Burgwedel Biotech GmbH
A subsidiary of Merck & Co., Inc., USA

MSD

BURGWEDEL BIOTECH GMBH
Im Langen Felde 5
30938 Burgwedel
Germany
Telefon 05139 897 0
Telefax 05139 897 115

CERTIFICATE OF ANALYSIS

Product	:	M + PAC
No. of Bulk Vaccine	:	C165
Batch No.	:	C165 B
Label/Pack No.	:	..... 3 A
Date of Manufacture	:	28.01.2015
Destination	:	Hungary / Czech Republic / Slovak Republic
Expiry Date	:	12-2016

		DATE	SPECIFICATION		RESULT
The following tests were performed on the **aqueous phase** of C165 :					
1. Analytical Data			**specified**	**actual**	
Aluminium	:	09.02.15	1.0 – 1.4 mg/ml	1.2 mg/ml	passed
The following tests were performed on the **bulk** vaccine C165 :					
			specified	**actual**	
2. Sterility Test	:	04.02.15 – 25.02.15	no growth		passed
3. Rel. Potency Test	:	05.02.15	1.47 – 4.24	2.51	passed
4. Analytical Data					
Thiomersal	:	16.02.15	0.085 – 0.115 mg/ml	0.109 mg/ml	passed
Visual Appearance/ Stability	:	17.02.15	off-white oily emulsion, no phase separation		complies
pH	:	11.02.15	6.2 – 7.5	6.7	passed
The following tests were performed on **filling lot** C165 B :			**specified**	**actual**	
1. Sterility Test	:	24.03.15 – 14.04.15	no growth		passed
2. Extractable Volume	:	09.04.15	actual ≥ nominal volume		passed
3. Viscosity	:	09.04.15	3 – 10 mPa s	5 mPa s	passed
4. pH	:	09.04.15	6.2 – 7.5	6.5	passed

I hereby certify that the above information is authentic and accurate. This batch of product has been manufactured, including packaging/labelling and quality control at the above mentioned site 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, packaging and analysis records were reviewed and found to be in compliance with GMP.

Burgwedel

17. APR. 2015

Qualified Person

Dr. Markus Luy

16. April 2015

Quality Control

Dr. Andreas Busche

Burgwedel Biotech GmbH
A subsidiary of Merck & Co., Inc., USA
MSD

We hereby clarify and confirm that the inactivated Mycoplasma vaccine

M + PAC / ThoroVAX vet.

Batch No.: C165 B

has been manufactured in accordance with GMP and is released under the requirement of the marketing authorisation issued in:

Austria :	8-20248 [50 ml / 100 ml]	Czech Republic :	97/068/02-C [50 ml / 100 ml]
Denmark :	MT 33449 [100 ml]	Slovak Republic :	97/041/05-S [50 ml / 100 ml]
Belgium :	BE-V277243 [100 ml]	Hungary :	2149/2/07 [100 ml]
France :	AMM FR/V/7806278 0/2001 [50 ml / 100 ml]	Italy :	AIC 103526012 [50 ml] AIC 103526051 [100 ml]
United Kingdom :	Vm 01708/4583 [50 ml / 100 ml]	Slovenia :	5363-949/2005 [50 ml / 100 ml]
Germany :	PEI.V.03209.01 [50 ml / 100 ml]	Portugal :	AIM R706/02 DGV
Greece :	37020 [50 ml / 100 ml]	Spain :	1456 ESP [50 ml / 100 ml]
Ireland :	10996/236/001 [50 ml / 100 ml]	Sweden :	MT 18310 [50 ml / 100 ml]
Romania :	050719 [50 ml / 100 ml]	Cyprus :	CY00101V [50 ml / 100 ml]
Poland :	1641/06 [50 ml / 100 ml]		

Burgwedel, 15.04.2015

BURGWEDEL BIOTECH GMBH

.....
Dr. Markus Luy
Qualified Person

Burgwedel Biotech GmbH
A subsidiary of Merck & Co., Inc., USA

MSD

BATCH PROTOCOL OF THE PRODUCTION AND THE QUALITY CONTROL TESTS OF THE VACCINE " M + PAC / ThoroVAX vet."

