s47F

Certificate of Compliance

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

Manufacturing License No:
DE_HE_01_MIA_2015_0069

Product Name:	RABIPUR VIAL +AMP +1N AU
Dosage Form:	Vial
Package Size:	1
Material:	704138
Batch:	652011A
Quantity:	21573
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: 27.11.2017 s47F

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

Certificate of Analysis

Rabipur 1 Ds.

Batch Number:	652011A	**Material Code:**	704138
Date of Manufacturing:	18.07.2017	**Expiry Date:**	29.02.2020
Start of Shelf Life:	16.08.2017	**Storage Condition:**	+ 2°C to + 8°C

Test	Specification	Result
Rabies glycoprotein	-	13,38 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 %)	-	2,3 IU/Ds
Estimated potency	Result >= 2,5 IU/Ds	4,6 IU/Ds
Upper fiducial limit (<= 400 %)	-	9,1 IU/Ds
Endotoxin	Result < 25 IU/Ds	< 1 IU/Ds
Residual moisture	Result <= 3,0 %	1,4 %

Product Specification Reference: 274261corresponds to LSOP9000054667

Approved By: s47F

Qualified Person

Date: 24.11.2017

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

Paul-Ehrlich-Institut

Paul-Ehrlich-Institut, Postfach 11 42, 63207 Langen

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

Administrative Code: N2.01.01.0245
Certificate number: 3729/17
Date of issue: 20.11.2017

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:	652011A-Z
Type of container:	Vial
Total number of containers in this batch:	35.484
Number of doses per container:	1 dose
Date of start of period of validity:	16 August 2017
Expiry date:	15 August 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
11

LOT RELEASE PROTOCOL

RABIPUR®

Lot No. 652011A-Z

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

TABLE OF CONTENT LRP page number

GENERAL CHAPTER Page 1
CERTIFICATION Page 2
OVERVIEW Page 3
MANUFACTURING FLOW Page 4
SEMI-FINISHED PRODUCT (FILLING LOT) Page 5
FINAL BULK Page 7

CONCENTRATE CHAPTERS Page 9
STARTING MATERIALS AND CONTROL CELLS CHAPTER Page 21
ATTACHMENTS Page 51

CERTIFICATION

I herewith certify that Rabipur® batch no. 652011A-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

13.11.2017	s47F Sachkundige Person/ Qualified Person	s47F
Date		Name and Signature Qualified Person

OVERVIEW

Identity Number	516
Lot Numbers	
Semi-Finished Lot	516 652011
Final Bulk	516 652010
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	35484
Date of Manufacture (Blending)	18.07.2017
Start of Shelf Life	16.08.2017
Expiry Date Semi-Finished Product (Filling Lot)	15.08.2021
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	2876560007
- Manufacnurer 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 Culnure, 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	T315_1 T315_2 T315_3 T315_4 T317_1 T317_2 T317_3 T317_4 T324_1 T324_2 T324_3 T324_4
Virus Suspension 593C Inactivated Virus Suspension 593B	T315-1 T317-1 T324-1
Antigen Concentrate 593A	T315-1A T317-1A T324-1B
Final Bulk	516 652010
SemiFinished Product	516 652011

SEMI-FINISHED PRODUCT (Filling Lot)

Production Details for Semi-Finished Product, Lot No. 516 652011 (Doc. No. 9000046070)

Date of Filling	20.07.2017
Date of Lyophilization	20.07.2017
Type of Container	Vial
Number of Containers before Visual Inspection	35659
Number of Containers after Visual Inspection	35484
Filling Volume	1 mL
Recommended Reconstitution Volume	1 mL

Test Details for Semi-Finished Product, Lot No. 516 652011

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
24.08.2017	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	
15.08.2017	29.08.2017	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			
16.08.2017	13.09.2017	5,3 IU/dose	2,2 IU/dose	13,0 IU/dose
24.08.2017	21.09.2017	3,8 IU/dose	1,3 IU/dose	10,5 IU/dose
Geometric Mean				
26.09.2017		4,6 IU/dose	2,3 IU/dose	9,1 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 652011

