15 June 2017
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Suvaxyn PRRS MLV (EMEA/V/C/004276/0000)

Common name: Porcine respiratory and reproductive syndrome virus vaccine (live)

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

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Introduction

On 19 May 2016, the applicant Zoetis Belgium SA submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Suvaxyn PRRS MLV, through the centralised procedure falling within Article 3(1) and point 1 of the Annex of Regulation (EC) No 726/2004 (product developed by means of a biotechnological process).

The eligibility to the centralised procedure was agreed upon by the CVMP on 9 July 2015 as Suvaxyn PRRS MLV is developed by means of a biotechnological process (Article 3(1) of the Annex of Regulation (EC) No 726/2004).

Suvaxyn PRRS MLV is indicated for active immunisation of clinically healthy pigs from 1 day of age in a porcine respiratory and reproductive syndrome (PRRS) virus contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1).

Suvaxyn PRRS MLV is a live vaccine that contains as active component porcine reproductive and respiratory syndrome virus (PRRSV), strain 96V198, at $10^{2.2}$ -$10^{5.2}$ $CCID_{50}$/dose. Suvaxyn PRRS MLV is intended to be administered as a single 2 ml intramuscular (IM) injection to fattening pigs from 1 day of age. Specifically for breeding gilts and sows a single IM dose of 2 ml is given prior to introduction into the sow herd approximately 4 weeks prior to breeding. A single booster dose is given every 4 months.

Suvaxyn PRRS MLV is presented in vials of 15 ml of lyophilisate containing 25, 50 or 125 doses and vials of 50, 100 or 250 ml of solvent. It is presented in packs containing one vial of lyophilisate (25, 50 or 125 doses) and containing one vial of solvent of 50, 100 or 250 ml, respectively.

The rapporteur appointed is Esther Werner and the co-rapporteur is Frédéric Klein.

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

On 15 June 2017 the CVMP adopted an opinion and CVMP assessment report.

On 24 August 2017 the European Commission adopted a Commission Decision granting the marketing authorisation for Suvaxyn PRRS MLV.

Marketing authorisation under exceptional circumstances

Not applicable.

Scientific advice

Not applicable.

MUMS/Limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (version 1.4 dated 18 March 2015) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided 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 Community or in a third country.

Manufacturing authorisations and inspection status

Suvaxyn PRRS MLV is manufactured in the EU by Zoetis Belgium SA, Rue Laid Burniat 1, 1348 Louvain-la-Neuve, Belgium.

The site has a manufacturing authorisation issued on 05 February 2016 by the Belgian authority (Agence Fédérale des Médicaments et des Produits de Santé, AFMPS). The manufacturer was inspected 19 January 2017, and it is stated in the certificate issued on 24 March 2017 that the manufacturer complies with the principles and guidelines of Good Manufacturing Practise (GMP).

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

GMP status of the active substance and of the finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Chemical, pharmaceutical and biological / microbiological information (quality)

Qualitative and quantitative particulars of the constituents

Qualitative and quantitative particulars

Composition

Suvaxyn PRRS MLV, a modified live vaccine, is presented as 'lyophilisate and solvent for suspension for injection'.

The lyophilisate (freeze-dried fraction) contains as active component PRRSV, strain 96V198, at $10^{2.2}$ -$10^{5.2}$ CCID50/dose and as excipient "L2 freeze-drying stabilizer" composed of Dextran 40, Casein hydrolysate, Lactose monohydrate, Sorbitol 70% solution, Sodium hydroxide, Water for injections (WFI) and dilution medium (UltraCULTURE™). The solvent (liquid fraction) contains Sodium Chloride and WFI.

Container and closure

The vaccine is presented in glass vials of 25, 50 and 125 doses (lyophilisate) and in HDPE vials of 50, 100 and 250 ml (solvent) in accordance with the European Pharmacopoeia (Ph. Eur.). These vials are closed with stoppers of bromobutyl rubber (lyophilisate) and chlorobutyl rubber (solvent) which are in accordance with the Ph. Eur. and sealed with aluminium caps.

Product development

The vaccine Suvaxyn PRRS MLV represents a conventional modified live viral vaccine and consists of a lyophilisate containing the vaccine antigen and a solvent containing sodium chloride. For final vaccine formulation the lyophilisate is suspended in the solvent before administration.

The PRRSV strain 96V198 was isolated in Belgium and belongs to genotype 1 and to subtype 1, which is the predominant PRRSV subtype found in Western Europe. Current scientific knowledge has demonstrated the relevance of this strain to the European epidemiological situation. The degree of protective immunity is dependent on the characteristics of both the PRRS vaccine and challenge strains (genetically/antigenically similar strains against more distantly related strains). Therefore, it is expected that the PRRSV strain 96V198, belonging to the predominant subtype, will provide protection, in most cases, against EU strains currently circulating.

The host cell system for virus propagation, the cell line BHK-21-C12-26 has been created, which is a clone of BHK-21 hamster kidney cells engineered by a biotechnological process to express the CD163 PRRSV receptor. Based on this receptor, the cell line allows PRRSV strains to attach and infect cells and therefore overcome the problem of lack of infectivity in other known cell lines. After serial passages, the PRRSV vaccine strain candidate, 96V198 clone 1, has been adapted to growth and attenuated on the cell line BHK-21-C12-26. Additional data and further essential and elementary information to this genetically modified cell line (description, construction, control and stability) have been provided.

Description of the manufacturing method

The production procedure involves four phases: firstly, the production of the cell substrate; secondly, the production of the PRRSV antigen; and thirdly, the preparation and control of the finished product. As a fourth phase the production of the solvent is given.

For mass cultivation, the virus is propagated in BHK21-C12-26 cells. Thereafter, the virus harvests are clarified by ultrafiltration and may be concentrated. Afterwards, the antigen bulks are stabilised. For preparation of the lyophilisate, antigen bulks are blended with the other excipients (e.g. L2 stabilizer, medium), filled aseptically into glass vials and then freeze-dried via routine lyophilisation cycles. The filled vials are closed with stoppers and sealed with aluminium caps. The vaccine lot is then stored at -20 °C or below until used in packaging.