Product Name : M + PAC / ThoroVAX vet.

Product Licence No.:

Austria :	8-20248 [50 ml / 100 ml]	Czech Republic :	97/068/02-C [50 ml / 100 ml]
Denmark :	MT 33449 [100 ml]	Slovak Republic :	97/041/05-S [50 ml / 100 ml]
Belgium :	BE-V277243 [100 ml]	Hungary :	2149/2/07 [100 ml]
France :	AMM FR/V/7806278 0/2001 [50 ml / 100 ml]	Italy :	AIC 103526012 [50 ml] AIC 103526051 [100 ml]
United Kingdom :	Vm 01708/4583 [50 ml / 100 ml]	Slovenia :	5363-949/2005 [50 ml / 100 ml]
Germany :	PEI.V.03209.01 [50 ml / 100 ml]	Portugal :	AIM R706/02 DGV
Greece :	37020 [50 ml / 100 ml]	Spain :	1456 ESP [50 ml / 100 ml]
Ireland :	10996/236/001 [50 ml / 100 ml]	Sweden :	MT 18310 [50 ml / 100 ml]
Romania :	050719 [50 ml / 100 ml]	Cyprus :	CY00101V [50 ml / 100 ml]
Poland :	1641/06 [50 ml / 100 ml]		

Product Bulk No. : C165

Date of Manufacture : 28.01.2015

Date of Expiry : 12 - 2016 (France/Spain/Germany/Austria/Italy/ Portugal/Greece/Cyprus/Romania/ Czech Republic/Slovak Republic/ Hungary/Slovenia/Poland/ Denmark/Sweden/Belgium)
27-01-2017 (UK / Ireland)

Total Volume : 5008.1 Liter

<u>This Set of Documents Consists of the Following Protocols:</u>

1.0 Production Summary
2.0 Blending of the Final Product
3.0 Quality Control Tests
4.0 Summary of QC Tests
5.0 Release Document

1.0 PRODUCTION SUMMARY

Product	:	BA Mycoplasma Hyopneumoniae
UIN	:	100059
Component of	:	M+Pac, ThoroVAX vet.

DATA OF THE PRODUCTION PROCESS

1.1 Production of Antigen Suspension

Serotype	:	Mycoplasma Hyopneumoniae
Batch	:	**55222**
Expiry Date	:	09.04.15

1.2 Seed Material

1.2.1	Master Seed	:	ATCC #25934 MSB+7 from 30/10/97
1.2.2	Working Seed	:	MSB+11 from 24.06.2005
1.2.3	Prod. Working Seed	:	MSB+15; 15L12
		Date of production	: 15.12.2012
		Last testing date	: 12.03.2013

1.3

Growth and Harvest	Date	
Start of Prod. Seed :	04.04.14	
Start of Prod. Culture :	05.04.14	
Harvest Prod. Culture:	09.04.14	
Inactivation (with BEI):	09.04.14 – 10.04.14	Period.: [23 h]
Neutralization (Thiosulphate):	10.04.14	

1.4

Pre-inactivation tests		Date	Specification	Result
Identity	:	09.04.14	Serotype	Complies
Purity	:	16.04.14	pure	Passed

1.5

Post-inactivation tests		Date	Specification	Result
Inactivation Control	:	15.04.14 – 07.05.14	No growth	Passed
Excess Thiosulphate	:	15.04.14	excess detectable	Passed

1.6

Concentration (Ultrafiltration)		Date	
Date of Concentration:		14.04.14	by factor: 11
Final Volume	:	164.5 Liter	

1.7

Post-concentration tests		Date	Specification	Result
Inactivation Control	:	15.04.14 – 07.05.14	No growth	Passed
Antigen Content	:	24.04.14	≥ 4 dose/ml	12 dose/ml
pH (IPC)	:	14.04.14	7.2 - 8.2	8.0
Sterility (Ph.Eur.)	:	16.04.14 – 30.04.14	No growth	Passed

1.8 Storage at 2-8°C : 14.04.14

1.9 Deviation no ☒ yes ☐

written by [illegible] checked by [illegible]

Date Date

1.0 PRODUCTION SUMMARY

Product	:	BA Mycoplasma Hyopneumoniae
UIN	:	100059
Component of	:	M+Pac, ThoroVAX vet.