Further Tests

Test	Method	Requirement	Result	Date
Residual Water (LSOP 9000053147)	Karl Fischer method according to Ph. Eur.	max 3,0%	1,4 %	16.08.2017
pH Value (LSOP 9000047122)	Potentiometric determination according to Ph. Eur.	pH 7,3 – 8,3	pH 7,6	16.08.2017
Bacterial Endotoxins (LSOP 9000054775)	LAL-Test according to Ph. Eur.	Less than 25 IU per single dose	< 1 IU/mL	10.08.2017
Bovine Serum Albumin (LSOP 9000054759)	Immunochemical method according to Ph. Eur. (ELISA)	max. 50 ng per single dose	2 ng/Ds	15.08.2017
Glycoprotein Content (LSOP 9000055019)	Rabies glycoprotein (ELISA)	None (results are collected for potential later correlation with the respective potency test)	13,38 IU/mL	22.08.2017

FINAL BULK

Production Details for Final Bulk, Lot No. 516652010

(Doc. No. 9000046037)

Date of Formulation	18.07.2017		
Volume	Storage Temperature	Storage Time	Approved Storage Period
46.42 kg	+2 °C to +8 °C	2 days	≤ 6 days

Test Details for Final Bulk, Lot No. 516 652010

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.		
Before Sterile Filtration			
Date		Result	
On	Off		
04.08.2017	18.08.2017	Pass	
After Sterile Filtration			
Date		Result	
On	Off		
04.08.2017	18.08.2017	Pass	

Glycoprotein content (LSOP 9000055019)

Method	ELISA
Requirement	10,4 – 20,8 IU/ml
Date	Result
20.07.2017	17,3 IU/mL

COMMENTS

N/A

ATTACHMENTS

Details on Potency Test
Statement Human Albumin
OMCL Certificate Human Albumin

RABIES ANTIGEN CONCENTRATE, Lot No. 593AT315-1A

1. VIRUS SUSPENSION

1.1. Production Details for Virus Suspension, Lot No. 593CT315 (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	24.02.2016
Date of Harvest of Sub-Batches	01.03.2016
Storage Temperature	+2°C to +8°C
Storage Time	00 h 10 min
Approved Storage Time	≤ 24 hours

1.2. Test Details for Virus Suspension, Lot No. 593CT315

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	
22.03.2016	05.04.2016	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	
05.04.2016	03.05.2016	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
17.03.2016	21.03.2016	7.6 Log $TCID_{50}$/mL	Pass

1.3. Production Details for Filtered Virus Suspension Lot No. 593CT315 (SOP No. 274054)

Date of Filtration	01.03.2016

1.4. Test Details for Filtered Virus Suspension, 593CT315

Total Nitrogen (SOP No. 103347)

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

Date		Result
Start	End	
08.03.2016	08.03.2016	1.2 mg/mL

Beta-Propriolactone (SOP No. 243472)

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

Date	Result
11.03.2016	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
01.03.2016	pH 7.3

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593BT315 (Doc. No. 274054)

Date of inactivation	Start	End
	01.03.2016	02.03.2016
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. 593BT315

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	
17.03.2016	11.04.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
08.03.2016	2.19 IU/mL

3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593AT315-1A (Doc. No. 274056)

Date of Purification and Concentration	03.03.2016
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. 593AT315-1A

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	
08.03.2016	22.03.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
08.03.2016	185 IU/mL

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

RABIES ANTIGEN CONCENTRATE, Lot No. 593AT317-1A

1. VIRUS SUSPENSION

1.1. Production Details for Virus Suspension, Lot No. 593CT317 (Doc. No. 274053)

Date of Inoculation of 4 Sub-Batches	01.03.2016
Date of Harvest of Sub-Batches	07.03.2016
Storage Temperature	+2°C to +8°C
Storage Time	00 h 00 min
Approved Storage Time	≤ 24 hours

1.2. Test Details for Virus Suspension, Lot No. 593CT317

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	
23.03.2016	06.04.2016	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	
05.04.2016	03.05.2016	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	7.8 Log $TCID_{50}$/mL	Pass