For preparation of the solvent, sodium chloride is dissolved in water for injections up to final volume and aseptically filled into HDPE vials. The filled vials are stoppered and sealed with aluminium caps. The solvent lot is stored at room temperature until used in assembly process and at +2–8 °C once assembly.

The production process is considered as standard for the manufacturing of viral vaccines. In general, the production process is well described in the essential parts. Nevertheless, one remaining issue requires clarification in order to confirm that the production process generates consistent vaccine batches. This concerns long-term storage of virus antigens and finally the stability of batches blended with aged virus antigen.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Specifications of excipients and other starting materials listed in the Ph.Eur. are in compliance with the relevant monographs.

Specific materials not listed in a pharmacopoeia

Starting materials of biological origin

Concerning the PRRSV (strain 96V198) as active ingredient specifications are defined, information and analytical methods are provided. The preparation and control process of both master and working seed viruses comply with the current European regulations and requirements.

Stability data are provided for the virus antigen bulks. Therefore, antigen bulks can be stored 24 months before blending as finished product batches. However, due to the ongoing stability study additional data are awaited in order to justify the complete proposed shelf life.

Regarding the BHK21-C12-26 cell line as starting material of biological origin essential and elementary information to this genetically modified cell line (description, construction, control, and stability) are provided.

Specifications of excipients and other starting materials of biological origin are defined and analytical methods are provided.

Starting materials of non-biological origin

Specifications of excipients and other starting materials of non-biological origin are defined and analytical methods are provided.

In-house preparation of media and solutions consisting of several components

The in-house preparation of media and other reagents are well described.

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

The starting materials of biological origin comply with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathies agents via human and veterinary medicinal products (EMEA/410/01-Rev.2). The overall TSE risk associated with the modified live vaccine is considered negligible.

Control tests during the manufacturing process

During the manufacture the following in-process control tests are carried out to assure the quality parameters:

- Determination of antigen content (Infectious virus titration).
- Sterility test.

Test descriptions and the limits of acceptance are presented. The test methods for in-process controls are satisfactorily validated.

Data is presented for in-process results for four consecutive antigen bulks.

Control tests on the finished product

The control on the lyophilisate (freeze-dried fraction) is performed on each batch and is carried out to assure the quality parameters. The following tests are performed:

Description (appearance).

Residual humidity.

Sterility test.

Absence of mycoplasma.

Absence of extraneous agents.

Identification.

Potency (titration).

The control on the solvent (liquid fraction) is performed on each batch and is carried out to assure the quality parameters. The following tests are performed:

Description (appearance).

Sterility test.

Identification.

Acidity/Alkalinity.

Content of sodium chloride.

Test descriptions are provided. The potency test is an infectious virus titration to determine and quantify the antigen content intended. The specifications and limits of acceptance proposed at release and at the end of shelf life are appropriate to control the quality of the finished product. The control methods are satisfactorily validated in order to confirm that the production and control processes generate consistent vaccine batches.

Batch-to-batch consistency

The results of analysis of ten consecutive batches of the finished product -lyophilisate and solvent- are presented which comply with the required specification.

Stability

The proposed shelf life of the lyophilisate (freeze-dried fraction) is 18 months at +2–8 °C after a previous storage at -20 °C or below for up to 15 months. Regarding the justification of this proposed shelf life, stability data were gathered for 17 batches of the finished product. But, these batches were stored either at +2–8 °C or at -20 °C or below for up to 21 months. Finally, only three technical batches (produced with pre-Master Seed Virus [MSV]) have been stored for 15 months at -20 °C and then kept for 12 additional months at +2–8 °C. All batches have passed the control tests on the finished product and met the proposed specifications. It is stated that the 3 technical batches are fully representative of the commercial product.

A confirmatory stability study including batches of all lyophilisate presentations (25, 50 and 125 doses) has been initiated and is still ongoing. Therefore additional data are awaited in order to justify the complete proposed shelf life.

At present, based on the presented data a shelf life of 12 months at +2–8 °C after a previous storage at -20 °C or below for up to 15 months is justified for the lyophilisate (freeze-dried fraction).

An overage of $10^{1.1}$ CCID50/dose is proposed to guarantee the minimum virus titre of $10^{3.3}$ CCID50/dose at time of batch release and of $10^{2.2}$ CCID50/dose at end-of-shelf life. This overage

is justified by the presented data.

The proposed shelf life of the solvent (liquid fraction) is 63 months at +2–8 °C. Historical stability data are available for solvent batches filled in glass vials and stored at +15–25 °C for up to 63 months. But, regarding the justification of the proposed shelf life a confirmatory stability study including batches of all solvent presentations (50, 100 and 250 ml) filled in HDPE vials and stored at +15–25 °C has been initiated and is still ongoing. Therefore additional data are awaited in order to justify the complete proposed shelf life. The most relevant parameter to be controlled is acidity/alkalinity. This is considered acceptable.

At present, for the solvent a shelf life of 24 months at +2–8 °C is considered acceptable due to presented data for storage at +15–25 °C.

Environmental risk assessment for products containing or consisting of genetically modified organisms

Please refer to Part 3 - Safety.

Overall conclusions on quality

Information regarding the qualitative and quantitative composition, the starting materials, production method, quality controls, and stability are provided in this part of the dossier. Ten consecutive batches of the finished product -lyophilisate and solvent- are provided in order to demonstrate batch-to-batch consistency.

The production processes, the control of the starting materials, the in-process controls and the quality control on the finished product are described in sufficient detail to give confidence that the manufacture will yield a safe, effective and stable vaccine of consistent quality. The production methods as well as the in-process and final product quality controls are appropriate to ensure the compliance with the specifications and a reproducible and consistent quality of the vaccine.