DATA OF THE PRODUCTION PROCESS

1.1 Production of Antigen Suspension

Serotype	:	Mycoplasma Hyopneumoniae
Batch	:	**55225**
Expiry Date	:	01.07.15

1.2 Seed Material

1.2.1	Master Seed	:	ATCC #25934 MSB+7 from 30/10/97
1.2.2	Working Seed	:	MSB+11 from 24.06.2005
1.2.3	Prod. Working Seed	:	MSB+15; 15L12
		Date of production	: 15.12.2012
		Last testing date	: 12.03.2013

1.3

Growth and Harvest	Date	
Start of Prod. Seed :	25.06.14	
Start of Prod. Culture :	26.06.14	
Harvest Prod. Culture:	01.07.14	
Inactivation (with BEI):	01.07.14 – 02.07.14	Period.: [24 h]
Neutralization (Thiosulphate):	02.07.14	

1.4

Pre-inactivation tests		Date	Specification	Result
Identity	:	01.07.14	Serotype	Complies
Purity	:	08.07.14	pure	Passed

1.5

Post-inactivation tests		Date	Specification	Result
Inactivation Control	:	07.07.14 – 29.07.14	No growth	Passed
Excess Thiosulphate	:	11.07.14	excess detectable	Passed

1.6

Concentration (Ultrafiltration)		Date	
Date of Concentration:		04.07.14	by factor: 11
Final Volume	:	169.5 Liter	

1.7

Post-concentration tests		Date	Specification	Result
Inactivation Control	:	07.07.14 – 29.07.14	No growth	Passed
Antigen Content	:	09.07.14	≥ 4 dose/ml	9 dose/ml
pH (IPC)	:	04.07.14	7.2 - 8.2	7.9
Sterility (Ph.Eur.)	:	08.07.14 – 22.07.14	No growth	Passed

1.8 Storage at 2-8°C : 04.07.14

1.9 Deviation no ☒ yes ☐

written by [illegible] checked by [illegible]

Date Date

2.0 BLENDING OF THE FINAL PRODUCT

Product : M + PAC / ThoroVAX vet.
Bulk No. : C165
Date of Blend : 28.01.15

DATA OF THE BLENDING PROCESS

AQUEOUS PHASE (=C165 +)				
Components	Batch No.	Expiry Date Antigen	Volume [Litres]	Cumulative Volume [Litres]
Mycoplasma hyopneumoniae	55222 55225	09.04.15 01.07.15	84.8 168.6	253.4
Ethyl Alcohol	214554	---	100.2	353.6
Glycerol	C147	---	500.0	853.6
3% $Al(OH)_3$	C150	---	500.0	1353.6
0.85% NaCl	214614 / 214870	---	2644.8	3998.4
10% Thiomersal	BMGM409121 / BMGM409131	---	5.7	4004.1
0.5 M NaOH	213617	---	4.0	4008.1
		Total volume :		4008.1
EMULSION				
Oily Phase (Tween 80; Span 80; Mineral Oil), Batch No. C164			1000.0	1000.0
Aqueous Phase			4008.1	5008.1
		Formulation volume :		5008.1 Liter

3.0 QUALITY CONTROL TESTS

Product : M + PAC / ThoroVAX vet.

