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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for ERYSENG (EMEA/V/C/002761/0000)

Common name: 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 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 contains inactivated *Erysipelothrix rhusiopathiae*, strain R32E11. The proposed indication is for active immunisation of pigs from 6 months of age 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 4 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 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 substance 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 the active substance which confirms that the active substance is 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 ingredient of the vaccine is inactivated *Erysipelothrix rhusiopathiae*, strain R32E11 and complies with the specific European Pharmacopoeia (Ph. Eur.) monograph, swine erysipelas vaccine (inactivated) 0064.

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 container is a colourless glass multidose, airtight bottle with a rubber stopper and aluminium capsule, or a 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 polyethylene terephthalate (PET) in line with the 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 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. It is well documented that vaccination with inactivated *Erysipelothrix rhusiopathiae* (*E. rhusiopathiae*) is successful in the treatment of erysipelas infection. 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*, in line with the monograph, showed which was the most appropriate concentration of adjuvant components and the combination with giving the best serological response was chosen.

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 for swine erysipelas vaccine (inactivated) states that the vaccine should be immunogenic with respect to *E. rhusiopathiae* serotypes 1 and 2. While ERYSENG 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 according to GMP. 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 are determined. The seed lot systems are in line with requirements of the Ph. Eur. monograph 0062. A sterilised fermenter is used to homogenate the inactivated antigen 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 for the antigen is provided and is in line with requirements of Ph. Eur. monograph 0062. A maximum allowable pre-inactivation titre for *E. rhusiopathiae* is provided and is met by routine batches. 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 *E. rhusiopathiae* was isolated from a laboratory in Germany. Identity and source of the active ingredient are controlled in line with requirements of Ph. Eur. monograph 0062 on vaccines for veterinary use.

To support the stability of the antigen, a batch of *E. rhusiopathiae* antigen stored for the maximum time established at 2–8 °C was used to manufacture a batch of the related multi-component ERYSENG PARVO vaccine for which satisfactory 27 month stability data are available. ERYSENG is identical to ERYSENG PARVO with the exception of the additional parvovirus antigen. Antigen titre data from additional *E. rhusiopathiae* antigen batches stored for periods of 18–19 months at 2–8 °C are also provided. From a combination of these data the use of antigen batches stored at 2–8 °C in the manufacture of vaccine batches that remain stable throughout the 24 month 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 on vaccines for veterinary use and Ph. Eur. monograph 5.2.5 on substances of animal origin for the production of immunological veterinary medicinal products (where relevant).

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

Transmissible spongiform encephalopathy (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 *E. rhusiopathiae* strain R32E11antigen 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 enzyme-linked immunosorbent assay (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 test for the *E. rhusiopathiae* antigen satisfactory information on the specificity of the antibody used for the *E. rhusiopathiae* R32E11 strain included in the vaccine is given.

The criteria for replacement of the antibodies for ELISA testing of antigen and vaccine batches are considered adequate.

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 *E. rhusiopathiae* antigen) and the specifications are provided.

The validation conducted for the release tests are in general acceptable and according to 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 *E. rhusiopathiae* potency test for release of the final vaccine is an *in vitro* test based on ELISA test used to quantify the antigen. The use of an *in vitro* potency test in place of the mouse potency test described in Ph. Eur. monograph 0064 is in accordance with the 3Rs principles of reduction, refinement and replacement of animal tests.

The *in vitro* ELISA test has been shown to be capable of discriminating between vaccine batches with variable *E. rhusiopathiae* antigen content. As the amount of antigen used in vaccine blending does not vary from batch to batch, the potency test can be accepted as being suitable to check the batch to batch consistency of the antigen content of routine vaccine batches particularly as tests to check the content of the adjuvant components are also performed on each vaccine batch.

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

Data demonstrating the stability indicating potential of the ELISA test to detect a decline in immunogenic properties of the vaccine over the shelf life has also been provided.

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

The results of the analysis of three production scale ERYSENG batches and a number of ERYSENG PARVO batches (containing the same *E. rhusiopathiae* antigen) 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 18 month results to date do not indicate any trends for the parameters tested. Considering this and as satisfactory 27 months data are available for the larger ERYSENG PARVO vaccine, the 24 month shelf life specified for the ERYSENG vaccine in section 6.3 of the summary of product characteristics (SPC) is supported.