Regarding the stability, the virus antigen bulk is demonstrated to be stable over the shelf life of 24 months (at -40 °C).

For the lyophilisate (freeze-dried fraction) a shelf life of 15 months at -20 °C followed by 12 months storage at +2-8 °C is justified.

For the sodium chloride solvent a shelf life of 24 months is acceptable when filled in HDPE plastic vials and stored at room temperature (+15-25 °C) or at +2-8 °C.

Based on the review of the data on quality, the manufacture and control of Suvaxyn PRRS MLV are considered acceptable.

In addition, the applicant is recommended to provide the following information [post authorisation]:

1. The data on the stability of the PRRSV antigen should be provided at the end of the ongoing study, or immediately in case of potentially out-of-specification results in the course of the study.
2. The data on the stability of final product batches should be provided at the end of the ongoing study, or immediately in case of potentially out-of-specification results in the course of the study.
3. Inclusion of the total protein amount as a final product test is recommended for information only.

Part 3 – Safety

Safety documentation

All laboratory safety studies were performed under Good Laboratory Practice (GLP) conditions, the field trials conformed to Good Clinical Practice (GCP) requirements, relevant EU Directives, Guidelines and Ph. Eur. were taken into account.

Safety of the administration of one dose, one overdose and repeated administration of one dose

The safety of one dose, repeated dose and overdose were assessed in one relevant study after intranasal (IN) and IM vaccine administration in seronegative 1-day-old piglets born from PRRSV antibody negative sows that originated from PRRS free farms. The IN route was finally withdrawn as a route of administration during assessment of the efficacy data (see section 4 efficacy).

The dissemination and shedding capability of the PRRS vaccine virus was also investigated. A pilot vaccine batch (MSV+3, the least attenuated passage) prepared at the required maximum single dose ($10^{5.2}$ CCID50/2 ml) and overdose ($10^{6.2}$ CCID50/2 ml) was used. Another safety evaluation conducted after IM vaccine administration in 2-week-old piglets followed the same design but was of supportive character only as a vaccine batch at passage level MSV+5 was used instead of MSV+3 and the piglets were not of minimum age. Non-vaccinated sentinel animals were included in these studies.

The clinical observation encompassed monitoring of local and systemic reactions, measurements of body temperature and body weight.

Serology was performed with the commercially available ELISA IDEXX test kit; viraemia and viral loads were determined by real-time RT-PCR. Nasal, viral and oral swabs (shedding), tissue of several lymph nodes and organs (dissemination) were investigated for the presence of PRRS vaccine virus.

Post-mortem macroscopic examinations of the injection sites and lungs were carried out. Slices of neck musculature and lung lobes were examined microscopically in the case of any macroscopic abnormalities including immunohistochemistry.

After IN and IM vaccine administration of a single dose, a repeated single dose or a 10-fold overdose no clinical signs were detected except a transient temperature increase of up to 1 °C and short lasting apathy and tremor in few piglets of the IM overdose group.

The average temperature increase never exceeded 1.5 °C in the vaccinated pigs compared to the basal average temperature before vaccination and none of the vaccinated piglets showed an increase in rectal temperatures greater than 2 °C compared to the individual piglet baseline before vaccination (the criteria for vaccine safety). As a consequence, the corresponding SPC section was amended by adding the maximum individual temperature increase observed.

The local reactions observed were limited to small soft painless swellings after IM overdose vaccination.

All vaccinated piglets were viraemic until day 14 post vaccination. The PRRS vaccine virus was widely disseminated at very high levels in the bodies of the IN and IM vaccinated 1-day-old piglets and of non-vaccinated sentinels as well. PRRS vaccine virus was detected sporadically in oral and rectal swabs but constantly at high levels in nasal swabs even though decreasing over time. Thus, spreading to non-vaccinated in-contact piglets was demonstrated.

Besides information gathered from the safety studies, a transient fever was observed a few hours after

the PRRS challenge in the 2 studies of the duration of immunity (DOI) after vaccination of piglets. This fever could be an indication for a phenomenon which is known as antibody dependant enhancement of infections which is occurring when the antibody level goes below the optimal (virus-neutralising) level. However this transient fever resolved spontaneously.

Examination of reproductive performance

Three studies have been conducted to assess the potential impact of the vaccine on pre-breeding and during pregnancy:

- An overdose followed by single dose study in seronegative sows at different stages of gestation or pre-breeding.
- An overdose followed by single dose study in seropositive sows at the second half of gestation.
- A repeated single dose study in seropositive sows at the second half of gestation.

The following points were assessed:

- Reproductive performance including dates of birth, total born piglets, number and general aspects of born alive and born dead piglets. The piglet's viability was recorded until weaning, the end of the study.
- Post-mortem macroscopic analysis of the lungs of all piglets.
- Viraemia using real-time RT-PCR.
- Serology via commercially available ELISA IDEXX test kit.
- Local and systemic reactions.
- Body temperature (applicant's criterion: average temperature increases in vaccinated pigs do not exceed 1.5 °C compared to the average temperature before vaccination; no sow has an increase >2 °C).

The vaccine safety has been evaluated in PRRSV antibody negative sows after an overdose vaccine administration followed by a single dose 14 days later, either prior to breeding or in the 1st (55 day) or 2nd (87 day) half of gestation. Diluent receiving control groups were included. Overdose and single dose vaccination was completed approximately 30 days prior to insemination in the pre-breeding group.

Some individual temperature increases were clearly above 1 °C after overdose vaccination. Local reactions encompassed painless soft to hard swellings of varying extent depending on the vaccine dose administered (ranges between 0.3 x 0.3 cm up to 2.0 cm); sometimes the skin was reddened. The most pronounced injection site reaction lasted for nine days.

Regarding reproductive performance parameters, similar results were obtained for the vaccinated and non-vaccinated pre-breeding group. In addition, similar survival rates were achieved in the two pre-breeding groups for piglets at weaning, on day 21.

