EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for ERYSENG PARVO (EMEA/V/C/002762/0000)

Common name: porcine parvovirosis and swine erysipelas vaccine (inactivated)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

On 22 January 2013 the applicant Laboratorios HIPRA, S.A. submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for ERYSENG PARVO in accordance with Regulation (EC) No 726/2004 (new active substance).

The product was considered eligible by the Committee on 12 July 2012 under Article 3(2)(b) of Regulation (EC) No 726/2004 as it constitutes a technical innovation related to the adjuvant. The rapporteur appointed was D. Murphy and co-rapporteur K. Lehmann.

ERYSENG PARVO contains inactivated porcine parvovirus, strain NADL-2 and inactivated *Erysipelothrix rhusiopathiae*, strain R32E11. The proposed indication is for the active immunisation of pigs from 6 months of age for protection of their progeny against transplacental infection caused by porcine parvovirosis, and to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

On 8 May 2014 the CVMP adopted an opinion and CVMP assessment report.

On 8 July 2014, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the European Union (EU) or in a third country has been provided.

The CVMP considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the EU or in a third country.

Manufacturing authorisations and inspection status

The active substances and the vaccine are manufactured and batch release for the EU is done by Hipra, Spain.

A valid good manufacturing practice (GMP) certificate for the Hipra facility was issued by the Spanish Agency for Medicines and Medical Devices.

A declaration signed by the qualified person (QP) is provided for each active substance which confirms that the active substances are manufactured in line with GMP requirements.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the

manufacturing sites were considered in line with legal requirements.

Part 2 – Quality

Composition

The active substances of the vaccine are inactivated porcine parvovirus (PPV), strain NADL-2 and inactivated *Erysipelothrix rhusiopathiae*, strain R32E11. The active substances comply with the specific European Pharmacopoeia (Ph. Eur.) monographs: 0965 on porcine parvovirus vaccine (inactivated) and 0064 on swine erysipelas vaccine (inactivated), respectively.

The adjuvant includes aluminium hydroxide, diethylaminoethyl-dextran (DEAE-dextran) and ginseng solution. The components of the adjuvant are to Ph. Eur. standard. The use of aluminium hydroxide as an adjuvant is well established however the combination of DEAE-dextran and ginseng is innovative. The ginseng is used as an immunomodulator and it has been shown in publications that the use of ginseng and aluminium hydroxide act synergistically to improve the antibody response.

The vaccine is supplied as a suspension and no solvent is required.

Container

Glass and plastic bottles are used for the vaccine. The containers are colourless glass multidose, airtight bottle, rubber stopper and aluminium capsule or clear and colourless plastic multidose, airtight bottle with a rubber stopper and aluminium capsule. The glass containers are made of Ph. Eur. Type I glass with 20 ml (10 doses), 50 ml (25 doses) and 100 ml (50 doses) volume. The plastic containers are made of polyethylene terephthalate (PET) in line with requirements of Ph. Eur. monograph 3.2.2 with volumes of 20 ml (10 doses), 50 ml (25 doses), 100 ml (50 doses) and 250 ml (125 doses).

Development pharmaceutics

ERYSENG PARVO is a suspension for injection to be administered by intramuscular route in pigs from 6 months of age. It contains inactivated *Erysipelothrix rhusiopathiae*, strain R32E1 and inactivated porcine parvovirus (PPV), strain NADL-2. It is well documented that vaccination with inactivated *Erysipelothrix rhusiopathiae* (*E. rhusiopathiae*) and PPV is successful in the treatment of both erysipelas infection and reproductive failure caused by parvovirus in swine. Therefore initial studies were focussed on the adjuvant as a way to improve the antibody response of the vaccine. Duration of immunity studies were carried out with fixed concentrations of antigen and varied components of innovative adjuvants containing ginseng and aluminium hydroxide. Serological and challenge studies with *E. rhusiopathiae* and PPV, in line with the specific monographs, showed which was the most appropriate concentration of adjuvant components and the combination giving the best serological response was chosen.

The PPV strain NADL-2 is a classical antigen. The relevance of the strain has been satisfactorily addressed in Part 4.

Epidemiological studies have demonstrated that most strains of *E. rhusiopathiae* isolated from swine showing clinical signs of erysipelas fall into serotypes 1 and 2, with the most effective strains having been found to incorporate serotype 2. The vaccine contains strain R32E11 which belongs to serotype 2. The specific Ph. Eur. monograph on swine erysipelas vaccine (inactivated) states that the vaccine should be immunogenic with respect to *E. rhusiopathiae* serotypes 1 and

2. While ERYSENG PARVO contains only one serotype, the applicant performed challenge studies with serotype 1 and 2 in order to demonstrate cross protection.

Efficacy data supports the choice of the antigens, the adjuvants and the antigen concentration needed to prevent the release of non-efficacious batches.

Method of manufacture

The production of the vaccine is performed in two phases: the production of the antigens and the vaccine blending. Each stage of the process takes place under laminar air flow conditions in a grade A environment under GMP. Production of the PPV involves the collection of viral harvest, which is inactivated to prepare the final inactivated virus harvest. Residual live virus test and haemagglutination units (HAU) titre are performed on the inactivated harvests and sterility, HAU titre and PPV quantification (by enzyme-linked immunosorbent assay (ELISA)) are determined for the inactivated pool. The *E. rhusiopathiae* is grown in culture medium where purity and viable bacterial count are determined. The concentrated bacteria suspension is then inactivated in two steps. Residual live bacteria, sterility and quantification (by ELISA) are determined. The seed lot systems are in line with requirements for Ph. Eur. monograph 0062. A sterilised fermenter is used to homogenate the inactivated antigens and combine them with the sterile components of the adjuvant. Control tests are performed and the vaccine is then filled aseptically and the finished product is stored at 2–8 °C. Inactivation kinetics data for both antigens was provided and were in line with requirements of Ph. Eur. monograph 0062. Maximum allowable pre-inactivation titres for *E. rhusiopathiae* and PPV were provided and are met in routine batches. Both inactivation times are within 67% of the total inactivation time as outlined as the limit in Ph. Eur. monograph 0062. The manufacture of the vaccine is standard and in line with the requirements of Annex I to Directive 2001/82/EC.

Control of starting materials

Active substance

The original strain of PPV was isolated from porcine leukocytes and was supplied from the United States. The original strain of *E. rhusiopathiae* was isolated from a laboratory in Germany. Identity, source and extraneous agents testing for actives are controlled in line with requirements of Ph. Eur. monograph 0062 on vaccines for veterinary use.

To support the stability of the antigens, a batch of PPV and *E. rhusiopathiae* antigen stored for the maximum time established at 2–8 °C was used in the manufacture of two different vaccine batches for which satisfactory 27 month stability data are available. Antigen titre data are also provided for additional PPV and *E. rhusiopathiae* antigen batches stored at 2–8 °C for periods of 19–24 months and 18–19 months respectively. From a combination of these data the use of PPV and *E. rhusiopathiae* antigen stored at 2–8 °C in the manufacture of vaccine batches that remain stable throughout the 24 months shelf life of the vaccine was considered acceptable.

