536	4.93072	0.085
Treatments	7	46.5302	6.64717	46.5302	0.000 (***)
Theoretical variance			1.00000		
Total	7	46.5302	6.64717		

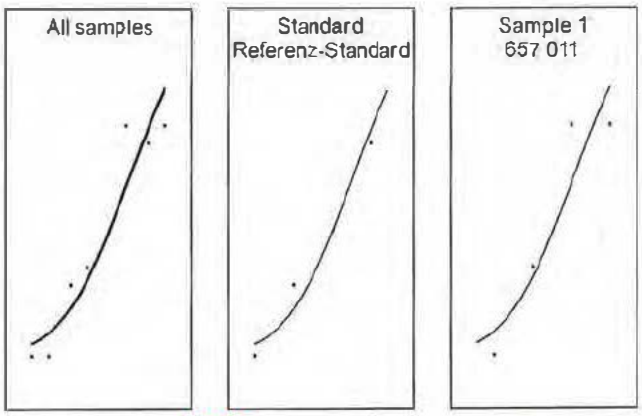
Standard			
Id.	Referenz-Standard		
(IU/ml)	Lower limit	Estimate	Upperlimit
Potency	10.7700	10.7700	10.7700
Rel. to Ass.	100.0%	100.0%	100.0%
Rel. to Est.	100.0%	100.0%	100.0%
IU/ED50	0.244269	0.504205	1.28139
Rel. to Ass.	78.0%	198.3%	409.4%
Rel. to Est.	39.3%	100.0%	206.4%

Sample 1			
Id.	657 011		
(IU/ml)	Lower limit	Estimate	Upper limit
Potency	4.19660	11.5506	35.0449
Rel. to Ass.	?	?	?
Rel. to Est.	36.3%	100.0%	303.4%
ml/ED50	0.0218766	0.0436518	0.0972852
Rel. to Ass.	?	?	?
Rel. to Est.	44.9%	100.0%	199.5%

ID: GSKI/DEU

Anlage C
Seite 112
19. NOV. 2017

Substance	Rabies
Method	9000054770-11
Assay number	14
Technician	s47F
1.+ 2. Immunisierung	12.10. + 19.10.2017
Challenge	26.10.2017
Testende	09.11.2017
Tierart/Lieferant	Maus/CR



Executed by: s47F s47F Calculated by s47F s47F Approved by: s47F s47F

ID: GSK1/DEU

Anlage C
Seite 2/2
19. NOV. 2017 s47F

Substance	Rabies
Method	9000054770-11
Assay number	16
Technician	s47F
1.+2. Immunisierung	20.10. +27.10.2017
Challenge	03.11.2017
Testende	17.11.2017
Tierart/Lieferant	Mäuse/CR

Remarks: Validitätskriterien (PD50, Vertrauengrenzen, LD50, Linearität/Parallelität) entsprechen/~~entsprechen nicht~~ den Anforderungen

21. NOV. 2017 s47F

Standard	
Id.	Referenz-Standard
	WF-3
Ass. pot.	10.77IU/ml
Doses	(1)
0.1ml	16/20
0.02ml	9/20
0.004ml	3/20
0.0008ml	2/20

Sample 1	
Id.	657 011
GLIMS-ID	8990969
Ass. pot.	?IU/ml
Doses	(1)
0.2ml	15/20
0.04ml	7/20
0.008ml	3/20
0.0016ml	1/20

Model: r/n=(phi(x)) where x=c+b*ln(dose)
Design: Completely randomised
Weight function: w=n/(m*(1-m))
Theoretical variance: 1

Common slope(factor): b = 0.479912 (0.359391 to 0.600433)
Correlation | r |: 0.978689 (Weighted)

Source of variation	Degrees of freedom	Sum of squares	Mean square	Chi-square	Probability
Preparations	1	0.204591	0.204591	0.204591	0.651
Regression	1	42.8993	42.8993	42.8993	0.000 (***)
Non-parallelism	1	0.0221135	0.0221135	0.0221135	0.882
Non-linearity	4	1.87551	0.468878	1.87551	0.759
Standard	2	1.32509	0.662546	1.32509	0.516
Sample 1	2	0.550420	0.275210	0.550420	0.759
Treatments	7	45.0015	6.42878	45.0015	0.000 (***)
Theoretical variance			1.00000		
Total	7	45.0015	6.42878		