Bulk No. : C165

3.1 Analytical Data

Type of Test		Date	specified	actual
Aluminium (SOP QC/1704)	:	09.02.15	1.0 – 1.4 mg/ml	1.2 mg/ml

Result : **Passed**

3.0 QUALITY CONTROL TESTS

Product	:	M + PAC / ThoroVAX vet.
Bulk No.	:	C165

CONTROL TESTS ON BULK PRODUCT

3.2 Sterility Test (Ph.Eur. 2.6.1.)

3.2.1 Effectiveness of the media in absence of the test material.
Media: 1. Caso-Bouillon + 1% Tween, Batch-No. 214599 / 214757
2. Thioglycollate + 1% Tween, Batch-No. 214664

Result : suitable

3.2.2 Sterility of bulk material

40 ml of bulk material were inoculated into fluid thioglycollate medium +1% Tween. and casein soy broth + 1% Tween according to Ph.Eur. 2.6.1. After 14 days samples were subcultured and incubated for another ≥ 4 days as follows:

a) Casein soy broth cultures at 20-25°C.
b) Fluid thioglycollate cultures at 30-35°C

Media were inspected regularly during this period.

Test on	:	04.02.15
Subculture	:	18.02.15
Test off	:	25.02.15

Result : Passed

3.2.3 Effectiveness of the media in presence of the test material

Date	:	25.02.15

Result : suitable

3.0 QUALITY CONTROL TESTS

Product : M + PAC / ThoroVAX vet.

Bulk No. : C165

CONTROL TESTS ON BULK PRODUCT

3.3 Rel. Potency Test (SOP QC/0402)

Using a "competitive Inhibition ELISA-test" as described in SOP QC/0402E the potency of the vaccine is measured and related to the validated standard reference B978REF#.

Req. : Relative potency of test vaccine to ref. vaccine 1.47 – 4.24

Date : 05.02.15

Result : 2.51

Passed

3.4 Analytical Data

Type of Test		Date	specified	actual
Thiomersal (SOP QC/1705)	:	16.02.15	0.085 - 0.115 mg/ml	0.109 mg/ml
pH (SOP QC/1706)	:	11.02.15	6.2 – 7.5	6.7
Visual Appearance/ Stability (SOP QC/1712)	:	17.02.15	off-white oily emulsion, no phase separation	complies

Result : **Passed**

3.0 QUALITY CONTROL TESTS

Product	:	M + PAC / ThoroVAX vet.
Bulk No.	:	C165
Batch No	:	C165 B
Filling performed	:	21.03.15

CONTROL TESTS ON FINAL PRODUCT

3.5 Sterility Test (Ph.Eur. 2.6.1.)

Effectiveness of the media in absence of the test material.
Media: 1. Caso-Bouillon + 1% Tween, Batch-No. 214910
2. Thioglycollate + 1% Tween, Batch-No. 214876

Result : suitable

Sterility of filled Container

100 ml of 10 vials were inoculated into fluid thioglycollate medium +1% Tween and casein soy broth + 1% Tween according to Ph.Eur. 2.6.1. After 14 days samples were subcultured and incubated for another ≥ 4 days as follows:

a) Casein soy broth cultures at 20-25°C.
b) Fluid thioglycollate cultures at 30-35°C

Media were inspected regularly during this period.

Test on	:	24.03.15
Subculture	:	07.04.15
Test off	:	14.04.15

Result : Passed

3.6 Analytical Data

Type of Test		Date	specified	actual
pH (SOP QC/1706)	:	09.04.15	6.2 – 7.5	6.5
Viscosity (SOP QC/1709)	:	09.04.15	3 – 10 mPa s	5 mPa s

Result : Passed

3.0 QUALITY CONTROL TESTS

Product	:	M + PAC / ThoroVAX vet.
Bulk No.	:	C165
Batch No	:	C165 B
Filling performed	:	21.03.15

CONTROL TESTS ON FINAL PRODUCT

3.7 Test for Extractable Volume (SOP QC/1708)

Volume of one container is determined using a calibrated graduated cylinder (see Ph. Eur. 2.9.17).

Req.: Extractable volume is not less than the nominal volume.