Excipients

Certificates of analysis are provided for all starting materials listed in the pharmacopeia. Simethicone and monosodium glutamate are tested in line with the United States Pharmacopoeial Convention (USP) 30 National Formulary (NF) 25. Starting materials not listed in the pharmacopeia are described in line with Ph. Eur. monograph 0062 and Ph. Eur. monograph 5.2.5 (where relevant) and extraneous agents testing is carried out in line with the table of extraneous agents to be tested for the production and control of veterinary vaccines omissions are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Transmissible spongiform encephalopathies (TSE) concerns relating to materials of animal origin are addressed for starting materials in line with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3). The risk of transmission of animal spongiform encephalopathies is considered negligible.

Control tests during production

The in-process tests performed during production of the PPV (strain NADL-2) antigen are: bacterial and fungal sterility, viral titre, identity, residual live virus, residual inactivant, pH and PPV quantification by ELISA.

The in-process tests performed during production of the *E. rhusiopathiae* strain R32E11 antigen are: Gram stain, viability/purity, identity, turbidity, pH, count of viable colonies, concentration of total bacteria, residual live bacteria, bacterial and fungal sterility and *E. rhusiopathiae* quantification by ELISA.

In general, the in-process tests are adequately described and satisfactorily validated according to the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) GL2 on validation of analytical procedures: methodology (CVMP/VICH/591/98-Final) and VICH GL1 on validation of analytical procedures: definition and terminology (CVMP/VICH/590/98-Final). For the ELISA quantification tests proposed for each antigen data demonstrating the specificities of the antibodies used in each test for the *E. rhusiopathiae* R32E11 and PPV NADL-2 strains included in the vaccine were provided. Details of the criteria for replacement of some reagents used in the ELISA testing of antigen and vaccine batches have been provided.

The sterility of the vaccine is based on the aseptic nature of the manufacturing process including the use of sterile starting materials. Validation of the sterile filtration process for the ginseng solution has been provided and complies with the recommendation in the CVMP Note for guidance on manufacture of the finished dosage (EMEA/CVMP/126/95).

Batch protocols are provided for a sufficient number of production scale vaccine batches which support the consistency of production.

Control tests on the finished product

The description of the methods used for the control of the finished product (appearance, pH, concentration of aluminium hydroxide, ginsenosides, DEAE-dextran and residual inactivant, extraneous agents, sterility, volume control and potency of the PPV and *E. rhusiopathiae* antigens) and the specifications are provided.

The validation conducted for the release tests are in general acceptable and according to the VICH GL2 on validation of analytical procedures: methodology (CVMP/VICH/591/98-Final) and VICH GL1 on validation of analytical procedures: definition and terminology (CVMP/VICH/590/98-Final).

The PPV and *E. rhusiopathiae* potency tests for release of the final vaccine are *in vitro* tests based on ELISA tests used to quantify each antigen. The use of *in vitro* potency tests in place of the mouse and guinea-pig potency tests described in Ph. Eur. monographs 0064 and 0965 respectively is in accordance with the 3R's principles of reduction, refinement and replacement of animal tests.

The ability of the PPV and *E. rhusiopathiae* ELISA potency tests to detect immunogenic portions of the PPV and *E. rhusiopathiae* antigens which correlate with protection in the target species has also been demonstrated.

Sufficient data were provided that demonstrated the ability of the PPV and *E. rhusiopathiae* ELISA potency tests to detect an immunogenic portion of the antigens and which correlates with protection in the target species. The proposed acceptance limits for the PPV and *E. rhusiopathiae* ELISA potency test are justified and based on the results obtained according to the immunogenicity testing requirements of Ph. Eur. monographs 0965 and 0064 as appropriate.

Information of the reference standards used in each of the PPV and *E. rhusiopathiae* ELISA potency tests are given including details on the preparation, storage and the criteria for acceptance of replacements standards in each test. Sterility testing of the vaccine is performed according to Ph. Eur. monograph 2.6.1.

The results of a number of batches were presented and all specifications were met.

Stability

Three consecutive vaccine blends filled in 20 ml and 100 ml glass presentations and 20 ml and 250 ml PET presentations (i.e. representing the minimum and maximum fill volumes for the glass and PET presentations) have been entered into a stability testing programme.

The stability vials are stored at 2 °C – 8 °C with testing conducted at 3 monthly intervals during the first year and at 18, 21, 24 and 27 months thereafter i.e. up to 3 months beyond the end of the proposed 24 month shelf life for the vaccine.

The 27 month results do not indicate any trends for the parameters tested therefore the 24 month shelf life specified for the vaccine in section 6.3 of the summary of product characteristics (SPC) is supported.

ERYSENG PARVO is a multi-dose vaccine which is instructed to be used immediately after opening. The availability of different vaccine pack sizes allows the user to adjust the vial size to the number of animals to be vaccinated at any one time so that all of the vial contents can be used immediately.

Overall conclusions on quality

The composition of the vaccine has been adequately described and complies with the required monographs. The adjuvant which is the innovative part of this vaccine has been justified. The strains chosen are satisfactory and the relevance of the strains has been satisfactorily addressed in Part 4. The vaccine contains only one *E. rhusiopathiae* serotype 2 but studies have demonstrated cross protection between serotype 1 and 2 with ERYSENG PARVO.

The manufacture follows standard processes; a seed lot system in line with Ph. Eur. requirements is described. The identity, source and extraneous agents testing for materials are presented in line with requirements of Annex I of Directive 2001/82/EC. The maximum pre-inactivation titres for *E. rhusiopathiae* and PPV have been determined and are met by routine batches. The omission of required extraneous agents testing has been justified. The TSE concern is addressed in line with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3), confirming a risk of negligible level.

The tests performed during production and for release of the vaccine in general meet the requirements of Ph. Eur. monograph 0062 on vaccines for veterinary use; Ph. Eur. monograph 0064 on swine erysipelas vaccine and Ph. Eur. monograph 0965 on porcine parvovirus vaccine.

Information provided on the antigen-antibody interactions measured in the batch potency tests support the ability of each test to detect immuno-relevant epitopes in each of the vaccine antigens which correlate with protection in the target species. In addition, the stability indicating potential of each ELISA test to detect a decline in immunogenic properties of the vaccine over the shelf life has been satisfactorily demonstrated.

The stability of the vaccine has been investigated over a 27 months period hence the 24 months shelf life referred to in the SPC is appropriate.

Recommendations for future quality development

Not applicable.

Part 3 – Safety

ERYSENG PARVO suspension for injection for pigs is a vaccine containing inactivated porcine parvovirus, strain NADL-2 and inactivated *E. rhusiopathiae*, strain R32E11. The adjuvant component of the vaccine consists of aluminium hydroxide gel, DEAE-dextran and ginseng. This adjuvant combination has already been included as a component in another vaccine for which the applicant holds a marketing authorisation.

The active substances are included in ERYSENG PARVO at the following concentrations per 2 ml dose:

Inactivated porcine parvovirus, strain NADL-2, RP >1.15 (Relative potency, ELISA),

Inactivated *E. rhusiopathiae*, strain R32E11, ELISA >3.34 $IE_{50\%}$ (units measured at ELISA inhibition at 50%).