1.3. Production Details for Filtered Virus Suspension Lot No. 593CT317 (SOP No. 274054)

Date of Filtration	07.03.2016

1.4. Test Details for Filtered Virus Suspension, 593CT317

Total Nitrogen (SOP No. 103347)

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

Date		Result
Start	End	
16.03.2016	16.03.2016	1.1 mg/mL

Beta-Propriolactone (SOP No. 243472)

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

Date	Result
24.03.2016	300 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
07.03.2016	pH 7.3

2. INACTIVATED VIRUS SUSPENSION

2.1. Production Details for Inactivated Virus Suspension, Lot No. 593BT317 (Doc. No. 274054)

Date of inactivation	Start	End
	07.03.2016	08.03.2016
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	291 L	

2.2. Test Details for Inactivated Virus Suspension, Lot No. 593BT317

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	
17.03.2016	11.04.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	≥ 0.52 IU/mL

Date	Result
15.03.2016	2.37 IU/mL

3. ANTIGEN CONCENTRATE

3.1. Production Details for Antigen Concentrate, Lot No. 593AT317-1A (Doc. No. 274056)

Date of Purification and Concentration	09.03.2017
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. 593AT317-1A

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	
14.03.2016	28.03.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
15.03.2016	210 IU/mL

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

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

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. 593AT324-1B (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. 593AT324-1B

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	
31.03.2016	14.04.2016	Pass

Glycoprotein Content (SOP No. 100376)

Method	ELISA
Requirement	52 - 585 IU/mL
Date	Result
29.03.2016	256 IU/mL

4. COMMENTS

N/A

5. ATTACHMENTS

N/A

1. STARTING MATERIALS for Lot 593DT315

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	C26/13A-04	C26/13A-04	C26/13A-04	C26/13A-04
Preparation Date of Working Seed Lot	17.09.2015	17.09.2015	17.09.2015	17.09.2015
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	07.01.2016	07.01.2016	07.01.2016	07.01.2016

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

Cell Culture System	Chicken Fibroblast Cell Cultures			
Flock Number	20402			
Delivery Date of incubated Eggs	23.02.2016			
Manufacturing Date of Cell Culture	24.02.2016			
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	072/02	072/02	072/02	072/02
FCS SOP222018	0039	0040	0039	0040
Medium 3 + NaHCO3 SOP271811	022/02	022/02	022/02	022/02
Medium 3 + HSA SOP300719	052/05	052/05	052/06	052/06
Size of Sub-Batch	71 L	71 L	71 L	71 L
Population doubling level (PDL) of produced cells when inoculated with virus seed	2.2 Cells x 10^6/mL	2.3 Cells x 10^6/mL	3.1 Cells x 10^6/mL	2.5 Cells x 10^6/mL
For details see attachment: Details on SPF Eggs to 593DT315				

3. CONTROL CELL CULTURES, Lot No. 593DT315

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)
	24.02.2016	25.02.2016

3.2. Test Details for Control Cell Cultures, Lot No. 593DT315

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	
25.02.2016	11.03.2016	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	
11.03.2016	11.03.2016	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	
11.03.2016	25.03.2016	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	
11.03.2016	25.03.2016	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	
11.03.2016	25.03.2016	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	
11.03.2016	21.03.2016	22.03.2016	22.03.2016	Pass

4. COMMENTS

n.a.

5. ATTACHMENTS

Details on SPF Eggs to 593DT315
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

Date of Delivery: 23.02.2016
SPF Eggs : 4120

Details of the consignment:

Latest Sampling Date	**08.02.2016**

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.