ERYSENG 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. The vaccine contains only one *E. rhusiopathiae* serotype 2 but studies have demonstrated cross protection between serotype 1 and 2 with ERYSENG.

The manufacture follows standard processes; a seed lot system in line with the requirements of the Ph. Eur. 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* have been determined and is met by routine batches. The TSE concern is addressed in line with EMA/410/01 rev.3, confirming a negligible level of risk.

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 and Ph. Eur. monograph 0064 on swine erysipelas vaccine.

Information provided on the antigen-antibody interaction measured in the batch potency test supports the ability of the test to detect immune-relevant epitopes of the *E. rhusiopathiae* antigen which correlate with protection in the target species. In addition, the stability indicating potential of the ELISA test to detect a decline in the immunogenic properties of the vaccine over the shelf life has been satisfactorily demonstrated.

The stability of the vaccine has been investigated up to 18 months. As a 24 months shelf life for the larger component ERYSENG PARVO is supported by 27 months results, hence a shelf life of 24 months for ERYSENG can be accepted particularly as the ERYSENG stability evaluation will be continued through to the 27 month time point.

Recommendations for future quality development

Not applicable.

Part 3 – Safety

ERYSENG suspension for injection for pigs is a vaccine containing inactivated *Erysipelothrix 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 ingredient is included in ERYSENG at the following concentrations per 2 ml dose:

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

The application for ERYSENG is submitted in parallel with an application for marketing authorisation for a larger bivalent vaccine, ERYSENG PARVO, which contains an additional active ingredient, inactivated porcine parvovirus, strain NADL-2. The data presented in the dossier for the combination vaccine ERYSENG PARVO are considered applicable to the monovalent vaccine ERYSENG in accordance with the principles outlined in the CVMP Note for guidance on requirements for combined veterinary vaccines (EMA/CVMP/IWP/52/97-Final), i.e. safety tests conducted using a combined vaccine may be used to demonstrate the safety of a vaccine containing a smaller number of components providing the components (antigens, composition of excipients and/or adjuvants) are identical in each case and it is only the number of active ingredients which is changed. Given that ERYSENG is identical to ERYSENG PARVO in terms of the qualitative and quantitative composition of excipients and adjuvants and it is only the number of active substances which is changed between these two immunological products, Part 3 of the dossier for ERYSENG is identical to that submitted for ERYSENG PARVO.

The vaccine is proposed by the applicant 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. These were conducted using the ERYSENG PARVO vaccine. 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 requirements:

- 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 (GLP).

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 and a repeated single dose in gilts and safety of the administration of an overdose, a single dose and a repeated 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 porcine parvovirus (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 conducted with ERYSENG PARVO 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 this 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 for ERYSENG PARVO was considered acceptable. It was thus concluded that this can also be extrapolated for the safety of the administration of one dose for ERYSENG.

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 conducted with ERYSENG PARVO 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 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 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 euthanised and necropsy and histopathological analysis was 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, it can be concluded that the administration of one dose, an overdose and the repeated administration of one dose of ERYSENG 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 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 related bivalent vaccine ERYSENG PARVO on reproductive performance when used in pregnant gilts or lactating sows, which are used for the evaluation of ERYSENG.

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

It is accepted that the safety of the use of ERYSENG PARVO, and thus also the safety of ERYSENG, 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 substance being a principle of biological origin intended to produce active immunity is not in the scope of Regulation (EC) 470/2009,
- the adjuvant components of ERYSENG 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 set at 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. This study is also used for the evaluation of ERYSENG. 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 for ERYSENG PARVO, conducted in accordance with the CVMP Guideline on user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006), which is also submitted in support of the user safety assessment for ERYSENG. The active ingredients of ERYSENG PARVO, 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. The user safety assessment and the conclusions drawn with respect to the data presented in the ERYSENG PARVO application are equally applicable for ERYSENG. The lack of the PPV active ingredient in ERYSENG compared to ERYSENG PARVO does not impact on the user safety assessment since there are no hazards identified for the user with respect to either of the active ingredients.