The vaccine is proposed for use in pigs; for the active immunisation of female pigs from six months of age for the protection of progeny against transplacental infection caused by porcine parvovirus (PPV) and for the active immunisation of male and female pigs to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2. The basic vaccination scheme consists of two intramuscular doses of 2 ml, separated by an interval of 3–4 weeks. The second injection should be given at 3–4 weeks before mating. Revaccination consists of a single dose of 2 ml administered at 2–3 weeks prior to each subsequent mating (approximately every six months).

Safety documentation

Five laboratory studies and one field study have been presented in support of the safety of ERYSENG PARVO. The applicant has investigated the safety of the immunological veterinary medicinal product in accordance with Annex I to Directive 2001/82/EC and in accordance with the following:

- Ph. Eur. monograph 5.2.6 on evaluation of safety of veterinary vaccines and immunosera
- Ph. Eur. monograph 0965 on porcine parvovirus vaccine (inactivated)
- Ph. Eur. monograph 0064 on swine erysipelas vaccine (inactivated)

– VICH GL44 on target animal safety for veterinary live and inactivated vaccines.

Laboratory tests

Five laboratory studies investigating the safety of ERYSENG PARVO were presented. Three of the five studies were combined safety and efficacy trials, which are summarised in depth in Part 4. The safety evaluation in the combined studies related to the safety of the administration of one dose, and the results are briefly summarised in the following section on safety of the administration of one dose. The remaining two laboratory trials investigated the safety of the administration of one dose, an overdose and the repeated administration of one dose in gilts of the minimum age recommended for vaccination and in pregnant gilts, respectively and are summarised under 'safety of the repeated administration of one dose'.

Laboratory safety trials were carried out in compliance with good laboratory practice.

On the basis of the efficacy studies conducted, the amount of antigens included in the vaccine is fixed.

In the pivotal laboratory safety studies on safety of the administration of an overdose, a single dose in gilts and safety of the administration of an overdose, a single dose in pregnant gilts, batches were used which contained the proposed fixed concentration of *E. rhusiopathiae*. In the second study, the proposed fixed concentration of PPV was used. In the first study, the batch used contained a higher amount of PPV per ml than the proposed fixed concentration however this is acceptable given that it was a safety-only study and thus represented a worst case scenario.

Safety of the administration of one dose

The following studies investigated primarily efficacy parameters but also the safety of one dose.

Safety of 1x dose in gilts (dose determination study for PPV component). Eleven seronegative gilts were vaccinated according to the basic vaccination schedule with the proposed formulation of ERYSENG PARVO. The highest mean temperature increase, 0.31 °C, was observed after the second vaccine dose, decreasing thereafter. The highest individual increase in temperature after vaccination in the vaccinated group was 1.2 °C (two days after the first dose). No local reactions were observed following the first or second dose. No abnormal clinical signs attributable to vaccination were observed.

Safety of 1x dose (basic vaccination schedule: two 1x doses, prior to mating and re-vaccination schedule during the lactation period (1x dose) in seronegative gilts (duration of immunity study for PPV component)). Thirty seronegative gilts were vaccinated with the proposed formulation of ERYSENG PARVO. The highest mean temperature increase, 0.34 °C, was observed at 6 hours post-vaccination, decreasing thereafter. During the lactation period when the booster dose for re-vaccination was administered (approximately one week after parturition), the highest mean temperature increase, 0.89 °C, was observed at one day post-vaccination. The highest individual increase observed was 1.72 °C (at one day after the booster dose). No local reactions, abnormal clinical signs or systemic reactions were observed after vaccination.

Safety of 1x dose in gilts and boars (dose determination for *E. rhusiopathiae* component). Ten gilts and ten boars (seronegative) were vaccinated according to the basic vaccination schedule with the proposed formulation of ERYSENG PARVO (groups A and C respectively). The highest increase in temperature was observed at 6 hours post-vaccination after each dose; after the first dose, the mean temperature increase was 0.68 °C and 0.57 °C in group A and C, respectively, and after the second dose, the highest mean increase was 0.51 °C and 0.44 °C in group A and C, respectively. The highest individual increase in gilts was 1.32 °C and in boars was 1.60 °C (both at 6 hours

post-vaccination 1). Injection site reactions were reported in 1/10 gilts in group A and 1/10 boars in group C following the first vaccination, and in 3/10 gilts in group A and 1/10 boars in group C following the second vaccination. Reactions consisted of a hard spot in the skin <1 cm diameter at the injection site, which were observed on the day of or the day after vaccination and which resolved at most within 9 days after appearing. No other local or systemic reactions were observed. Histopathological investigation of injection site reactions was performed and macroscopic and microscopic findings were consistent with those described for aluminium hydroxide-adjuvanted vaccines; lesions were only observed when the interval between vaccination and necropsy was shorter, whereas the tissue damage attributed to aluminium hydroxide had disappeared from the site of administration of the first dose by 50 days post-vaccination.

For each of the above three studies, there were no individual increases in temperature above 2 °C, nor did the average increase in temperature for a group exceed 1.5 °C. On the basis of the above the safety of the administration of one dose of the vaccine in gilts and boars was considered acceptable.

Safety of one administration of an overdose

Refer to section 'Safety of the repeated administration of one dose'.

Safety of the repeated administration of one dose

Two safety-only laboratory studies were presented, each investigating the safety of the administration of an overdose, a single dose and the repeated administration of a dose; one in gilts and one in pregnant gilts. It is noted that it is no longer a requirement to perform overdose testing for inactivated vaccines; therefore the applicant has evaluated a worst case scenario in the studies.

Safety of the administration of an overdose, a single dose and a repeated single dose, and evaluation of the injection site macroscopically and microscopically in gilts. Ten seronegative gilts of six months of age received a 2x overdose on day 0, followed by a single dose on day 14 and another single dose on day 28 of the study, using a batch with the proposed concentration of E*. rhusiopathiae* but a higher concentration of PPV than proposed for the final formulation. A group of five gilts were maintained as a control group that received placebo injections (PBS). Follow-up consisted of evaluation of clinical signs, including local reactions, body temperature and serology. At the study end on day 42, animals were terminated and necropsy and histopathological analysis were performed.

- After the administration of a 2x dose, the highest mean temperature increase was 0.63 °C (6 hours post-vaccination, at which time the mean temperature was 39.58 °C and 39.12 °C in the vaccinated and control group, respectively) and the highest individual increase after the administration of a 2x dose was 0.95 °C (at 6 hours post-vaccination). After the administration of the 1x dose on day 14, the highest mean temperature increase in the vaccinated group was 0.40 °C (6 hours post-vaccination), while the highest individual increase in vaccinated gilts was 1.47 °C at 3 days post-vaccination. After the administration of the third dose (1x dose on day 28), the highest mean temperature increase in the vaccinated group was 0.36 °C (6 hours post-vaccination), while the highest individual increase was 1.28 °C (4 hours post-vaccination).
- Local reactions were observed after each vaccine administration; after the administration of a 2x dose, five of ten gilts developed local reactions. In one of the five animals, moderate inflammation (2–5 cm diameter) was reported at two days post-vaccination, and was absent by five days post-vaccination. In the other four animals, mild inflammation (< 2 cm diameter) developed on the first or second day post-vaccination, and was present for a total

of two days for three animals and for 12 days for one animal. After the 1x dose on day 14, all ten gilts were reported to have local reactions, again consisting of mild to moderate inflammation at the injection site occurring at one or two days post-vaccination, and persisting for one to four days. After the repeated administration of a single dose (1x dose on day 28), seven of nine gilts had local reactions at the injection site, this time only mild inflammation developing on the first or second day post-vaccination which persisted for one to two days.