The results of the groups vaccinated in the 1st or 2nd half of pregnancy are comparable to the controls except for the means of weak born piglets (1st: Control (C) 1.28 versus Vaccinates (V) 2.71; 2nd: C-0.8 versus V-1.37) and the resulting percentage weak born/total born alive piglets (1st: C-11.16% versus V-21.2%; 2nd: C-4.98% versus V-13.54%). The mean of dead born piglets is also higher in the group of 2nd half vaccinated sows (V-3.25 versus C-1.21). Viraemia was detected in 75% of the piglets born alive and in 80% of the mummified born in the group of seronegative sows vaccinated in the 2nd half of their pregnancy, whereas all piglets of the other groups were PRRSV negative. Thus, the vaccine virus,

as must be expected, will be transmitted via the placenta in the case of vaccination in the 2nd half of pregnancy. At weaning on day 21, more than 90% of the piglets belonging to the 2nd half of pregnancy vaccinated sows became PRRSV positive which is indicative for shedding and spreading of the vaccine virus. The results give a clear indication at least not to vaccinate seronegative sows in the second half of gestation as this negatively affected the reproductive performance. This is properly reflected in the SPC.

Presumably based on the fact that the highest probability of vaccine use will be in PRRSV seropositive sows in the 2nd half of pregnancy, the vaccine's safety has been evaluated in PRRSV antibody positive sows in the 2nd half of gestation (90/91 day) after an overdose vaccine administration followed by a single dose 14 days later. A diluent receiving control group was included.

The reproductive performance parameters were comparable between the two groups except for the pre-weaning mortality which was higher in the vaccinated group (14.6%) compared to the control group (5.4%). As known by literature, virus replication in the endometrial/placental tissues is described to be a prerequisite for PRRSV-induced reproductive failure. This placental transmission of PRRSV to foetuses was demonstrated by virus detection in blood samples of foetuses or live born piglets. As PRRSV could not be detected in blood samples from any piglet at birth or at weaning, an effect of PRRSV on the piglet mortality can be ruled out. A possible reason for the pre-weaning mortality could have been due to the very high number of piglets born alive in the vaccinated group; this resulted in difficulties to nurse for the smallest piglets within the litters. In this case, the risk of crushing and reduced viability of those piglets is higher. Subsequently, several piglets had to be euthanized for welfare reasons. The highest percentage of pre-weaning mortality was recorded for one sow with 31% in the group of vaccinates; this sow was treated for the milk flow on the days post-farrowing. As a consequence, three pigs from this sow had to be euthanized and two died. The applicant's reasoning is comprehensible as no viraemia was detected in any serum sample collected from piglets at birth or at weaning. As no viraemic piglet was born; thus no PRRS vaccine virus is transmitted via placenta.

Average temperature increases in vaccinated pigs did not exceed 1.5 °C compared to the average temperature before vaccination. No sow had an increase >2 °C. However, some individual temperature increases were above 1 °C after overdose vaccination. Local reactions encompassed painless to painful swellings of hard consistency ranging up to 5.0 cm after single dose vaccination accompanied by skin reddening and increased heat. The longest period of persistence was 31 days after single-dose-administration and 44 days after overdose administration. The overdose administration caused widespread erythematous swelling in the whole neck of two sows that lasted for six days. It was assumed that PRRSV antibody positivity and multipara status of the sows in conjunction with circulating memory cells due to numerous vaccinations against PRRSV prior to the study might have induced hypersensitivity reactions when high antigen amounts were administered as in the overdose part of the study.

To exclude such an effect after simple single-dose-administration, the study was carried out to assess if single-dose administrations would induce comparable results. The safety was assessed in PRRSV antibody positive sows during the 2nd half of pregnancy (day 87) after repeated administration of a single vaccine.

As regards the body temperature measured, there is no difference to the other study.

With regard to the local reactions, one half of the sows vaccinated developed a reaction which lasted for 6 days after the 1st vaccination and after the 2nd second dose reactions up to 1 cm in diameter which lasted for 5 days. Post-mortem analyses showed multiple nodules in two vaccinated sows, which histologically turned out to be moderate to severe granulomatous myositis.

Regarding reproductive performance, similar results were obtained at parturition in the two groups; the survival rates at weaning were also comparable. No viraemia was detectable in any serum sample examined at parturition or at weaning.

As no study has been performed in lactating sows, the SPC wording has been revised accordingly.

Examination of immunological functions

The potential impact of the vaccine administration on immunological functions has been evaluated in 2-week-old piglets. Potential adverse effects were investigated by comparing the PCV2 antibody response using an Immuno-Peroxidase-Monolayer-Assay (IPMA) after vaccination with half dose of the MAH's PCV vaccine between pigs that had been previously vaccinated with the PRRS MLV vaccine in question or saline solution.

2-week-old piglets were chosen because this age was considered the most sensitive category in terms of potential adverse effects on the immune system. Furthermore, within the first 4 weeks of the piglets' life, other immunological products such as PCV2 and *M. hyo* vaccines would also be administered, and the vaccine in question might also become part of future combined vaccination schemes or multivalent vaccines.

Therefore, the decision was taken to use Suvaxyn PCV, a single-dose inactivated PCV1-2 chimeric vaccine for use in piglets at an age of three weeks or older against the infection with PCV2. As pinpointed by the applicant referring to relevant literature, it has been demonstrated under experimental conditions that PRRSV infection enhances PCV2 replication and PCV2-associated diseases in double infected pigs suggesting an immunomodulatory effect of PRRSV upon the immune response against PCV2. Therefore, the capacity to develop an immune response against PCV2 in response to Suvaxyn PCV vaccination was considered a suitable indicator of any potential adverse effects the vaccination with Suvaxyn PRRS MLV might have on the immune functions of young piglets.