ROH 279051 0465

Osterholz-Scharmbeck, 17.02.2016

23. FEB. 2016 s47F

s47F [redacted]

Signature of VALO BioMedia GmbH

Anlage 5 zum BPR 593-01
der Charge 593DT 315
Seite 2 von 3 23. FEB. 2016 [redacted]

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23. FEB s47F

Consignee: GSK Vaccines Gmbh
Marburg , 35006

Date of Delivery: 23.02.2016
SPF Eggs : 4120

Flock	Hatch Date	Age of Flock	Laying Date	number of eggs
20402	25.05.2015	37	11. - 13. 02. 2016	4570
Start of incubation	Start of candling	No. of eggs discarded	% fertility	No. of eggs delivered
15.02.2016 540	23.02.2016 600	186	4,1	4384
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	23.02.2016 14:00 Uhr	08.08.2016

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25.02.16 s47F

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23. FEB. 2016 s47F

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23. FEB. 2016 s47F

Anlage 5 zum BPR 593-01
der Charge 593DT 315
Seite 3 von 3
23. FEB. 2016 [redacted]

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:	C26/13A	**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:	C26/13A	**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 GKID50/ml	6,7 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:	C26/13A	**Material Code:**	OKGU004 / OHGU00S
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:** 11.07.14

Issued by: s47F [redacted] System: LIMS

1. STARTING MATERIALS for Lot 593DT317

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	C26/13A-04	C26/13A-04	C26/13A-04	C26/13A-04
Preparation Date of Working Seed Lot	17.09.2015	17.09.2015	17.09.2015	17.09.2015
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	07.01.2016	07.01.2016	07.01.2016	07.01.2016

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

Cell Culture System	Chicken Fibroblast Cell Cultures
Flock Number	40304
Delivery Date of incubated Eggs	29.02.2016
Manufacturing Date of Cell Culture	01.03.2016
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	072/03	072/03	072/03	072/03
FCS SOP222018	2220180040	2220180040	2220180040	2220180040
Medium 3 + NaHCO3 SOP271811	022/02	022/02	022/03	022/03
Medium 3 + HSA SOP300719	052/07	052/07	052/08	052/08
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	2.2 Cells x 10^6/mL	2.5 Cells x 10^6/mL	2.2 Cells x 10^6/mL
For details see attachment: Details on SPF Eggs to 593DT317				

3. CONTROL CELL CULTURES, Lot No. 593DT317

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)
	01.03.2016	02.03.2016

3.2. Test Details for Control Cell Cultures, Lot No. 593DT317

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	
02.03.2016	18.03.2016	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	
18.03.2016	18.03.2016	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	
18.03.2016	01.04.2016	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	
18.03.2016	01.04.2016	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	
18.03.2016	01.04.2016	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	
18.03.2016	29.03.2016	06.04.2016	07.04.2016	Pass

4. COMMENTS

N/A

5. ATTACHMENTS

Details on SPF Eggs to 593DT317
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 0468

29. FEB. 2016

s47F

Date of Delivery: 29.02.2016
SPF Eggs : 4120

Details of the consignment:

Latest Sampling Date	15.02.2016

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, 24.02.2016

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Anlage 5 zum BPR 593-01
der Charge 593DT 317
Seite 2 von 3

s47F [redacted]
Signature of VALO BioMedia GmbH

29. FEB. 2016
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29. FEB. 2016
s47F

Consignee: GSK Vaccines Gmbh
Marburg , 35006

ROH 279051 0468

29. FEB 2016
s47F

Date of Delivery: 29.02.2016
SPF Eggs : 4120

Flock	Hatch Date	Age of Flock	Laying Date	number of eggs
40304	08.03.2015	49	[illegible]	4540
Start of incubation	Start of candling	No. of eggs discarded	% fertility	No. of eggs delivered
21.02.2016	[illegible]	428	9,3	4112
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	29.02.2016 14:00 Uhr	09.05.2016

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Anlage 5 zum BPR 593-01
der Charge 593DT 317
Seite 3 von 3

29. FEB 2016
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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:	C26/13A	**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: [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:	C26/13A	**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 GKID50/ml	6,7 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:	C26/13A	**Material Code:**	OKGU004 / OHGU00S
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 (Qualified Person s47F **Date:** 11.07.14

Issued by: s47F System: LIMS

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

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

s47F

Signature of VALO BioMedia GmbH

GXP COPY

15. MRZ. 2016

15. MRZ. 2016

s47F

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

15. MRZ. 2016 s47F

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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: s47F (Qualified Person) s47F **Date:** 10.07.14