- No abnormal clinical signs attributable to vaccination were observed.
- At necropsy, no external lesions were observed at the injection sites. Macroscopic lesions were observed, most frequently at the site of injection of the third dose for which the interval between vaccination and necropsy was the shortest (two weeks). At the site of administration of the 2x dose, lesions were observed in 5/10 gilts; four animals showed discolouration of muscular fibres (0.5 cm width x 2 cm length), and one animal had a unique capsulated nodule. At the site of administration of the first 1x dose, lesions were observed in 5/10 gilts; two animals showed discolouration of muscular fibres and three animals showed a series of small firm areas of discolouration within the muscular tissue. At the site of administration of the second 1x dose, lesions were observed in 9/10 gilts; mostly discolouration of muscular fibres (five animals). Three animals showed a well-delineated firm area of discolouration within muscular tissue. A capsulated nodule in one gilt, with purulent-like contents was thought to have been caused by iatrogenic contamination when injecting the third vaccine dose. The macroscopic lesions were consistent with expected lesions for vaccines containing aluminium hydroxide as adjuvant, i.e. small granulomas. Microscopic evaluation of the lesions demonstrated that the lesions corresponded to granulomatous multifocal inflammation (with areas of muscular necrosis surrounded by mononuclear inflammatory cells and occasionally granulation tissue/fibrosis).

On the basis of this study, the CVMP concluded that the administration of one dose, an overdose and the repeated administration of one dose is safe in animals of the youngest age recommended for vaccination.

Safety of the administration of an overdose, a single dose and a repeated single dose in pregnant gilts. Ten seronegative pregnant gilts (from six months of age) received a 2x dose on day 0, followed by a single dose on day 14 and another single dose on day 28 of the study, using a batch with the proposed fixed concentration of *E. rhusiopathiae* and PPV. Three gilts were in the 1st month of gestation, two gilts in the 2nd month and five gilts in the 3rd month of gestation at day 0. A group of two gilts were maintained as a control group that received placebo injections (PBS). Follow-up consisted of clinical signs, local reactions, body temperature, serology and observation until the end of pregnancy when effects on gestation and on the offspring were evaluated. At end of this study, animals were terminated for necropsy. Foetal tissue was analysed for presence of PPV and PPV antibodies.

After the administration of a 2x dose, the mean temperature increased only very slightly; the highest mean temperature increase was 0.39 °C (6 hours post-vaccination, at which time the mean temperature was 38.69 °C and 38.84 °C in the vaccinated and control group, respectively) and the highest individual increase after the administration of a 2x dose was 0.99 °C (at 6 hours post-vaccination). After the administration of the 1x dose on day 14, the highest mean temperature increase in the vaccinated group was 0.40 °C (6 hours post-vaccination), while the highest individual increase in vaccinated gilts was 0.96 °C at 6 hours post-vaccination. After the administration of the third dose (1x dose on day 28), the highest mean temperature increase in the vaccinated group was 0.43 °C (6 hours post-vaccination), while the highest individual increase was 0.83 °C (6 hours post-vaccination).

- In contrast to the study performed in non-pregnant gilts of six months of age, no local reactions were observed in any animal after any of the vaccine doses.
- No abnormal clinical signs were observed.
- No adverse effects on reproductive parameters were observed; no abortions or teratogenic effects on the progeny were observed. The mean number of liveborn piglets was 6.7 in the vaccinated group and 7.0 in the control group (for 60% of vaccinated pregnant gilts, all piglets in the litter were liveborn). The mean number of stillborn piglets was 0.50 and the mean number of mummified piglets was 0.30 in the vaccinated group whereas no piglets were stillborn or mummified in the two animals in the control group.
  - For two of the three gilts vaccinated in the 1st month of gestation, there was one stillborn piglet in each of the litters (9 and 3 liveborn). The other remaining gilt in this group had 5 liveborn piglets.
  - For two gilts vaccinated during the 2nd month of gestation, all piglets were liveborn.
  - Of five gilts vaccinated during the 3rd month of gestation, three gilts had a litter of all liveborn piglets. One gilt had five liveborn and three mummified piglets, however the length of the foetuses clearly indicated mummification prior to administration of the vaccine doses. The remaining gilt gave birth to three stillborn piglets after parturition had been induced, however the applicant provided satisfactory justification that the stillbirths in this gilt were not vaccine-related.

On the basis of this study, the CVMP accepted that the administration of one dose, an overdose and the repeated administration of one dose during pregnancy is safe.

Examination of reproductive performance

ERYSENG PARVO is an inactivated vaccine intended for use in non-pregnant animals, in which case it is not specifically required to investigate the effects on reproductive performance unless data suggest that the starting material from which the product is derived may be a risk factor (e.g. for live vaccines). However, the applicant provided studies conducted specifically to examine the safety of the vaccine on reproductive performance when used in pregnant gilts or lactating sows.

The applicant considers that no reproductive disturbances have been reported in any study and no warnings in the SPC advising that ERYSENG PARVO should not be used during pregnancy or lactation are necessary.

In study on duration of immunity of PPV component, safety of basic vaccination scheme and revaccination scheme during lactation phase in gilts, there were no abnormal effects on reproductive parameters after the basic vaccination schedule prior to the first gestation (the PPV challenge was conducted during the second gestation in which efficacy against transplacental infection with PPV was demonstrated).

In study on evaluation of the safety of the administration of an overdose, a single dose and a repeated dose of ERYSENG PARVO in pregnant gilts, summarised in the previous section, it can be concluded that the vaccine is safe for use during pregnancy.

It is accepted that the safety of the use of ERYSENG PARVO during pregnancy, although not specifically intended for use during pregnancy in accordance with the vaccination schedule, has been demonstrated to be safe.

Examination of immunological functions

Studies investigating the effect of the vaccine on immunological functions have not been presented, on the basis that the vaccine is an inactivated vaccine for which no adverse effects on the immunological functions are to be expected. This is considered acceptable, given that the vaccine contains inactivated antigens only and thus no replication in immune system cells is therefore possible, and no other detrimental effects on the vaccinated animal's immune system would be anticipated.