Date	:	09.04.15
Result	:	**suitable**

4.0 SUMMARY OF QC TESTS

Product	:	M + PAC / ThoroVAX vet.
No. of Bulk Vaccine	:	C165
Batch No.	:	C165 B
Date of Manufacture	:	28.01.15
Date of Expiry	:	12 - 2016 (France/Spain/Germany/Austria/ Italy/Portugal/Greece/Cyprus/Romania/ Czech Republic/Slovak Republic/ Hungary/Slovenia/Poland/Denmark/ Sweden/Belgium)
		27-01-2017 (UK / Ireland)

		DATE	SPECIFICATION	RESULT	
The following tests were run on the aqueous phase of "C165 +":					
1. Analytical Data			**specified**	**actual**	
Aluminium	:	09.02.15	1.0 – 1.4 mg/ml	1.2 mg/ml	passed
The following tests were run on the bulk vaccine "C165 ":					
			specified	**actual**	
2. Sterility Test	:	04.02.15 – 25.02.15	no growth		passed
3. Rel. Potency Test	:	05.02.15	1.47 – 4.24	2.51	passed
4. Analytical Data					
Thiomersal	:	16.02.15	0.085 - 0.115 mg/ml	0.109 mg/ml	passed
Visual Appearance/ Stability	:	17.02.15	off-white oily emulsion, no phase separation		complies
pH	:	11.02.15	6.2 – 7.5	6.7	passed
The following tests were run on filling lot "C165 B":			**specified**	**actual**	
1. Sterility Test	:	24.03.15 – 14.04.15	no growth		passed
2. Extractable Volume	:	09.04.15	actual ≥ nominal volume		passed
3. Viscosity	:	09.04.15	3 – 10 mPa s	5 mPa s	passed
4. pH	:	09.04.15	6.2 – 7.5	6.5	passed

Burgwedel,

15. April 2015

Dr. Andreas Busche
Quality Control

5.0 RELEASE DOCUMENT

1. Applicant : BURGWEDEL BIOTECH GMBH
2. Product : M + PAC / ThoroVAX vet.
3. Type of Product : Oily emulsion vaccine stabilized by ethanol and glycerol containing inactivated Mycoplasma Hyopneumoniae antigen adsorbed onto Aluminium hydroxide.
4. Product Licence No.:

Austria :	8-20248 [50 ml / 100 ml]	Czech Republic :	97/068/02-C [50 ml / 100 ml]
Denmark :	MT 33449 [100 ml]	Slovak Republic :	97/041/05-S [50 ml / 100 ml]
Belgium :	BE-V277243 [100 ml]	Hungary :	2149/2/07 [100 ml]
France :	AMM FR/V/7806278 0/2001 [50 ml / 100 ml]	Italy :	AIC 103526012 [50 ml] AIC 103526051 [100 ml]
United Kingdom :	Vm 01708/4583 [50 ml / 100 ml]	Slovenia :	5363-949/2005 [50 ml / 100 ml]
Germany :	PEI.V.03209.01 [50 ml / 100 ml]	Portugal :	AIM R706/02 DGV
Greece :	37020 [50 ml / 100 ml]	Spain :	1456 ESP [50 ml / 100 ml]
Ireland :	10996/236/001 [50 ml / 100 ml]	Sweden :	MT 18310 [50 ml / 100 ml]
Romania :	050719 [50 ml / 100 ml]	Cyprus :	CY00101V [50 ml / 100 ml]
Poland :	1641/06 [50 ml / 100 ml]		

5. Bulk No. : C165
6. Batch No. : C165 B
7. Lot Quantification
   - 7.1 Total No. of Containers : 24 141 à 100 ml
   - 7.2 No. of Doses / Container : 50/vial (single shot)
100/vial (serial shot)
8. Expiry Date
   - 8.1 Date of Manufacture : 28.01.2015
   - 8.2 Date of Potency Test : 05.02.2015
   - 8.3 Date of Expiry : 12 – 2016 (France/Spain/Germany/Austria/Italy/Portugal/Greece/Cyprus/Romania/Czech Republic/Slovak Republic/Hungary/Slovenia/Poland/Denmark/Sweden/Belgium)
27-01-2017 (UK / Ireland)

Remarks: After reviewing all manufacturing and testing data, we confirm that the product has been manufactured and tested in accordance with Good Manufacturing Practice.

Burgwedel,

15. APR. 2015 .....
Dr. Markus Lay
Qualified Person

16. April 2015 .....
B. Fürst
Production Manager