Institute for State Control of Veterinary Biologicals and Medicines
Hudcova 56a
621 00 Brno
Czech Republic
(Reference Member State)

DECENTRALISED PROCEDURE – REPEAT USE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

BIOSUIS Salm emulsion for injection for pigs

(CZ, AT, DE, EE, EL, FR, HU, IE, IT, PL, SK)

FIXR Salmonella emulsion for injection for pigs

(BE, NL)

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	CZ/V/0151/001/E/001
Name, strength and pharmaceutical form	BIOSUIS Salm emulsion for injection for pigs (CZ, AT, DE, EE, EL, FR, HU, IE, IT, PL, SK) FIXR Salmonella emulsion for injection for pigs (BE, NL)
MAH	Bioveta, a. s. Komenského 212/12 683 23 Ivanovice na Hané Czech Republic
Active substance(s)	Inactivated strains of: *Salmonella enterica* subsp. *enterica* sv. Typhimurium *Salmonella enterica* subsp. *enterica* sv. Derby *Salmonella enterica* subsp. *enterica* sv. Infantis
ATC Vetcode	QI09AB14
Target species	Pigs (pregnant gilts and sows)
Indication for use	For the passive immunisation of piglets by the active immunisation of pregnant gilts and sows in order to induce colostral antibodies against strains of *Salmonella enterica* subsp. *enterica* serovar Derby, *S. enterica* subsp. *enterica* serovar Infantis and *S. enterica* subsp. *enterica* serovar Typhimurium. In suckling piglets passive immunisation leads to a decrease in colonisation of inner organs (ileo-caecal lymph nodes, ileal wall and colon wall) by the above *Salmonella* serovars.

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	03/07/2019
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	RMS: CZ CMS: AT, BE, DE, EE, EL, FR, HU, IE, IT, NL, PL, SK
Concerned Member States for repeat use procedure	UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

One vaccine dose (1 ml) contains:

Active substances:

Inactivated strains of:
Salmonella enterica subsp. *enterica* sv. Typhimurium RP ≥ 1*
Salmonella enterica subsp. *enterica* sv. Derby RP ≥ 1*
Salmonella enterica subsp. *enterica* sv. Infantis RP ≥ 1*

*) Relative potency (RP) is determined by comparison with the reference serum obtained after vaccination of mice with a vaccine batch that has successfully passed the challenge test in the target animals.

Adjuvant:

Montanide ISA 206 VG	0.54 ml
Excipients:	
Formaldehyde	max. 0.50 mg/ml
Thiomersal	0.1 mg/ml

The vaccine is supplied in High-density polyethylene (HDPE) vials or type I glass vials with pierceable chlorobutyl rubber stoppers and aluminum caps or flip-off caps. The packing 1 x 10 ml, 1 x 50 ml and 1 x 100 ml are supplied in carton box. The packing 10 x 10 ml is supplied in plastic box with ten holes.
a) single package
1 x 10 ml – glass vial
1 x 50 ml, 1 x 100 ml – polyethylene vial (volumes 60 ml and 120 ml)
b) multi package
10 x 10 ml – glass vial

The particulars of the containers and controls performed are provided and conform to the regulation of monographs 3.2.1, 3.2.2 and 3.2.9 of the European Pharmacopoeia.

The choice of the vaccine strains, of the vaccine composition, adjuvant and inactivating agent are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. A corresponding manufacturing licence and GMP certificates are provided.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substances are inactivated strains *Salmonella enterica* subsp. *enterica* sv. Typhimurium, *Salmonella enterica* subsp. *enterica* sv. Derby, *Salmonella enterica* subsp. *enterica* sv. Infantis

The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Starting materials of non-biological origin used in production comply with indicate pharmacopoeia monographs or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur monographs and European guidelines, any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline and satisfactorily tested according to current European requirements.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control tests during production

The tests performed during production (purity control, identity test, density control, inactivation control, bacterial endotoxins, sterility test, pH determination, thiomersal, formaldehyde, viscosity and determination of particle size) are described in detail and the results of 3 consecutive runs, conforming to the specifications, are provided.

E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. Relevant validations are provided.

The tests include in particular:
- appearance
- extractable volume
- sterility
- potency and identity
- pH value
- airtightness
- thiomersal
- formaldehyde
- bacterial endotoxins
- viscosity
- determination of particle size

F. Batch to batch consistency

The consistency of production has been demonstrated and the results of 3 consecutive runs, conforming to the specifications, are provided.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances (inactivated antigens 12 months and bulk of the vaccine 1 month before filling) when stored under the approved conditions (2-8 °C).

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (2 years) when stored under the approved conditions (2-8 °C).

The in-use shelf-life of the broached vaccine (10 hours) is supported by the data provided.

H. Other Information

Not applicable.

III. SAFETY ASSESSMENT

The vaccine is administered twice with volume of 1 ml intramuscularly in two weeks interval to gilts or sows from 10 months of age (first dose is administered 4 weeks before expected parturition and the second dose 2 weeks later).