Study of residues

No studies on residues have been performed. Given that:

- the active substances being principles of biological origin intended to produce active immunity are not in the scope of Regulation (EC) 470/2009,
- the adjuvant components of ERYSENG PARVO are aluminium hydroxide, DEAE-dextran and ginseng and that aluminium hydroxide and ginseng are included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010, each as an allowed substance for which no maximum residue limit (MRL) is required. DEAE-dextran is included in the list of substances considered as not falling within the scope of Regulation (EU) No 470/2009, and that
- all excipients present in the vaccine are either listed in Commission Regulation (EU) No. 37/2010 in Annex I (Allowed substances) (sodium chloride), are included in the list of substances considered as not falling within the scope of Regulation (EU) No 470/2009 (simethicone) or are food stuffs or food additives (disodium phosphate dodecahydrate, potassium dihydrogen phosphate, potassium chloride, sodium hydroxide) for which no MRL is required,

a withdrawal period of zero days can be accepted.

Interactions

No studies have been presented concerning the interaction of this product with any other veterinary medicinal products. The following standard statement has been included in the SPC section 4.8 and package leaflet:

> No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

Field studies

One multicentre field study was conducted with ERYSENG PARVO to investigate the safety and efficacy under field conditions of the use of the vaccine against *E. rhusiopathiae* and porcine parvovirus, which included a total of 712 female pigs (348 nulliparous gilts and 364 multiparous sows) from five farms in Spain. Farms included in the study were in the practice of vaccinating against PPV and swine erysipelas, and although it was a criteria that nulliparous gilts were included that had never been previously vaccinated, some animals were seropositive against PPV (approximately 101 gilts) and *E. rhusiopathiae* (approximately 15 gilts), indicating at least some degree of infection pressure from the two pathogens. Multiparous sows were included in the study if they had been previously vaccinated against PPV and *E. rhusiopathiae*.

Half of the enrolled animals were vaccinated with ERYSENG PARVO and the other half were vaccinated with a positive control; a commercially available inactivated vaccine containing PPV and *E. rhusiopathiae*. A negative control group was not included in the study for ethical reasons. Nulliparous gilts were vaccinated according to the basic vaccination schedule whereas multiparous sows were vaccinated with a single booster dose. Reproductive parameters were evaluated in the context of the analysis of efficacy, and an evaluation of safety under field conditions was undertaken.

The efficacy results are not discussed in this section (refer to Part 4). The following safety results are reported:

- No adverse effects on reproductive parameters were observed.
- There were no individual increases in temperature above 2 °C; however the maximum individual increase of 1.98 °C occurred in a nulliparous gilt at 6 hours after the first dose of the vaccine. The maximum individual temperature in a multiparous sow was at 1.86 °C at one day after the booster vaccination. Similar maximum individual increases were also observed in each of the corresponding positive control groups. Nevertheless, the average increases for the respective groups were modest; there were no mean increases exceeding 1.5 °C. The peak in the increase in temperature generally occurred in animals at 6 hours post-vaccination, and the mean increase at that time was 0.37 °C in nulliparous gilts (after first dose) and 0.44 °C in multiparous sows.

Monitoring of adverse reactions was performed after each vaccination in all 712 animals. Based on this monitoring, the applicant states that no adverse effects were recorded. However, throughout the study, monitoring of general clinical signs was performed in subset of 265 animals. General clinical signs that were specifically monitored (on the day of vaccination, 6 hours, one day and two days post-vaccination and then on a weekly basis) were the presence of systemic reactions, bristling hair and/or bristles in a poor state, prostration and anorexia. Other observations were also to be recorded. None of the gilts or sows in the ERYSENG PARVO group were reported to have 'anomalous' general clinical signs. However, in the ERYSENG PARVO nulliparous group, 2 gilts (3%) were reported with 'slight prostration' (inactive but responds to weak stimuli), and in the ERYSENG PARVO multiparous group, 9 sows (13%) were reported with slight prostration and/or anorexia. These clinical signs were observed following vaccination, but were considered to be of very slight character and all animals were recovered 24 hours later. (It is noted that 8% of nulliparous gilts and 20% of multiparous sows in the positive control group were reported with similar clinical signs).

- Local reactions (assessed in 265 animals) were observed in over half of the animals vaccinated with ERYSENG PARVO (53% of nulliparous gilts and 57% of multiparous animals). Reactions consisted of a hard lump in the skin < 1 cm diameter at the site of injection, which were absent by one week post-vaccination and/or inflammation < 2 cm or between 2–5 cm diameter, which in the vast majority of cases resolved within two weeks post-vaccination.

It can be concluded that the safety results obtained in the field generally reflect those documented in the laboratory studies – temperature increases and local reactions were observed following vaccination. No adverse effects on reproductive parameters were observed during the study. The occurrence of some mild, transient clinical signs (slight reduction in activity and/or anorexia) within the 24 hours after vaccination is noted; however, similar effects were observed in animals in the control group and these effects were not observed in the laboratory studies performed using ERYSENG PARVO. The applicant argued that the observed clinical signs were most likely related to the handling of the animals.

User safety

A user safety assessment was provided, conducted in accordance with the CVMP Guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006). The active substances of the vaccine, porcine parvovirus and *E. rhusiopathiae*, are both inactivated antigens and are therefore not pathogenic for humans. The remaining components in the formulation are the adjuvant, composed of aluminium hydroxide, DEAE-dextran and ginseng, and the vaccine excipients, which are commonly used in many other veterinary vaccines. It is noted that the inclusion of ginseng is not particularly common for other veterinary vaccines, although it has been included as an adjuvant in a centrally authorised product (Rhiniseng) and another vaccine for which the applicant holds a marketing authorisation, (Suiseng). However, it is not considered that the presence of ginseng solution in the vaccine poses a risk to the user given that ginseng is not considered to be a toxic substance and is used as a dietary supplement in humans. The CVMP MRL Summary Report for ginseng (extension of use) (EMEA/CVMP/352217/2006) states that 'ginseng is a normal component of the diet in humans and is generally recognised as safe for humans.'

It is accepted that there are no components present in the vaccine which would present a risk to the user. The main risk of exposure to the user is from accidental self-injection, however the vaccine will be supplied under prescription and the persons administering the vaccine will be expected to have a high level of expertise in administering such veterinary medicinal products. Furthermore, should accidental self-injection occur, given the absence of any hazards identified with respect to the components of the vaccine, this exposure to the product would not be considered to present any risk to the user.

Therefore, the conclusions of the user safety assessment, that the use of the vaccine does not present an unacceptable risk to the user, are accepted. The SPC and package leaflet state the following advice to the user 'In case of adverse reactions following accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.'

Environmental risk assessment

The applicant has presented a brief environmental risk assessment for ERYSENG PARVO, consisting of a Phase I assessment, conducted in accordance with the CVMP Note for Guidance: Environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95-Final). This was considered appropriate considering the nature of the product, an inactivated vaccine to be administered by injection.

Given that the vaccine is composed of two inactivated antigens, porcine parvovirus and *E. rhusiopathiae*, there is no risk that live microorganisms could be disseminated into the environment, either following improper use of the vaccine or following administration to an animal (as the antigens are incapable of replication within the target animal). None of the components of the adjuvant (aluminium hydroxide, DEAE-dextran and ginseng) or the excipients (simethicone, PBS and sodium hydroxide) are toxic. Therefore, none of the components of the vaccine formulation are expected to pose any risk to the environment.