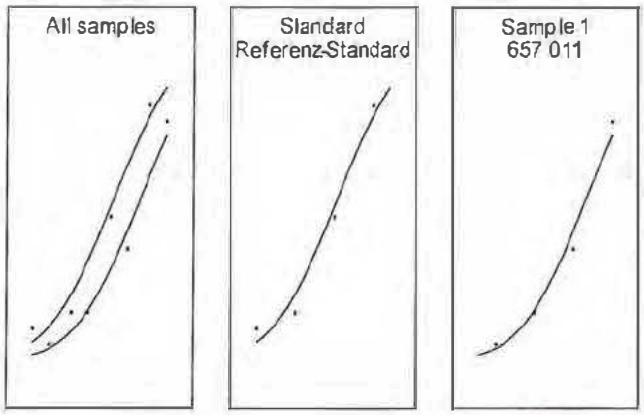
Standard			
Id.	Referenz-Standard		
(IU/ml)	Lower limit	Estimate	Upper limit
Potency	10.7700	10.7700	10.7700
Rel. to Ass.	100.0%	100.0%	100.0%
Rel. to Est.	100.0%	100.0%	100.0%
IU/ED50	0.121483	0.236260	0.504846
Rel. to Ass.	198.1%	423.3%	823.2%
Rel. to Est.	46.8%	100.0%	194.5%

Sample 1			
Id.	657 011		
(IU/ml)	Lower limit	Estimate	Upper limit
Potency	1.30785	3.61698	9.58192
Rel. to Ass.	?	?	?
Rel. to Est.	36.2%	100.0%	264.9%
ml/ED50	0.0331815	0.0653198	0.147492
Rel. to Ass.	?	?	?
Rel. to Est.	44.3%	100.0%	196.9%

ID: GSK1/DEU

Anlage C
Seite 1/2
21. NOV. 2017

Substance	Rabies
Method	9000054770-11
Assay number	16
Technician	s47F
1.+ 2. Immunisierung	20.10. + 27.10.2017
Challenge	03.11.2017
Testende	17.11.2017
Tierart/Lieferant	Mäuse/CR



Executed by: [redacted] Calculated by: s47F s47F Approved by: s47F s47F 21.11.17

GSK Vaccines	Berechnung der gewichteten mittleren Aktivität gem. Ph.Eur. und Vorgehen bei OOS-Resultaten bei Aktivitätsbestimmungen	Laboratory Test Record
LTR-Nr.: LTR-22518906	*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		
Labor / Bereich: Bioassays	**Laufende Test-Nr.:** 35	225189-00000267

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

Präparat: Rabies *Product:*	**Ch.B.:** 657 011 *Batch-No.:*
LIMS-ID: 8990971 *LIMS-ID*	**Lfd.-Nr.:** entfällt *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.:*	9000054770-11

	Kombination der Ergebnisse aus V-Nr: *Mean of result of test no.:*	**Probit-Vorgangs-Nr:** *Probit calculation no.:*
1.	Test-Nr. 14	N/A
2.	Test-Nr. 16	N/A
3.	N/A	N/A

Ergebnis: *Result:*	6,2 IE/Dosis	3,01 IE/Dosis	12,91 IE/Dosis
	Wirksamkeit *Activity*	**Unteres Konfidenzintervall** *Lower confidence limit*	**Oberes Konfidenzintervall** *Upper confidence limit*

Berechnung durchgeführt *Calculation done by:*	**Datum** *Date*	21. NOV. 2017	**Unterschrift** *Signature*	s47F

Bemerkungen:

LIMS Reportname 225189-00000267 User: CB199233 Druckdatum: 11:02 21.11.2017

GSK Vaccines	Berechnung der gewichteten mittleren Aktivität gem. Ph.Eur. und Vorgehen bei OOS-Resultaten bei Aktivitätsbestimmungen *Calculation of weighted mean activity according to Ph.Eur. and procedure in case of OOS-results in activity assays*	Laboratory Test Record
LTR-Nr.: LTR-225189-06 SOP-Nr.: SOP-225189-06 Labor / Bereich: Bioassays	**Laufende Test-Nr.:** 35	Seite 2 von 2 225189-00000267

3 Ergebnis *(Result)*

Präparat *Product*	Ch.-Bez. *Batch-No.*	LIMS-ID *LIMS-ID*	LIMS-Eintrag *LIMS Entry*	Bewertung *Assessment*	Beurteilung *Validation*
Rabies	657 011	8990971	Ja *Yes* / Nein *No*	Pass / Fail	valid / invalid