Issued by: s47F System: LIMS

Substance	Rabies
Method	9000054770-11
Assay number	8
Technician	s47F
1.+ 2. Immunisierung	16/08/2017 + 23/08/2017
Challenge	30/08/2017
Testende	13/09/2017
Tierart/Lieferant	Mäuse/CR

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

15. SEP. 2017 s47F

Standard	
Id.	Referenz-Standard
	WF-3
Ass. pot.	10.77IU/ml
Doses	(1)
0.1ml	18/20
0.02ml	10/19
0.004ml	2/20
0.0008ml	1/20

Sample 1	
Id.	652 011
GLIMS-ID	8758994
Ass. pot.	?IU/ml
Doses	(1)
0.2ml	13/20
0.04ml	13/20
0.008ml	6/20
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 = 0.545191 (0.419892 to 0.670490)
Correlation | r |: 0.917244 (Weighted)

Source of variation	Degrees of freedom	Sum of squares	Mean square	Chi-square	Probability
Preparations	1	7.55718E-05	7.55718E-05	7.55718E-05	0.993
Regression	1	51.2221	51.2221	51.2221	0.000 (***)
Non-parallelism	1	1.97705	1.97705	1.97705	0.160
Non-linearity	4	7.68269	1.92067	7.68269	0.104
Standard	2	1.17433	0.587164	1.17433	0.556
Sample 1	2	6.50836	3.25418	6.50836	0.039 (*)
Treatments	7	60.8819	8.69741	60.8819	0.000 (***)
Theoretical variance			1.00000		
Total	7	60.8819	8.69741		

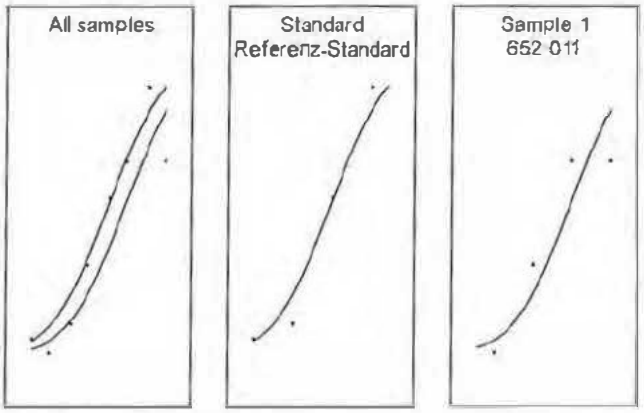
Standard			
Id.	Referenz-Standard		
(IU/ml)	Lower limit	Estimate	Upper limit
Potency	10.7700	10.7700	10.7700
Rel. to Ass.	100.0%	100.0%	100.0%
Rel. to Est.	100.0%	100.0%	100.0%
IU/ED50	0.109278	0.201181	0.390294
Rel. to Ass.	256.2%	497.1%	915.1%
Rel. to Est.	51.5%	100.0%	184.1%

Sample 1			
Id.	652 011		
(IU/ml)	Lower limit	Estimate	Upper limit
Potency	2.20492	5.34676	12.9734
Rel. to Ass.	?	?	?
Rel. to Est.	41.2%	100.0%	242.6%
ml/ED50	0.0205452	0.0376268	0.0725714
Rel. to Ass.	?	?	?
Rel. to Est.	51.8%	100.0%	183.1%

ID: GSK3/BEL

Anlage A
Seite 1/2
15. SEP. 2017

Substance	Rabies
Method	9000054770-11
Assay number	8
Technician	s47F
1.+2. Immunisierung	16/08/2017 + 23/08/2017
Challenge	30/08/2017
Testende	13/09/2017
Tierart/Lieferant	Mäuse/CR



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

Anlage A
Seite 2/2
15 SEP. 2017
s47F

Substance	Rabies
Method	9[redacted]00054770-11
Assay number	9
Technician	s47F [redacted]
1.+ 2. Immunisierung	24/08/2017 + 31/08/2017
Challenge	07/09/2017
Testende	21/09/2017
Tierart/Lieferant	Mäuse/CR