As acknowledged in EMEA/CVMP/074/95-Final, in the majority of cases, the nature of IVMPs are such that they will have a very low environmental risk potential, and that for inactivated vaccines to be administered by injection, the hazards and risks from the active substances are likely to be negligible.

In conclusion, it is accepted that the risk to the environment following use of ERYSENG PARVO as recommended can be considered negligible. There is no need for any specific additions to the SPC

or product packaging other than the standard disposal statement for inactivated immunologicals which the applicant has included in section 6.6 of the SPC:

> Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

Overall conclusions on the safety documentation

The laboratory safety studies showed that there were no individual temperature increases above 2 °C, nor did the average temperature increase for a group exceed 1.5 °C. Temperature increases were observed following vaccination, with maximum temperature increases observed at six hours post-vaccination, decreasing thereafter. Injection site reactions were observed in some but not all studies; in nulliparous gilts at the minimum age recommended for vaccination, all animals developed local reactions in the pivotal safety study investigating the administration of 2x dose/1x dose/repeated 1x dose, while no local reactions were observed in pregnant gilts vaccinated with the same scheme. Macroscopic/microscopic investigation of injection site tissue revealed that lesions were consistent with the development of granulomas, a recognised feature of aluminium hydroxide adjuvanted vaccines. There were no abnormal clinical or systemic signs attributable to vaccination observed throughout the studies. The vaccine therefore complies with the safety requirements of the respective Ph. Eur. monograph for each antigen component. Although the vaccine is not specifically recommended for use during pregnancy (in accordance with the recommended vaccination schedule), it has been demonstrated that the vaccine is safe for use during pregnancy and therefore an exclusion against use during pregnancy is not required.

The use of the vaccine does not present an unacceptable risk to the user. Appropriate advice is included in the SPC and package leaflet directing the user to seek medical advice in the event that adverse reactions develop following accidental self-injection.

The product as presented does not pose a risk to the environment. The active substance being a substance of biological origin intended to produce active immunity does not fall within the scope of Regulation (EC) No. 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. In addition the other components of the vaccine are either listed in Table 1 of the annex of Commission Regulation No. 37/2010 or considered as not falling within the scope of Regulation (EC) No. 470/2009 when used as in this product. The withdrawal period is therefore set at zero days.

One multicentre, combined safety and efficacy field study was conducted in Spain, which included 712 female pigs; 356 animals were vaccinated with ERYSENG PARVO and 356 animals were vaccinated with a positive control. It can be concluded that the safety results obtained in the field generally reflect those documented in the laboratory studies – temperature increases and local reactions were observed following vaccination. No adverse effects on reproductive parameters were observed during the study.

In summary, the administration of ERYSENG PARVO when used in accordance with the recommended vaccination schedule can be considered to be safe for the target species.

Part 4 – Efficacy

Introduction and general requirements

ERYSENG PARVO is a vaccine containing inactivated porcine parvovirus, strain NADL-2 and inactivated *E. rhusiopathiae*, strain R32E11. The adjuvant component of the vaccine consists of

aluminium hydroxide gel, DEAE-dextran and ginseng, as previously mentioned in the introduction to Part 3, considered to be a novel adjuvant. The concentration of each antigen included in the vaccine is fixed (no minimum or maximum titre concept applies) at the following concentrations per 2 ml dose:

- Inactivated porcine parvovirus, strain NADL-2, RP >1.15 (Relative potency, ELISA)
- Inactivated *E. rhusiopathiae*, strain R32E11, ELISA >3.34 $IE_{50\%}$ (units measured at ELISA inhibition at 50%).

The vaccine is proposed for the active immunisation of female pigs for the protection of progeny against transplacental infection caused by porcine parvovirus and for the active immunisation of male and female pigs to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2. The basic vaccination schedule consists of the administration by the intramuscular route of two doses of 2 ml, separated by an interval of 3–4 weeks, with the second dose administered 3–4 weeks prior to mating. Revaccination consists of a single 2 ml dose administered 2–3 weeks prior to each subsequent gestation. The onset of immunity against swine erysipelas is 3 weeks after completion of the basic vaccination scheme and against porcine parvovirus is at beginning of the gestation period. The duration of immunity for foetal protection against PPV is each individual pregnancy (re-vaccination prior to each subsequent gestation is recommended) and the duration of immunity against *E. rhusiopathiae* has been demonstrated at 6 months.

General requirements

The efficacy data provided in support of the claimed indications for ERYSENG PARVO consists of four laboratory studies and one field trial. The laboratory studies investigating the immunogenicity of the vaccine were conducted in accordance with the requirements of the Ph. Eur. monograph 0965 on porcine parvovirus vaccine (inactivated) and Ph. Eur. monograph 0064 on swine erysipelas vaccine (inactivated). The applicant has confirmed that all efficacy trials were conducted in accordance with a fully-considered detailed protocol, and with pre-established systematic written procedures for the organisation, performance, data collection and documentation of the trials. The laboratory trials were certified to have been conducted in accordance with the principles of good laboratory practice and the field trial was conducted in accordance with the principles of good clinical practice.

Justification of the choice of vaccine strains

Porcine parvovirus (PPV)

The inclusion of PPV, strain NADL-2 in the vaccine is justified on a historical basis, given that other vaccines are available with this strain of parvovirus. It has been described in the literature that there are new strains that differ genetically and antigenically from the vaccine strains of PPV, e.g. PPV-27a and PPV-143a. The applicant presented bibliographic data to support that vaccination with classical PPV strains (not the strain specifically included in ERYSENG PARVO) afforded foetal protection in sows following challenge with the PPV-27a strain. Data was also presented in which post-vaccination sera of animals vaccinated with ERYSENG PARVO was tested by haemagglutination inhibition (HI) and serum neutralisation (SN) assays for cross-reactivity against the NADL-2 strain and the PPV-27a strain, demonstrating that sera from sows vaccinated with ERYSENG PARVO cross-reacted with high titres to both PPV-NADL2 and PPV-27a strains. Taking into account the historical use of this vaccine strain in PPV vaccines, the link between vaccination with vaccines based on genotype 1 strains and foetal protection following challenge with a genotype 2 strain, and the fact that high HI and SN titres were generated against both NADL-2 and

PPV-27a following vaccination with ERYSENG PARVO, it was accepted that the PPV strain included in ERYSENG PARVO is justified on an epidemiological basis.

E. rhusiopathiae

The *E. rhusiopathiae* strain included in ERYSENG PARVO, R32E11, is a serotype 2 strain. Two main serogroups, have been identified, based on agglutinin absorption studies. Epidemiological studies have demonstrated that most strains of *E. rhusiopathiae* isolated from pigs showing clinical signs of erysipelas fall into serotypes 1 and 2. In the efficacy trials included in the file, cross protection against serotype 1 is demonstrated by challenge. While the vaccine contains a serotype 2 strain, the trial was designed according to Ph. Eur. to demonstrate immunogenicity of the vaccine with respect to *E. rhusiopathiae* serotypes 1 and 2, by injecting each challenge serotype on different flanks of the pigs. Given that the vaccine was tested against the two Ph. Eur. recommended challenge serotypes and full cross-protection against serotype 1 was evident, it is considered that the choice of the vaccine strain is justified for *E. rhusiopathiae*.