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 and 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 (ERA) for ERYSENG PARVO submitted in support of the ERA for ERYSENG, consisting of a Phase I assessment, conducted in accordance with the CVMP Note for guidance on environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95-Final). This is considered appropriate considering the nature of the product, an inactivated vaccine to be administered by injection. The ERA and conclusions drawn with respect to the data presented in the ERYSENG PARVO application are equally applicable for ERYSENG. The lack of the PPV active ingredient in ERYSENG compared to ERYSENG PARVO does not impact on the ERA since no hazard to the environment is identified for either of the active ingredients.

Given that ERYSENG is composed of an inactivated antigen, *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 ingredients are likely to be negligible.

In conclusion, it is accepted that the risk to the environment following use of ERYSENG 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 conducted with ERYSENG PARVO 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 ingredient 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 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 is a vaccine containing 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 the antigen included in the vaccine is fixed (no minimum or maximum titre concept applies) at the following concentration per 2 ml dose:

> 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 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 application for ERYSENG is submitted in parallel with an application for marketing authorisation for a combination vaccine, ERYSENG PARVO, which contains an additional active ingredient, inactivated porcine parvovirus, strain NADL-2. The data presented in the dossier for the combination vaccine ERYSENG PARVO are applicable to the single component vaccine ERYSENG. In accordance with the principles outlined in the CVMP Note for guidance on requirements for combined veterinary vaccines (EMA/CVMP/IWP/52/97-Final), the approach of using results from challenge studies with a larger combination vaccine to support the efficacy of a monovalent vaccine is acceptable, provided that the components (antigens, composition of excipients and/or adjuvants) are identical in each case and that it is only the number of active ingredients which is changed, and provided that it can be confirmed that the presence of the PPV component in the combination vaccine does not contribute a synergistic effect to the efficacy of the *E. rhusiopathiae* component. Therefore, data generated for ERYSENG PARVO are provided in support of the efficacy of ERYSENG, together with an additional laboratory study designed to show a lack of interference of the PPV component on the response to vaccination with *E. rhusiopathiae*.

The basic vaccination schedule and re-vaccination scheme was investigated and established using the combination vaccine ERYSENG PARVO, which is tailored towards foetal protection during pregnancy. Therefore, the basic vaccination schedule for ERYSENG 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 (approximately 6 months after the basic vaccination scheme). The onset of immunity is 3 weeks after completion of the basic vaccination scheme and the duration of immunity is 6 months.

General requirements

The efficacy data provided in support of the claimed indications for ERYSENG PARVO, and therefore by extrapolation to ERYSENG, consist 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

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. This study is relevant to the assessment of ERYSENG in terms of safety only and is described in the safety section of the report.

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 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 by *E. rhusiopathiae*, serotype 1 and 2.

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. This study is relevant to the assessment of ERYSENG in terms of safety only and is described in the safety section of this report. Note that the vaccination/re-vaccination schedule for ERYSENG is based on the vaccination schedule for ERYSENG PARVO which is tailored towards the reproductive cycle of female pigs in order to protect foetuses during gestation from PPV infection.

Study of duration of immunity of the *E. rhusiopathiae* active ingredient of the ERYSENG PARVO vaccine. The efficacy of the re-vaccination schedule 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. 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 (2–3 weeks) prior to the second gestation. The booster dose was administered approximately 6 months after the basic vaccination scheme. 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 with serotype 2. On the basis of the latter study, the efficacy of the revaccination schedule/duration of immunity for *E. rhusiopathiae* is accepted. As a result, the CVMP accepted a re-vaccination schedule for ERYSENG of a single injection 2–3 weeks prior to each subsequent mating. The duration of immunity is therefore established at six months, which is the time in the above study between the first dose of the basic vaccination scheme and the administration of the first booster dose.