Pigs selected came from a PCV2 seropositive farm as seen by the presence of low levels of PCV2 antibodies in some of the pigs prior to the start of the study. However, at the time of PCV vaccination (4 weeks of age), the levels of maternally derived antibodies (MDA) against PCV2 detected in all pigs were low or undetectable (IPMA titres ≤ 80). A previous study investigated the development of PCV2 antibodies in response to half a dose of PCV vaccination in animals with low IPMA titres (≤ 80); approximately 3 weeks post vaccination the animals seroconverted indicating a lack of interference of low MDA levels with seroconversion. This is confirmed in the study presented: An increase of PCV2 antibody titres in the control group (vaccinated with PCV alone) between D28 and D42 (2 to 4 weeks post PCV vaccination). In the group vaccinated with Suvaxyn PRRS MLV and PCV, seroconversion was also observed between D28 and D42 in most pigs. Three out of 15 pigs showed an earlier increase of PCV2 antibodies (by D28, corresponding to 2 weeks post PCV vaccination). On day 42 (4 weeks post PCV vaccination), geometric mean titres at IPMA were 351 (PCV2 control group) and 1,404 (PRRS MLV + PCV group). By the end of the study (day 56, 6 weeks post PCV vaccination), mean titres were 525 and 611 in each group, respectively.

The piglets used in this study were PRRSV-antibody and PRRS-virus negative but not of minimum age. The vaccine used was at passage level MSV+3 and at maximum virus titre. The use of the least attenuated passage level is acceptable; it is assumed that any adverse effects on the immunological functions would – in the case of PRRS vaccine viruses – rather occur by the use of a passage level closer to the original isolate than at the passage levels that are used for vaccine production. Furthermore, results of the reversion to virulence study gave no cause of concern regarding potential virulence increase.

In summary, Suvaxyn PRRS MLV administered by the IM route did not adversely affect the

immunological function of 14-day-old piglets.

Special requirements for live vaccines

Spread of the vaccine strain

Spread of vaccine strain is covered in the sections dissemination in the vaccinated animal and under the environmental risk assessment.

Dissemination in the vaccinated animal

The potential of the vaccine virus to disseminate within the vaccinated animal and to spread to in-contact animals of the target species was assessed and demonstrated to occur in the two studies belonging to the one dose, repeated dose and overdose vaccine administration part.

Piglets of one study received a single vaccine dose of the maximum virus titre ($10^{5.2}$ CCID50/2 ml) on day 0 and were euthanized on day 14. Control pigs for all groups received the corresponding amount of vaccine diluent. Sentinel pigs were left non-vaccinated and were housed with the pigs belonging to the one-dose-groups. Grouping was as follows: IN-controls, IN-vaccinates, IN-sentinels; IM-controls, IM-vaccinates, IM-sentinels.

The spread of the vaccine strain was evaluated from vaccinated to unvaccinated sentinel pigs. Shedding (nasal mucus, oral fluids, and faeces) and dissemination in tissues in vaccinated animals was also investigated.

Blood samples as well as nasal, oral and faecal swabs were taken from piglets in all groups on days 4, 7, 9 and 14 and processed for detection of viral genome (by RT-qPCR directed to PRRSV ORF7).

At necropsy (day 14), lesions were reported if found. Portions of mesenteric and tracheobronchial lymph nodes and tonsils as well as spleen and two portions of lobes from lungs were individually collected from pigs in several groups. Dissemination of the vaccine virus was assessed by RT-qPCR.

None of the control piglets was ever viraemic. In sentinel groups all piglets were positive from day 7 and 9, respectively. In IN and IM vaccinated groups all piglets were positive during all the tested days except three in the IM group on day 7. As regards nasal shedding, none of the control piglets were ever positive. In the sentinel groups all piglets were positive at least at one point in time. In the IM and IN vaccinated groups all piglets were positive at least at one point in time, except two animals in the IN and three in IM group. As regards oral shedding, few samples from oral saliva were positive; all of them in the vaccinated groups: one pig in the IN and two in the IM group (day 7). As regards faecal shedding, ten samples from rectal swabs were positive; seven from vaccinated groups (three IN piglets and six IM) and one IM sentinel.

As regards the dissemination results, almost all samples were positive in both sentinel and vaccinated pigs. Most of the pigs had 5 out of 5 positive tissues.

Post-mortem evaluation revealed macroscopic lung lesions in 9 pigs belonging to the IM vaccinated (or sentinel) groups. All 9 pigs had interstitial pneumonia plus positive results in IHC for PRRSV.

Piglets of a second study received intramuscularly a single vaccine dose of maximum virus titre ($10^{5.2}$ CCID50/2ml) on day 0 and were euthanized on day 14. Control pigs for all groups received the corresponding amount of vaccine diluent. Sentinel pigs were left non-vaccinated and were housed comingled with the vaccinated pigs.

The spread of the vaccine strain was evaluated from vaccinated to unvaccinated sentinel pigs. Shedding (nasal mucus, oral fluids, and faeces) and dissemination in tissues in vaccinated animals was

also investigated.

Blood samples as well as nasal, oral and faecal swabs were taken from piglets in all groups on days 4, 7, 10 and 14 and processed for detection of viral genome (by RT-qPCR directed to PRRSV ORF7).

At necropsy (day 14), macroscopical lesions were reported if found. Portions of mesenteric and tracheobronchial lymph nodes and tonsils as well as spleen and two portions of lobes from lungs were individually collected from pigs in groups T01/sentinels and T04/vaccinates. Dissemination of the vaccine virus was assessed by RT-qPCR.

All piglets vaccinated were viraemic from day 10. One of the sentinel piglets was positive from day 10. The vaccine strain was detectable in increasing amounts. As regards nasal shedding, none of the sentinel piglets was positive. One vaccinated piglet was positive at one time point. Several vaccinated piglets shed vaccine virus via saliva. There was no faecal shedding, as all samples tested were PRRSV-negative even though the vaccine virus was widely disseminated in organs. There were no macroscopic lesions in any of the necropsied animals.

The exclusion of boars producing semen for PRRSV naïve herds from the use of the vaccine is typical for PRRS modified live vaccines even though no specific studies were conducted.