Establishment of a challenge model

No studies were conducted to establish a challenge model. This is considered acceptable as in the case of *E. rhusiopathiae* the relevant Ph. Eur. monograph is particularly prescriptive in the immunogenicity requirements detailing the challenge strains that should be used.

Laboratory trials

Determination of the vaccine dose/onset of immunity

A dose-response study was conducted for each of the antigenic components, in which various doses of the antigen were tested in a challenge study in accordance with the respective monograph. These two studies were the pivotal studies which demonstrated compliance of the vaccine with the Ph. Eur. requirements and established the onset of immunity. The investigation of the safety of the administration of one dose was also undertaken in these studies.

Study of efficacy against porcine parvovirus. In this study, investigating the dose-response for the PPV component, three treatment groups of 11 seronegative gilts were vaccinated with an experimental batch containing three different PPV concentrations. The concentration of *E. rhusiopathiae* was proposed fixed concentration for the vaccine. Animals were vaccinated with two doses, separated by an interval of three weeks, with the second dose administered 3–4 weeks prior to mating. An additional group of gilts were maintained as a control group (placebo injections of PBS). PPV challenge was conducted at day 40 of gestation for 7 gilts in each treatment group and in 5 control animals. Gilts were terminated at day 90 of gestation and foetuses were examined for the presence of PPV by the presence of virus and/or antibodies. For each of the three vaccinated groups, compliance with the immunogenicity requirements of the Ph. Eur. monograph (≥80% protection of foetuses from PPV infection) was demonstrated. The level of protection in all vaccinated groups was 100% (taking into account the absence of PPV virus and the absence of anti-PPV antibodies in foetuses). A dose-effect on the serological response was evident, however given that each of the three treatment groups were equally protected, it is not considered that this finding indicates a correlation between the antibody titre and protection from challenge. Although the minimum dose was efficacious, the PPV dose chosen for vaccine formulation was two-fold the lowest dose used in the study. The 'onset' of immunity for this component of the vaccine is therefore specifically linked to the protection of foetuses during the gestational period following the recommended vaccination schedule.

Study of efficacy against swine erysipelas. In the study investigating the dose-response and efficacy against *E. rhusiopathiae* in gilts, two groups of 10 gilts were vaccinated with batches containing two different *E. rhusiopathiae* antigen concentrations and a group of 10 boars was vaccinated with a batch containing the highest antigen concentration used for vaccination of gilts. The concentration of PPV was proposed fixed concentration for the vaccine. Animals were vaccinated with two doses, separated by an interval of three weeks. An additional group of five gilts and five boars were maintained as a control group (placebo injections of PBS). All animals were challenged three weeks (and one day) after administration of the second dose, with serotype 1 and serotype 2 at the same time but on different flanks of the pig. Validation and acceptance criteria were applied separately to the respective challenge sites. The Ph. Eur. monograph requires that ≥90% of the vaccinated pigs remain free from diamond skin lesions at the challenge site. It was reported that all three vaccinated groups complied with the requirements of the Ph. Eur. monograph for each serotype; protection was 90% in each group of gilts against serotype 1 and against serotype 2 challenge. In boars, that were vaccinated with the batch containing the highest antigen concentration, protection was 90% against serotype 1 and 100% against serotype 2. In addition, a statistically significant difference with respect to the challenge-related increase in temperature was observed between treatment groups: the maximum mean temperature in the control group was 40.02 °C at 6 days post-challenge, and was 39.13 °C and 39.14 °C in gilts vaccinated with high or low antigen concentration, respectively, and 39.23 °C in vaccinated boars. It is noted that, apart from skin lesions at the site of challenge and increased body temperature, no other clinical signs typical of swine erysipelas were observed/recorded following challenge.

On the basis of this study, the onset of immunity is established at three weeks after completion of the basic vaccination scheme, and the *E. rhusiopathiae* dose for vaccine formulation was selected the higher one, even though the lower dose was efficacious. Seroconversion occurred in all animals by three weeks after the first dose of the basic vaccination scheme. There did not appear to be a dose-dependent serological response.

The results of the study support a claim for the reduction of clinical signs, specifically skin lesions and fever, due to infection caused by *E. rhusiopathiae*, serotype 1 and 2, with the onset of immunity for swine erysipelas demonstrated at 3 weeks after completion of the basic vaccination scheme.

The amounts of antigens included in batches are fixed. Thus, there is no range proposed for batches and the concept of using batches of minimum titre for the analysis of efficacy does not apply to this application.

Efficacy of the re-vaccination scheme/duration of immunity

The duration of immunity/efficacy of the re-vaccination scheme was investigated in two laboratory studies, in both studies using batches containing the proposed fixed concentration of each antigen. Safety parameters were also evaluated in these studies.

Study of duration of immunity of the PPV active ingredient of the ERYSENG PARVO vaccine. The efficacy of the proposed re-vaccination scheme, which is that a single dose should be administered 2–3 weeks prior to each subsequent gestation was demonstrated by challenge during the second gestation. A group of 30 seronegative gilts were vaccinated according to the basic vaccination schedule before first gestation. The booster dose was administered during the lactation period following parturition. A group of 20 gilts were maintained as controls that received placebo injections (PBS), and a group of 2 gilts were untreated and maintained as sentinel animals. Seven vaccinated sows and 5 control sows were challenged with virulent PPV. The efficacy of the vaccine after the single booster dose was demonstrated; 100% of foetuses in the vaccinated group were

protected from foetal infection by PPV, while the percentage of piglets from the control gilts infected with PPV was 91.3%.

Study of duration of immunity of the *E. rhusiopathiae* active ingredient of the ERYSENG PARVO vaccine. The duration of immunity of the *E. rhusiopathiae* component of the vaccine in gilts was investigated by challenge with *E. rhusiopathiae* serotype 1 and serotype 2 at the time at which the second booster dose would be administered (approximately six months after the basic vaccination scheme). A group of 15 seronegative gilts were vaccinated according to the basic vaccination scheme of two doses prior to first gestation, followed by administration of a single dose prior to the second gestation. Challenge was conducted at the time at which the subsequent booster dose would be administered (i.e. before third gestation). Ten control gilts received placebo injections (PBS) and two non-vaccinated sentinel gilts were included in the study. The timing of the vaccination schedule of ERYSENG PARVO is tailored towards the PPV component of the vaccine for the protection of foetuses during gestation. The challenge was conducted in 15 vaccinated animals and 7 control animals as for the basic immunogenicity of the vaccine, and it was demonstrated that 93.3% (14/15) of vaccinated animals were protected against challenge with serotype 1 and serotype 2.

In summary, the efficacy of the recommended revaccination schedule/duration of immunity for the PPV component and the *E. rhusiopathiae* component is accepted. The design of the studies conducted to investigate the duration of immunity were specifically linked to the proposed timing of vaccination/re-vaccination in advance of each gestation in order to guarantee foetal protection against porcine parvovirus. Therefore, the duration of immunity for foetal protection against PPV is each individual period of gestation, with re-vaccination recommended in advance of each subsequent pregnancy, while the duration of immunity for *E. rhusiopathiae* has been demonstrated at six months (i.e. the interval between the basic vaccination scheme and re-vaccination prior to the next pregnancy).