Safety studies have been performed with a vaccine batch with maximum antigen content produced according the described production process.

Field studies have been performed with a representative vaccine batch produced according the described production process.

Laboratory trials

The safety of the administration of one dose and the repeated administration of one dose in the target animal is demonstrated in controlled laboratory study which included 8 vaccinated animals and 8 unvaccinated animals (gilts 10-12 months old). Rectal temperatures, general health status and local reactions were observed. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

The safety studies demonstrate that the administration of one dose and the repeated administration of one dose can be considered to be safe, when used in accordance with the recommended vaccination schedule. Appropriate warning regarding local site reactions following vaccination have been included in the SPC: Application site reactions in the form of erythema occurred commonly in field studies and persist mostly 2 to 4 days. A transient increase in rectal temperature (mean increase not greater than of 0.7 °C but may be up to 1.2 °C in individual animals) may commonly occur in the first 24 hours after injection.

The Commission Directive 2009/9/EC, the Notice to Applicant Volume 6B and the Ph. Eur monograph no. 50206 state that the safety of one administration of one overdose needs to be assessed only for live vaccines hence no overdose studies are included for this inactivated vaccine.

Effect on reproductive performance was conducted because the vaccine is intended for pregnant animals. Reproductive safety test was performed during laboratory testing of safety of the administration of one and repeated dose. The experiment monitored the daily weight gain of born piglets in order to verify the safety of the used vaccine to the progeny. There were monitored all piglets from 16 sows (8 vaccinated, 8 non-vaccinated) in this test. The piglets

were weighted daily for 7 days from birth and the data were recorded. The results were statistically processed. A statistical analysis by the pairwise T-test has shown that no statistical difference between the daily weight gains of piglets from vaccinated and non-vaccinated sows was found.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

The adjuvant and excipients used do not create residues in vaccinated animals. Based on this information, no withdrawal period is proposed.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Field studies

Combined safety and efficacy field trial was performed on target animals.

The vaccine was administered to sows and gilts according to the SPC scheme, i.e. in two doses (vaccination and revaccination before delivery) and then in one booster dose before the next expected farrow. The clinical trial was conducted on two farms. In total, 40 animals vaccinated with the tested vaccine were enrolled in the study. The control group consisting of 20 unvaccinated animals was administered only placebo. After the first farrowing, 120 born piglets were enrolled in the study for the purposes of serological and weight monitoring.

The safety evaluation was based on: observation of local and systemic reactions, measurement of rectal temperatures and evaluation of general health state. The piglets were weighed at the time of weaning and at the end of fattening. Average weight gains in these periods were compared between the group of piglets from vaccinated mothers and the group of piglets from control mothers.

In terms of safety, there were no inadequate local or systemic reactions and temperature increase related to the administration of the tested vaccine. The negative effect of vaccination was not observed at piglets.

The results from field trials reflect those observed in laboratory trials.

Environmental Risk Assessment

The applicant provided a first phase of environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

The assessment concluded that there is a negligible risk to the environment associated with use of the vaccine. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

All experiments conducted with BIOSUIS Salm in laboratory and field conditions were designed to meet the requirements of the relevant veterinary legislation, including European

Directive 2001/82/EC, as amended (2009/9/EC) and relevant European Pharmacopoeia monographs in force.

The efficacy of the product has been demonstrated in laboratory challenge studies in piglets for each *Salmonella* antigen included in the vaccine.

Efficacy studies have been performed with a vaccine batch with minimum antigen content produced according the described production process.

Field studies have been performed with a representative vaccine batch produced according the described production process.

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the vaccine reduces colonisation of inner organs (ileo-caecal lymph nodes, ileal wall and colon wall) in suckling piglets by the *Salmonella* serovars included in the vaccine. Colostral antibodies from vaccinated mothers were shown to be effective for progeny at 30 days of age against the mentioned pathogens when piglets are suckled up to 21 days of age.

The laboratory efficacy study included the following evaluation:

Onset of immunity

Efficacy was assessed by comparing the infection agent re-isolation following challenge in groups of piglets from vaccinated and non-vaccinated gilts and by and serology responses after vaccination in gilts in time of parturition and in piglets in time of challenge.

Altogether 8 pregnant gilts were used for the testing of onset of immunity in the challenge experiment for each of *Salmonella* serovar, i.e. challenge experiment with *Salmonella* Derby, S. Infantis and S. Typhimurium. Four gilts were vaccinated according to SPC. The second group of four non-vaccinated gilts were the control group. For each challenge test, consecutively 15 piglets were selected from 4 vaccinated mothers and 15 piglets from 4 non-vaccinated mothers. The selected piglets were separated from the mothers after 48 hours after the birth. Then followed challenge with particular *Salmonella* serovar. Challenge was performed with strains different from the strains, which has been used for the production of the vaccine. The piglets were euthanised after three days after the challenge. After the euthanasia of piglets, the selected organs were sampled.