In conclusion, the vaccine strain is widely disseminated to PRRSV target tissues (lung, spleen, tonsils and lymph nodes) as well as spread to in-contact animals after IN and IM vaccination of 1-day-old piglets. As regards the lung lesions, alveolar macrophages are the target cells for PRRSV, and, since the vaccine strain is live, replication in target cells was expected. As no clinical signs were observed in pigs with lung lesions sufficient attenuation of this PRRS vaccine strain can be assumed. The corresponding SPC points on dissemination and spread of vaccine strain are satisfactory.

Reversion to virulence of attenuated vaccines

The potential reversion to virulence of the modified live PRRSV vaccine strain PRRS MLV MSV+1 was assessed following serial passages (5-times) in 1-day-old piglets. 85 PRRSV seronegative cross-bred male and female piglets were included. The first inoculation was done using the recommended route of administration, either IM or intranasally (IN). Subsequent passages were done in both groups via the natural route of infection (IN). Passage inocula were prepared from oro-nasal secretions collected on day 8 or 9 post-vaccination/inoculation.

Blood samples were collected on days 6 or 7 and 8 or 9 to determine the presence of PRRS vaccine virus by RT-qPCR. Oral and nasal swabs were collected on days 8 and 9 after inoculation (two from each animal). Clinical observation encompassed a monitoring period of 10 days per passage; a scoring system (0 = normal, 1 = mild, 2 = moderate, 3 = severe) was used. Body temperature was measured on days 0, 2, 4, (6 – additional day for passage 5), 7, 8, 9, (11 – additional day for passage 5). Viraemia was determined by RT-qPCR. Post-mortem examination and histological examination was done on day 10+1 post inoculation; lung lesions were evaluated using a scoring system.

Mild to moderate abnormal clinical observations were recorded for 21 piglets (15 IM and 6 IN) during the monitoring period except for one piglet in group IN-passage 3 that was euthanized due to very poor general conditions and depression. As regards the body temperature, at passage 1, none of the piglets from groups IN or IM developed body temperatures ≥40.5 ºC at any time point after inoculation. As regards passage 5, none of the original IM piglets had fever. At passage 3, 4 and 5 level, individual animals developed temperatures >40 °C.

Following vaccination (passage 1), all pigs became viraemic regardless of the route of administration (IN or IM). In the original IM group, the virus could be recovered from blood and oro-nasal secretions up to passage 5. However, no apparent increase in viral load was observed. In the original IN group, no

shedding through oro-nasal secretions could be detected after passage 3 and none of the piglets developed viraemia either. This negative result was not confirmed when the same passage was repeated using 10 extra piglets (passage 3 repetition). Therefore, oro-nasal secretions of passage 3 repeat were used to proceed with the next passage and PRRS vaccine virus was detected up to passage 5.

With regard to post-mortem lung analyses, from the 35 IM piglets at the end of the study, 7 pigs (20%) had a positive score. All of them but one (passage 2) were scored by 1 (mild lesions). This one piglet was given a score of 2 (moderate lesions); it showed the highest percentage of lung consolidation (16%). However, the pattern of the observed lung lesions (cranioventral consolidation) was compatible with a bacterial infection, also supported by the clinical condition of that pig (diarrhoea) and the necropsy findings (enteritis). The other remaining pigs were given a score of 0 (no lesions).

From the 47 piglets vaccinated/inoculated in the IN group, 23 pigs (49%) had a positive score. All of them but one pig (passage 3 repetition) were scored as 1 (mild lesions) and none of the piglets scored 3 (severe lesions). The highest incidence of piglets with lesions as well as the highest mean percentage of lung lesions was observed in passage 3 repetition. In passages 4 and 5, both the percentage of positive pigs and the mean percentage of lung lesions decreased.

MSV+1, passage 45, was used in order to equal or exceed the maximum release titre expected in the finished product.

The study followed VICH guideline 41/Reversion to virulence: five serial passages were conducted in the target species using the recommended route of administration (IN and IM) followed by the natural route of infection (IN) that is most likely to lead to reversion. Passage inocula were prepared from the most likely source of spread of the organism (nasal swabs). General clinical observations were performed. The time interval between inoculation and harvest for each passage has been justified upon the characteristics of the test organism. Preliminary studies performed with the vaccine strain indicated that the peak of viraemia occurs before day 10 after inoculation. Likewise, the severity of lung lesions is more important at 10 days than at 21 days after inoculation. Therefore, the study protocol was amended so that pigs in the 5th passage were necropsied on day 10±1 instead of day 21±1.

Thus, animals of the 5th passage were observed for a shorter period (11 days) than 21 days recording parameters typical for the disease which could be indicative for an increase in virulence. As this 5th group showed no evidence of increased virulence, further testing up to 21 days was not done. This is in line with the requirements of Ph. Eur. monograph 50206 (Evaluation of safety of veterinary vaccines and immunosera; increase in virulence).

Overall, it was possible to serially passage the vaccine virus five times from piglets originally vaccinated by either the IM or IN route. There was no indication that the vaccine virus reverted to virulence. There was no increase and no decrease in virus titre or in the percentage of lung lesions detected in piglets included in later passages.

Biological properties of the vaccine strain

According to the applicant, there is no need for additional tests as this vaccine contains a PRRS virus strain conventionally attenuated through serial passages on a susceptible cell line. The tropism of the vaccine strain has been addressed in studies examining spread of the vaccine strain. This is accepted as the vaccine virus strain is conventionally attenuated. Even though it is produced on a recombinant cell line, this does not have any potential negative impact on the target species or the user (see also sections: environmental risk assessment and assessment required for veterinary medicinal products containing or consisting of genetically modified organisms).

Recombination or genomic re-assortment of the strains

Suvaxyn PRRS MLV contains a conventionally attenuated genotype 1 PRRS virus derived from a strain of moderate virulence originally isolated in Belgium. As this vaccine strain is also able to replicate in vaccinated pigs, it has the potential to recombine with field strains or other vaccine strains that may be concurrently replicating in the same pig.