Field trials

One multicentre field study was conducted, involving a total of 712 female pigs (348 nulliparous gilts and 364 multiparous sows) from five farms in Spain. Farms included in the study were in the practice of vaccinating against PPV and swine erysipelas, and although it was a requirement that nulliparous gilts were included that had never been previously vaccinated, some animals were seropositive against PPV (approximately 101 gilts) and *E. rhusiopathiae* (approximately 15 gilts), indicating at least some degree of infection pressure from the two pathogens. Multiparous sows were included in the study if they had been previously vaccinated against PPV and *E. rhusiopathiae.* Half of the animals were vaccinated with ERYSENG PARVO and the other half were vaccinated with a positive control; a commercially available inactivated vaccine containing PPV and *E. rhusiopathiae*. A negative control group was not included in the study for ethical reasons. Nulliparous gilts were vaccinated according to the basic vaccination schedule whereas multiparous sows were vaccinated with a single booster dose.

From an efficacy perspective, the study was designed to show that there were no differences between treatment groups concerning the presence of skin lesions due to *E. rhusiopathiae*, the number of mummified piglets due to PPV infection during gestation, or the serological response to vaccination. From the results presented, there were no differences between vaccinated groups for skin lesions due to *E. rhusiopathiae*, the mean number of mummified piglets or the mean antibody titres against each of the active components. However, given that infection pressure from either PPV or *E. rhusiopathiae* was not demonstrated in the field trial, the data are considered supportive only in terms of efficacy.

Overall conclusion on efficacy

The administration of ERYSENG PARVO, in accordance with the recommended vaccination schedule and route of administration, has been shown to prevent transplacental infection caused by porcine parvovirus, and to reduce skin lesions and fever caused by *E. rhusiopathiae* in male and female pigs.

The onset of immunity against *E. rhusiopathiae* infection is 3 weeks after the completion of the basic vaccination scheme. Foetal protection from PPV infection has been demonstrated for the duration of the gestation when vaccinated according to the recommended schedule. The duration of immunity is specifically linked to the re-vaccination schedule and covers the duration of gestation. The proposed re-vaccination schedule at 2–3 weeks prior to subsequent gestations (approximately six months after the basic vaccination scheme) has been demonstrated to maintain protection against swine erysipelas and protection of progeny from PPV challenge following administration of the first re-vaccination dose prior to the second gestation has also been demonstrated. It is the opinion of the CVMP that the target species for the PPV component should be restricted to breeding females.

Overall, it can be concluded that the efficacy of ERYSENG PARVO with respect to the indications as specified in the SPC section 4.2, has been demonstrated.

Part 5 – Benefit-risk assessment

Introduction

ERYSENG PARVO is a vaccine containing inactivated porcine parvovirus, strain NADL-2 and inactivated *E. rhusiopathiae*, strain R32E11 (serotype 2).

PPV infection is responsible for stillbirth, mummification, embryonic death and infertility (SMEDI) syndrome; transplacental infection of foetuses occurs readily and the severity of symptoms depends on the virulence of the virus strain and the time point of infection during gestation. Erysipelas is one of the oldest known diseases that affect growing and adult swine. Up to 50% of pigs in intensive pig production are considered to be colonised with *E. rhusiopathiae*. Disease outbreaks may be acute or chronic; acute outbreaks are characterised by sudden and unexpected deaths, febrile episodes, painful joints and skin lesions that vary from generalised cyanosis to the often-described diamond skin (rhomboid urticaria) lesions.

Although other vaccines are available for vaccination against porcine parvovirus and swine erysipelas, the adjuvant component of the vaccine consists of aluminium hydroxide gel, DEAE-dextran and ginseng and is considered to be a novel adjuvant system. This adjuvant combination has already been included as a component in another vaccine for which the applicant holds a marketing authorisation. ERYSENG PARVO is indicated for the active immunisation of female pigs for the protection of progeny against transplacental infection caused by porcine parvovirus and for the active immunisation of male and female pigs to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2.

The basic vaccination scheme consists of two intramuscular doses of 2 ml, separated by an interval of 3–4 weeks. The second injection should be given at 3–4 weeks before mating. Revaccination consists of a single dose of 2 ml administered at 2–3 weeks prior to each subsequent mating (approximately every six months).

Benefit assessment

Direct therapeutic benefit

Protection of offspring against transplacental infection by PPV was demonstrated in four laboratory studies in gilts in accordance with the requirements.

Protection of vaccinated gilts and boars against a combined challenge with *E. rhusiopathiae* serotype 1 and serotype 2 (where each challenge serotype was injected on different flanks of the pigs) was demonstrated, indicating cross-protection from the vaccine serotype 2 against *E. rhusiopathiae* serotype 1.

The product is efficacious for the active immunisation of female pigs for the protection of progeny against transplacental infection caused by *porcine parvovirus* and for the active immunisation of male and female pigs to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2.

The onset of immunity against porcine parvovirus is from the beginning of the gestation period and against *E. rhusiopathiae* three weeks after completion of the basic vaccination scheme.

Concerning duration of immunity against porcine parvovirus, vaccination provides foetal protection for the duration of gestation however revaccination should be performed prior to each gestation. Vaccination protects against swine erysipelas until the time of the recommended revaccination (approximately six months after the basic vaccination scheme).

Additional benefits

ERYSENG PARVO increases the range of available treatment possibilities against porcine parvovirosis and against swine erysipelas.

Risk assessment

The main potential risks are addressed as follows:

Quality:

The formulation, inactivation and manufacture of ERYSENG PARVO are well described. Specifications set should ensure that product of consistent quality will be produced.

For the target animal:

Adverse reactions following vaccination consist of transient temperature increases no greater than 2 °C which decrease spontaneously, and injection site reactions consisting of a small lump in the skin at the site of injection and mild to moderate inflammation which typically resolves within 4 days but occasionally may persist for longer (up to 12 days). The vaccine is not intended for use during pregnancy however a study was presented in order to demonstrate that the vaccine is safe for use during pregnancy.

For the user:

User safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

The product is not expected to pose a risk for the environment when used according to the SPC.

For the consumer:

Residue studies are not required. The withdrawal period is set at zero days.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall.

The vaccine has been demonstrated to be efficacious for the active immunisation of male and female pigs to reduce clinical signs (skin lesions and fever) of swine erysipelas caused by *Erysipelothrix rhusiopathiae*, serotype 1 and serotype 2.

The formulation, inactivation and manufacture of ERYSENG PARVO are well described. Specifications set should ensure that product of consistent quality will be produced.

The vaccine is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. A sufficient withdrawal period has been set.

Appropriate warnings have been included in the SPC and other product information.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

Conclusion

Based on the original and complementary data presented the CVMP concluded that the quality, safety and efficacy of ERYSENG PARVO were considered to be in accordance with the requirements of Directive 2001/82/EC.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommended the granting of the marketing authorisation for ERYSENG PARVO.