Protokoll richtig ausgefüllt und geprüft *The record is correctly filled out and checked*	~~21. NOV. 2017~~ 21. NOV. 2017 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)*	22.11.17 Datum *Date*	s47F Unterschrift *Signature*
	Verantwortlicher Mitarbeiter/Supervisor *Responsible operator / Supervisor*	
Der Test ist valide *Test is valid* **(siehe Tabelle)** *(See table)*	22.11.17 Datum *Date*	s47F rift *Signature*
	Laborleiter/Supervisor *Head of laboratory / Supervisor*	
AM erstellt *Deviation is initiated* Ja *Yes* ☐ Nein *No* ☒ AM Nr. *(DR No)* N/A	21. NOV. 2017 Datum *date*	s47F Unterschrift *Signature*
	Verantwortlicher Mitarbeiter *Responsible operator*	

Bemerkungen:

Charge 657011

	A	B	C	D	E	F	G	H	I	J
1	**EuPharm 6.2**	**Test-Nr. 14**	**Test-Nr. 16**							
2										
3	Activity (IE / Dose)	11,6000	3,6000							
4	Lower limit	4,2000	1,3000							
5	Upper limit	35,0000	9,6000							
6										
7	M	2,4510	1,2809				1,8660	2	0,3423	
8	Lower limit (M)	1,4351	0,2624							
9	Upper limit (M)	3,5553	2,2618							
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)	2,1203	1,9994							
13										
14	Weight (6.2.3)	3,4180	3,8438				7,2618	0,3711		
15	M (weighted 6.2.3)	8,3776	4,9236				1,8317	1,1044	2,5590	
16	Activity with CI						6,2443	3,0173	12,9228	
17										
18	Chisq (6.2.2)	1,3111	1,1659				2,4769	0,1155	**homogeneous**	
19										
20	Intra-assay	0,2926	0,2602							
21	Inter-assay	0,3423	0,3423							
22	Weight (6.2.4)	1,5752	1,6599				3,2352	0,5560		
23	M (weighted 6.2.4)	3,8609	2,1263				1,8506	0,7387	2,9626	
24	Activity with CI						6,3639	2,0932	19,3480	
25										
26	**Final (IE / Dose)**						**6,2443**	**3,0173**	**12,9228**	**4,2829**

gerechnet: 21.11.17 s47F

GSK Vaccines GmbH
P.O. Box 1630, 35006 Marburg, Germany
Emil-von-Behring-Straße 76, 35041 Marburg, Germany
Tel: +49 06421 386 – 0

Final Release Group
+49 6421 386 – 3977
+49 6421 386 - 6111
marburg.finalrelease@gsk.com

18.12.2017

Statement

Human Albumin used in the production of Rabipur® batch **657011A-Z**

Herewith I confirm that the Human Albumin lots listed in the table below were used for production of Rabipur Lot 657011A-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 657011A-Z		**OCABR Certification to Human Albumin Lots**
Lot Number Human Albumin (GSK Vaccines)	**Lot Number Human Albumin** (Baxter Bioscience/CSL Behring)	
2876560007	4362500025	OCABR Certificate to filling lotno. 0381700034

18.12.2017 s47F

s47F

(Qualified Person)

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:	0381700034
Type of container:	Bottle
Total number of containers in this batch:	7558
Nominal dose per container:	1
Date of start of period of validity:	18/02/2011
Date of expiry:	17/02/2014
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	20.05.2011

Certificate number: C-000979

Swiss Agency for Therapeutic Products swissmedic

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

Swissmedic | Hallerstrasse 7 | Postfach | CH-3000 Bern 9 | www.swissmedic.ch | Tel. +41 31 322 02 11 | Fax +41 31 322 02

SUMMARY PROTOCOL FOR PRODUCTION AND TESTING

OF STERILE WATER FOR INJECTION

FINAL PRODUCT

Lot 152160C

Name and address of manufacturer	GSK Vaccines S.r.l. - Bellaria - Rosia 53018 Sovicille - Siena (Italy)
Proprietary name of product	STERILE DILUENT FOR LYOPHILIZED VACCINES
Final lot	152160C
Type of container	Ampoule
No. of final containers	54,501
No. of doses of lyophilized vaccine to be reconstituted with each diluent final container	One
Volume of single human dose of vaccine (after reconstitution with diluent)	1.0 mL
Date of start period of validity	March 18, 2015
Expiry date	February 2020
Storage conditions of final product	Do not freeze

FINAL BULK LOT 152160C

Production details of final bulk

Name and address of manufacturer	GSK Vaccines S.r.l. - Bellaria - Rosia 53018 Sovicille - Siena (Italy)
Date of manufacturing (*)	March 18, 2015

Tests on final bulk

Appearance (Specification: Colourless clear liquid)

Method	Visual examination
Date of test	March 25, 2015
Result	Colourless clear liquid

Nitrates (Specification: ≤ 0.2 ppm)

Method	Colorimetric
Date of test	March 25, 2015
Result	< 0.2 ppm

Total Organic Carbon (TOC) (Specification: Complies to Eur. Ph.)