Although recombination between PRRS virus strains, including modified live vaccine strains, is acknowledged to occur, the more than 20 year history of the use of such vaccines suggests few if any consequences. Recombination of a vaccine virus with a virulent field strain can only occur in the presence of an active infection with the virulent strain on the same farm. The resulting mosaic viruses would be expected to be less pathogenic than the virulent parental virus and therefore have a beneficial or neutral effect on the farm. There are no reports in the literature of an attenuated PRRS vaccine virus (of either genotype) recombining in the field to produce a mosaic virus that is more pathogenic than the virulent virus from which it was derived. It is believed that any potential for recombination and re-assortment arising from use of the vaccine presents no implications for the safety of the product.

User safety

A user safety risk assessment was performed according to the CVMP Guideline on user safety for immunological products (EMEA/CVMP/IWP/54533/2006). Hazard identification and characterisation were presented; tasks and situations that lead to exposure were discussed in detail. These conclusions and the SPC proposal are fully acceptable.

The vaccine is a live attenuated vaccine containing no adjuvants, no antibiotics and no preservatives, only the active ingredient, the PRRS vaccine virus, and the excipients present in the L2 freeze-drying stabilizer (dextran 40, casein hydrolysate, lactose monohydrate, sorbitol 70% solution, sodium hydroxide, water for injections and dilution medium [UltraCULTURE™]) must be taken into consideration.

The active ingredient of the vaccine is live attenuated PRRSV strain 96V198. Swine (domestic and feral) are the natural hosts of PRRSV; it has been described that some avian species, mallard ducks in particular, are susceptible to PRRSV. The virus is not considered as a zoonotic agent. The raw materials used for the preparation of the active ingredient comply with the relevant Ph. Eur. requirements. It is therefore considered that the active ingredient does not present any hazard to the user in case of self-injection or other forms of exposure.

As regards the excipients, none of these are considered harmful to the user.

As regards the exposure, the vaccine is intended for administration to animals by IM administration. The vaccine should be administered by a veterinary practitioner (or another person under his responsibility) who is trained in vaccine administration to animals.

It is a freeze-dried product that requires re-suspension with a sterile solvent using syringes and capped containers, and therefore spillage risks of large amounts of product are considered negligible.

Risks are essentially associated with injuries from damaged primary package or with accidental self-injection of the product in the user's hand. However, such risk does not differ from risks associated with the use of other injectable products to the animals. The amount of product that might be accidentally injected is expected to be limited (≤ 2 ml) since the pain associated with injection will trigger a withdrawal reflex.

Therefore, the risk is limited to the person injecting the product to the animals.

As the product contains no ingredients that are toxic or infectious to humans, there is a minimal risk to any person either handling the vaccine or inadvertently injected with the vaccine.

In summary, the likelihood, the consequences and the level of risk of human exposure is considered to be very low; therefore, no specific risk management is required. The measures to be taken are those already in place for the use of all injectable veterinary medicinal products administered to pigs. No specific warning needs to be provided to the person administering the product to the animals, nor to the persons in direct contact with the animal.

Study of residues

No residue study has been carried out as this is not required.

MRLs

The active substance being a principle of biological origin intended to produce active immunity is not within the scope of Regulation (EC) No 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin.

The excipients are either allowed substances for which table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicates that no maximum residues limits (MRLs) are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product or are in the food additive list.

Some constituents of the dilution medium (UltraCULTURE^{TM}) are not covered by Table 1 of Commission Regulation (EU) No 37/2010 and the scope of Council Regulation 470/2009. Three constituents of the medium were not included within MRL classification. Following assessment of data provided, CVMP were satisfied that these substances are considered not pharmacologically active at the dose used.

Withdrawal period

The requested withdrawal period of zero days is considered acceptable.

Interactions

As no safety data are available on the use of Suvaxyn PRRS MLV with any other product a corresponding warning has been included in the SPC.

Field studies

The field safety studies followed the GCP requirements as laid down in VICH GL9. The batches used in the field safety and efficacy studies were formulated to contain an intermediate virus titre of $10^{4.8}$ CCID50 per dose of 2 ml. The field studies have been conducted in 1-day-old IM and IN vaccinated piglets in United Kingdom and Germany and in 2-week-old IM vaccinated piglets in United Kingdom and the Netherlands. The piglets belonged to farms with a history of PRRS virus infections; the mother sows/gilts had PRRSV-specific antibodies. Control groups received an equivalent volume of saline. The primary safety criteria were the summary of clinical observations, rectal temperatures, injection site reactions and body weights.

Overall, the results confirmed the outcome of the laboratory studies performed in piglets.

Further field trials were performed in sows pre-breeding, in the first and second half of gestation (UK, DE). Even though the primary safety criteria encompassed the summary of clinical observations, rectal

temperatures, injection site reactions and body weights only, the reproductive performance was also assessed from the safety aspect. The results of the field studies in sows correspond per se to the findings of the laboratory studies.

Environmental risk assessment

An assessment of the potential risk to the environment has been conducted in accordance with the Note for guidance on environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95).

Suvaxyn PRRS MLV is a live attenuated vaccine for pigs to be administered via the IM route.

There is a negligible risk for reversion to virulence of the vaccine strain over in vivo passages in pigs and therefore the spreading to in-contact pigs does not pose a safety risk. The only safety risk relates to the potential spreading of the vaccine strain to seronegative pregnant sows in the second half of gestation as the vaccine exposure of this subcategory of animals may have a negative impact on reproductive performances. The introduction of PRRS vaccine virus into areas where the virus is not yet present should be avoided.