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

25. SEP. 2017 s47F

Standard	
Id.	ReferenzStandard
	WF-3
Ass. pot.	10.77IU/ml
Doses	(1)
0.1ml	16/20
0.02ml	7/20
0.004ml	6/20
0.0008ml	2/20

Sample 1	
Id.	652 011
GLIMS-ID	[redacted]8758995
Ass. pot.	?IU/ml
Doses	(1)
0.2ml	15/20
0.04ml	8/20
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 = 0.452696 (0.337084 to 0.568308)
Correlation |r |: 0.949788 (Weighted)

Source of variation	Degrees of freedom	Sum of squares	Mean square	Chi-square	Probability
Preparations	1	0.160188	0.160188	0.160188	0.689
Regression	1	41.4821	41.4821	41.4821	0.000 (***)
Non-parallelism	1	0.621670	0.621670	0.621670	0.430
Non-linearity	4	3.89772	0.974430	3.89772	0.420
Standard	2	2.34901	1.17451	2.34901	0.309
Sample 1	2	1.54871	0.774354	1.54871	0.461
Treatments	7	46.1616	6.59452	46.1616	0.000 (***)
Theoretical variance			1.00000		
Total	7	46.1616	6.59452		

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	0.109037	0.218260	0.480965
Rel. to Ass.	207.9%	458.2%	917.1%
Rel. to Est.	45.4%	100.0%	200.2%

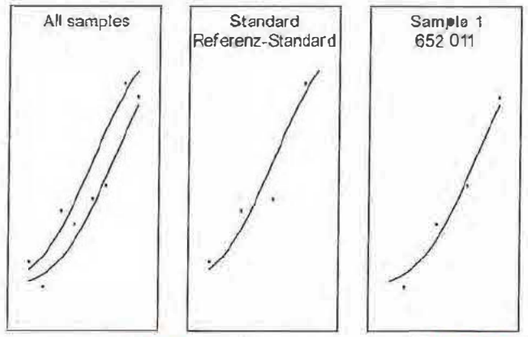
Sample 1			
Id.	652 011		
(IU/ml)	Lower limit	Estimate	Upper limit
Potency	1.32748	3.81789	10.5389
Rel. to Ass.	?	?	?
Rel. to Est.	34.8%	100.0%	276.0%
ml/ED50	0.0283352	0.0571676	0.132293
Rel. to Ass.	?	?	?
Rel. to Est.	43.2%	100.0%	201.8%

ID: GSK3/BEL

25. SEP. 2017 s47F

Anlage Nr. 7 LSP 90000 54770-11 LTR 9

Substance	Rabies
Method	9000054770-11
Assay number	9
Technician	s47F
1.+ 2. Immunisierung	24/08/2017 + 31/08/2017
Challenge	07/09/2017
Testende	21/09/2017
Tierart/Lieferant	Mäuse/CR



Executed by: s47F s47F Calculated by: s47F s47F Approved by: s47F s47F 27.09.17

ID: GSK3/BEL

Anlage 2 zu LSOP 9000054770-11 LTR 9 25. SEP. 2017 [redacted]

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		
Labor / Bereich: Bioassays	Laufende Test-Nr.: 23	225189-00000254

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

Präparat: *Product:* Rabies	**Ch.B.:** *Batch-No.:* 652 011
LIMS-ID: *LIMS-ID* 8758997	**Lfd.-Nr.:** *Running-No.:* entfällt

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.	LTR- Nr. 8	entfällt
2.	LTR- Nr. 9	entfällt
3.	entfällt	entfällt

Ergebnis: *Result:*	4,6 IE/Dosis	2,3 IE/ Dosis	9,1 IE / Dosis
	Wirksamkeit *Activity*	**Unteres Konfidenzintervall** *Lower confidence limit*	**Oberes Konfidenzintervall** *Upper confidence limit*

Berechnung durchgeführt *Calculation done by:*	**Datum** *Date*	26.09.17	**Unterschrift** *Signature*	s47F

Bemerkungen:

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.:** 23	Seite 2 von 2 225189-00000254

3 Ergebnis *(Result)*

Präparat *Product*	Ch.-Bez. *Batch-No.*	LIMS-ID *LIMS-ID*	LIMS-Eintrag *LIMS-Entry*	Bewertung *Assessment*	Beurteilung *Validation*
Rabies	652 011	8758997	(Ja *Yes*) / Nein *no*	(Pass) / Fail	(valid) / invalid

Protokoll richtig ausgefüllt und geprüft *The record is correctly filledout and checked*	26.09.17 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)*	27.09.17 Datum *Date*	s47F Unterschrift *Signature*
	Verantwortlicher Mitarbeiter/Supervisor *Responsible operator / Supervisor*	

Der Test ist valide *Test is valid* **(siehe Tabelle)** *(See table)*	27.09.17 Datum *Date*	s47F Unterschrift *Signature*
	Laborleiter/Supervisor *Head of laboratory / Supervisor*	

AM erstellt *Deviation is initiated* Ja *Yes* ☐ Nein *No* ☒ **AM Nr.** N/A *(DevNo.)*	26.09.17 Datum *date*	s47F Unterschrift *Signature*
	Verantwortlicher Mitarbeiter *Responsible operator*	

Bemerkungen:

Charge: 652 011 26.09.17 CB

	A	B	C	D	E	F	G	H	I	J
1	**EuPharm 6.2**	**Test-Nr. 8**	**Test-Nr. 9**							
2										
3	Activity (IE / Dose)	[illegible]	[illegible]							
4	Lower limit	[illegible]	[illegible]							
5	Upper limit	[illegible]	[illegible]							
6										
7	M	1,6677	1,3350				1,5014	2	0,0277	
8	Lower limit (M)	0,7885	0,2624							
9	Upper limit (M)	2,5649	2,3514							
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)	1,7765	2,0890							
13										
14	Weight (6.2.3)	4,8689	3,5211				8,3900	0,3452		
15	M (weighted 6.2.3)	8,1199	4,7006				1,5281	0,8514	2,2047	
16	Activity with CI						4,6093	2,3430	9,0678	
17										
18	Chisq (6.2.2)	0,0949	0,1313				0,2262	0,6344	**homogeneous**	
19										
20	Intra-assay	0,2054	0,2840							
21	Inter-assay	0,0277	0,0277							
22	Weight (6.2.4)	4,2908	3,2084				7,4992	0,3652		
23	M (weighted 6.2.4)	7,1557	4,2833				1,5254	0,7950	2,2557	
24	Activity with CI						4,5968	2,2145	9,5420	
25										
26	**Final (IE / Dose)**						**4,6093**	**2,3430**	**9,0678**	**3,8702**

gedruckt: 26.09.17 547F

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
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+49 6421 386 - 6111
marburg.finalrelease@gsk.com

07.11.2017

Statement

Human Albumin used in the production of Rabipur® batch **652011A-Z**

Herewith I confirm that the Human Albumin lots listed in the table below were used for production of Rabipur Lot 652011A-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 652011A-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 lot no. 0381700034

07.11.2017 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.

s47F

Signed	
Name and function of signatory	s47F 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

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SUMMARY PROTOCOL FOR PRODUCTION AND TESTING

OF STERILE WATER FOR INJECTION

FINAL PRODUCT

Lot 152159C

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	152159C
Type of container	Ampoule
No. of final containers	81,403
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 17, 2015
Expiry date	February 2020
Storage conditions of final product	Do not freeze

FINAL BULK LOT 152159C

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 17, 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. 17 - Mar. 23, 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 152159C

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 17, 2015
Filled volume	1.07 mL
Type of container	Ampoule
No. of final containers	81,403

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 26, 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	March 24, 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 24, 2015
Result	Particles ≥ 10 µm: 23/container Particles ≥ 25 µm: 0/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. 152159C of Sterile Water for Injection was manufactured and tested according to the procedures approved by competent authorities and complies with the quality requirements.

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Quality Assurance / Qualified Person

25 JUN 15

Date