Method	Eur. Ph.
Date of test	March 19, 2015
Result	Complies to Eur. Ph.

(*) - *The bulk preparation procedure consists on drawing, under aseptical condition, water for injection from the take off point of the distribution loop and sterilizing it, by 0.22 µm filtration, before transferring it into a sterile final bulk container. During the filling operations, the final bulk container is continuously fed with 0.22 µm filtered water for injection, in order to maintain constant the inner volume.*

Heavy metals (Specification: ≤ 0.1 ppm)

Method	Colorimetric
Date of test	March 26, 2015
Result	< 0.1 ppm

Conductivity (Specification: Complies to Eur. Ph.)

Method	Conductometric
Date of test	March 24, 2015
Result	Complies to Eur. Ph.

Bioburden (Specification: ≤ 10 CFU/100 mL)

Method	Inoculation on plates and colony count
Media	TSA
Volume tested	200 mL
Date of test	Mar. 18 - Mar. 24, 2015
Result	0 CFU/100 mL

Endotoxin content (Specification: < 0.25 IU/mL)

Method	LAL Test
Date of test	April 09, 2015
Result	< 0.06 IU/mL

FINAL LOT 152160C

Production details of final lot

Name and address of manufacturer	GSK Vaccines S.r.l. - Bellaria - Rosia 53018 Sovicille - Siena (Italy)
Date of filling	March 18, 2015
Filled volume	1.07mL
Type of container	Ampoule
No. of final containers	54,501

Tests on final lot

Appearance (Specification: Colourless clear liquid)

Method	Visual examination
Date of test	March 25, 2015
Result	Colourless clear liquid

Acidity or Alkalinity (Specification: Complies to Eur. Ph.)

Method	Colorimetric
Date of test	March 27, 2015
Result	Complies to Eur. Ph.

Oxidisable substances (Specification: Complies to Eur. Ph.)

Method	Eur. Ph.
Date of test	March 31, 2015
Result	Complies to Eur. Ph.

Chlorides (Specification: ≤ 0.5 ppm)

Method	Precipitation
Date of test	March 27, 2015
Result	< 0.5 ppm

Residue on evaporation (Specification: ≤ 0.004 %)

Method	Eur. Ph.
Date of test	April 07, 2015
Result	< 0.004 %

Conductivity (Specification: Complies to Eur. Ph.)

Method	Conductometric
Date of test	March 31, 2015
Result	Complies to Eur. Ph.

Ammonium (Specification: ≤ 0.6 ppm)

Method	Colorimetric
Date of test	March 30, 2015
Result	< 0.6 ppm

Sulphates (Specification: Complies to Eur. Ph.)

Method	Precipitation
Date of test	March 31, 2015
Result	Complies to Eur. Ph.

Calcium and magnesium (Specification: Complies to Eur. Ph.)

Method	Colorimetric
Date of test	March 30, 2015
Result	Complies to Eur. Ph.

Withdrawable content (Specification: ≥ 1.0 mL)

Method	USP
Date of test	March 23, 2015
Result	1.0 mL

Particulate contamination: sub-visible particles (Specification: Particles ≥ 10 µm: ≤ 6,000/container
Particles ≥ 25 µm: ≤ 600/container)

Method	Eur. Ph., method 1
Date of test	March 25, 2015
Result	Particles≥ 10 µm: 32/container
	Particles≥ 25 µm: 1/container

Endotoxin content (Specification: <0.25 IU/mL)

Method	LAL Test
Date of test	March 24, 2015
Result	<0.06 IU/mL

Sterility (Specification: Sterile)

Method	Eur. Ph., membrane filtration
Media	FTM and SCDM
No. of containers tested	40
Date of test	Mar. 20 - Apr. 03, 2015
Result	Sterile

CERTIFICATION

I herewith certify that Lot No. 152160C of Sterile Water for Injection was manufactured and tested according to the procedures approved by competent authorities and complies with the quality requirements.

s47F
s47F
Quality Assurance / Qualified Person

05 APR 15
Date