There were recorded significant differences in the number of *Salmonella* Derby, Infantis and Typhimurium detected in vaccinated and non-vaccinated animals in selected organs (ileo-caecal lymph nodes, wall of ileum and wall of colon).

Presence of specific post-vaccination antibodies against fliC proteins from *Salmonella* strains was demonstrated by serological testing (ELISA) in gilts on the day of parturition and in piglets on day of challenge. Post-infection antibodies against protein B (SipB) were not detected in serum of gilts or in serum of piglets on day of challenge.

Onset of immunity: passive protection commences from the start of colostrum intake.

Duration of immunity

The duration of immunity in piglets has been shown by challenge trial for each *Salmonella* antigen included in the vaccine.

Efficacy was assessed by comparing the infection agent re-isolation following challenge in groups of piglets from vaccinated and non-vaccinated gilts and by and serology responses after vaccination in gilts in time of parturition and 14 days after the booster vaccination and in piglets in time of challenge.

The study design was the same as in the study for onset of immunity. The weaning was done after 21 days after the birth. After application of the challenge strains to piglets 30 days after the birth, the animals were euthanized after three days after the challenge and the selected organs were sampled.

There were recorded significant differences in the number of *Salmonella* Derby, Infantis and Typhimurium detected in vaccinated and non-vaccinated animals in selected organs (ileo-caecal lymph nodes, wall of ileum and wall of colon).

Presence of specific post-vaccination antibodies against fliC proteins from *Salmonella* strains was demonstrated by serological testing (ELISA) in gilts on the day of parturition and 14 days after the booster vaccination (day of their theoretical next parturition) and in piglets on day of challenge. Post-infection antibodies against protein B (SipB) were not detected in serum of gilts or in serum of piglets on day of challenge.

Due to the results of challenge experiment, where the counts of invaded *Salmonella* in the inner organs were compared, the protective titres for piglets were set for the maternally derived antibodies measured after 30 days after the birth, i.e. on day of challenge of piglets and theoretical time of weaning. According to statistically complying results of measurements of antibody titres detected in serum of gilts on day of parturition and 14 days after the booster vaccination, the protective titres were set for the vaccinated gilts. The acquired results were used in further clinical evaluations of efficacy of vaccine.

Duration of immunity: in naturally suckled piglets protection will persist for 30 days (in piglets weaned at 21 days of age)

Field Trials

Combined safety and efficacy field trial was performed on target animals.

The clinical trial was conducted on two farms. In total, the study enrolled 60 pregnant sows and gilts about 4 weeks before farrowing. The sows and gilts were divided into groups of 20 vaccinated and 10 control pieces. The vaccine was administered in accordance with the procedure recommended in the package leaflet. The control group received the placebo. After farrowing, 2 piglets from each litter of the monitored sows, both vaccinated and controls, were enrolled in the study (in total 120 piglets).

The sows received a booster dose 2 weeks before the next farrowing.

Blood samples were collected from all animals in determined intervals for laboratory testing. The body weights of piglets were monitored at the time of weaning and at the end of fattening.

Results of serological tests of the control and vaccinated group of animals were compared statistically. The levels of antibodies were compared in vaccinated animals before and after vaccination. Antibody levels after vaccination were compared with the results obtained in the laboratory efficacy tests.

Based on a serological test, seroconversion was evidenced in the sows after vaccination. Antibody titres were monitored in piglets on the Day 4 and Day 30 after birth and compared with the titres of protective antibodies defined in challenge experiments within

laboratory studies. Based on these results, the efficacy of the vaccine was verified in field conditions.

V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Commitments

There were 3 commitments relating to the product.

Summary of the commitments is given below.

The list of agreed commitments				
No.	**Commitment Identification**	**Action need to be taken to fuifil the commitment ***	**Deadline**	**Requested by Member State**
1.	Validation for determination of number of germs (by plate method).	Validation report submission.	30.09.2019	RMS - CZ CMS - FR
2.	Determination the content of Montanide by determination of the specific weight of the vaccine by using a pycnometer.	Variation submission.	31.12.2020	CMS - DE CMS - FR
3.	Adding information to SPC/ PI regarding the DIVA kit which can be use for serological monitoring programs.	Variation submission.	As soon as kit becomes commercially available.	CMS - DE CMS - FR

The first commitment was satisfactorily resolved before start of this RUP procedure.

Validation of Salmonella germs determination was provided.

The other two commitments are pending. They will be fulfilled through the submission of variations within the specified time frame.

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Quality changes

Summary of change (Application number)	Section updated in Module 3	Approval date
CZ/V/0151/001/IB/001 A.2.b) Change in the (invented) name of the medicinal product – for nationally authorised products (New product name in BE and NL - FIXR Salmonella emulsion for injection for pigs.)	N/A	19/10/2019

Safety/efficacy changes

Summary of change (Type; application number)	Section updated in Module 3	Approval date
-		
-		

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