The following study was presented to support the use of the efficacy data from the combination vaccine ERYSENG PARVO for the single component vaccine ERYSENG:

Study on the serological response against PPV and/or swine erysipelas induced by ERYSENG PARVO and two single component vaccines (ERYSENG and an inactivated PPV). Three groups of 10 pigs seronegative for *E. rhusiopathiae* and PPV antibodies (male and female from 6 months of age) were vaccinated according to the basic vaccination schedule either with ERYSENG, ERYSENG PARVO or a monovalent PPV vaccine. The serological profiles after vaccination were compared between groups. (Results relating to PPV are not discussed as they are not relevant to the current application). By 21 days after the first dose, 9 of 10 animals vaccinated with ERYSENG were seropositive for *E. rhusiopathiae* antibodies, while 6 of 10 animals vaccinated with ERYSENG PARVO had seroconverted. By day 30, all animals in both groups had seroconverted. In general, the mean titres were marginally higher in the ERYSENG group compared to the ERYSENG PARVO group however there were no statistically significant differences between the groups. That is, the absence of the PPV component did not have a negative impact on serological response to the *E. rhusiopathiae* component. The objective of the study was achieved, that is, equivalent levels of anti-*E. rhusiopathiae* IgG antibodies were induced in both groups following vaccination with ERYSENG or ERYSENG PARVO. It is

satisfactorily justified that serological response is an appropriate surrogate marker for protection as although the host immune response to *E. rhusiopathiae* is complex and involves both humoral and cell-mediated arms of the immune response, the protective role for antibodies against infection is well-established. Therefore, it is accepted that there is a lack of a synergistic effect on the immune response to vaccination towards the *E. rhusiopathiae* component when animals are vaccinated with ERYSENG PARVO compared to ERYSENG alone. Thus, it is accepted that the challenge data conducted with *E. rhusiopathiae* serotypes 1 and 2 generated with ERYSENG PARVO can be extrapolated to support the efficacy of the smaller fall-out vaccine, ERYSENG.

Field trials

One multicentre field study was conducted with ERYSENG PARVO, involving a total of 712 female pigs (348 nulliparous gilts and 364 multiparous sows) from five farms in Spain. This study is provided in support of the safety and efficacy under field conditions of ERYSENG. 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 data presented in the dossier for the combination vaccine ERYSENG PARVO can be extrapolated to the single component vaccine ERYSENG and therefore the conclusions for ERYSENG PARVO are applicable to ERYSENG.

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

The onset of immunity is 3 weeks after the completion of the basic vaccination scheme. The studies conducted to investigate the duration of immunity were designed in accordance with the re-vaccination schedule for ERYSENG PARVO and were tailored towards demonstrating foetal protection during gestation; the proposed re-vaccination schedule at 2–3 weeks prior to subsequent gestations has also been demonstrated to maintain protection against swine erysipelas (approximately 6 months after administration of the basic vaccination schedule; thus the duration of immunity is 6 months in the SPC).

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

Part 5 – Benefit-risk assessment

Introduction

ERYSENG is a vaccine containing inactivated *E. rhusiopathiae*, strain R32E11 (serotype 2). It is a single component 'fall out product' of the larger combination vaccine ERYSENG PARVO, which contains inactivated porcine parvovirus, strain NADL-2, in addition to inactivated *E. rhusiopathiae.*

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 swine erysipelas, the adjuvant component of the vaccine consists of aluminium hydroxide gel, DEAE-dextran and ginseng and is recently introduced adjuvant system. This adjuvant combination has already been included as a component in another vaccine for which the applicant holds a marketing authorisation. ERYSENG is indicated for use for the active immunisation of pigs from six months of age to reduce clinical signs and lesions of swine erysipelas (SE). 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). The vaccination schedule is timed in accordance with the management of reproduction of females in accordance with the larger combination vaccine. The safety and efficacy data for ERYSENG PARVO are presented in support of the safety and efficacy data for ERYSENG, on the basis that data generated using the larger combination vaccine may support the safety and efficacy of the smaller monovalent vaccine in accordance with the principles of the CVMP Note for guidance on requirements for combined veterinary vaccines (EMA/CVMP/IWP/52/97-Final), provided that there is no synergistic effects of the larger combination vaccine on the antigenic components of the larger vaccine, which has been satisfactorily demonstrated by the applicant.

Benefit assessment

Direct therapeutic benefit

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 in four laboratory studies and one field trial, indicating cross-protection from the vaccine serotype 2 against *E. rhusiopathiae* serotype 1.

The product is 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 onset of immunity is three weeks after completion of the basic vaccination scheme and duration of immunity six months.

Additional benefits

ERYSENG increases the range of available treatment possibilities against swine erysipelas.

Risk assessment

The main potential risks are addressed as follows:

Quality:

The formulation, inactivation and manufacture of ERYSENG 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 is 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 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.