Considerations for the environmental risk assessment

Assessment of risk:

Hazard identification

- Vaccine organism

The vaccine organism is live attenuated PRRS virus. The potential hazard would be the shedding or spread of the live attenuated vaccine to any unvaccinated animals or non-target species. Swine (domestic and feral) are the natural hosts of PRRSV, although it has been described that some avian species, mallard ducks in particular, are susceptible to PRRSV. The virus is not considered as a zoonotic agent. The virus is produced on the recombinant cell line BHK21-C12-26. However, the physical vaccine is not to be considered as a genetically modified organism (GMO) as the probability for viable/living cells to survive the vaccine production process (and therefore be present in the finished product) is very low and current data confirm this assumption.

- Excipients

Excipients of the freeze-dried vaccine are dextran 40, casein hydrolysate, lactose monohydrate, sorbitol 70% solution, sodium hydroxide, water for injections and dilution medium (UltraCULTURE™).

Excipients of the solvent are sodium chloride and water for injections.

None of these substances are considered to present a potential hazard to the environment.

Assessment of likelihood:

The vaccine is to be administered individually to pigs by the IM route in a 2 ml dose. The lyophilisate is contained in glass bottles, which are sealed with a rubber stopper and an aluminium cap. The HDPE bottle of solvent is resistant to impact breakage and the seal is able to retain the stopper should the bottle be subjected to moderate impact or pressure. It is unlikely that there will be an accidental spillage even if the bottle is dropped or squeezed. After reconstitution of the lyophilisate in the solvent, the maximal volume of vaccine that could be released into the environment is 250 ml (125 doses of the vaccine) in the event of catastrophic bottle failure.

The data provided in Part 3 Safety shows that the vaccine strain is shed by vaccinated animals;

therefore the risk of spreading to the environment and/or target or non-target species exists.

Assessment of the consequence of a hazard occurring:

In the event of bottle failure, there would be a maximum of 250 ml of reconstituted vaccine present in the environment. The virus is sensitive to temperature and the higher the temperature the more rapidly infectivity is lost; even at 4 °C 90% of infectivity is lost within one week, although low titres of infectious virus may be detected for as long as 28 days. Infectivity is rapidly lost at pH levels below 6 and greater than 7.5. Humid conditions are required for persistence in the environment as the virus is rapidly inactivated by desiccation.

As regards shedding or spreading to unvaccinated animals of the target species, the impact would be limited, as detailed in Parts 3 Safety, Special requirements for live vaccines. There is a negligible risk for reversion to virulence of the vaccine strain over in vivo passages in pigs and therefore the spreading to in-contact pigs does not pose a safety risk in that regard. The only safety risk relates to the potential spreading of the vaccine strain to seronegative pregnant sows in the second half of gestation as the vaccine exposure of this subcategory of animals may have a negative impact on reproductive performances (see Part 3 Safety, Examination of reproductive performance.). It is therefore essential that the introduction of PRRS vaccine virus into areas where the virus is not yet present should be avoided.

In the event of shed or spread the impact on the environment would be limited as wild PRRS virus has been shown to have limited replicative ability in avian species only and, in those species, it does not cause any adverse effects or disease (Zimmerman *et al*, 1997). Also, the vaccine strain has clearly been shown to be attenuated, which further mitigates any risk.

Assessment of level of risk:

The conclusion based on the above analysis is that the level of risk to the environment is negligible.

Based on the data provided the ERA can stop at Phase I. Suvaxyn PRRS MLV is not expected to pose a risk for the environment when used according to the SPC.

Environmental risk assessment for products containing or consisting of genetically modified organisms

The vaccine is not considered as a GMO as the probability for viable/living genetically modified BHK21-C12-26 cells to survive the vaccine production process (and therefore be present in the finished product) is very low. Current data confirm this assumption.

Overall conclusions on the safety documentation

In general, the safety profile of the product is regarded as satisfactory when administered in compliance with the SPC. The SPC wording has been revised as regards potential adverse reactions such as the maximum individual increase of temperature after vaccination and more detailed description of the local reactions. As the vaccine administration during lactation has not been established, its use during lactation is excluded. Additionally, the use in herds where the prevalence of European PRRS virus has not been established is contraindicated.

A user safety assessment in line with the relevant guidance has been presented. The user safety for this product is considered acceptable when used as recommended.

The withdrawal period is set at zero days.

Based on the data provided the ERA can stop at phase I. Suvaxyn PRRS MLV is not expected to pose a

risk to the environment when used according to the SPC.

Part 4 – Efficacy

Suvaxyn PRRS MLV, a PRRSV modified live vaccine, is intended for the use in pigs for fattening from 1 day of age, gilts and sows.

The indications are:

For active immunisation of clinically healthy pigs from 1 day of age in PRRSV contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRSV (genotype 1).

Onset of immunity (OOI): 28 days after vaccination.

Fattening pigs:

DOI: 26 weeks after vaccination.

In addition, vaccination of seronegative 1-day-old piglets was demonstrated to significantly reduce lung lesions against challenge administered at 26 weeks post vaccination. Vaccination of seronegative 2-week-old piglets was demonstrated to significantly reduce lung lesions and oral shedding against challenge administered at 28 days and at 16 weeks post vaccination.

Sows and gilts:

DOI: 16 weeks after vaccination.

In addition, pre-pregnancy vaccination of clinically healthy sows and gilts, either seropositive or seronegative, was demonstrated to reduce the transplacental infection caused by PRRSV during the third trimester of pregnancy, and to reduce the associated negative impact on reproductive performance (reduction of the occurrence of stillbirths, of piglet viraemia at birth and at weaning, of lung lesions and of viral load in lungs in piglets at weaning).

The proposed administration route and amounts to be administered are:

Dosage:

IM injection: 2 ml in the neck.

Vaccination schedule:

Pigs for fattening:

A single dose of 2 ml is given to pigs from 1 day of age onwards, intramuscularly.

Gilts and sows:

A single dose of 2 ml is given to gilts prior to introduction into the sow herd, intramuscularly, approximately 4 weeks prior to breeding. A single booster dose is given every 4 months. Newly introduced PRRSV-naïve animals (e.g. replacement gilts from PRRSV-negative herds) should be vaccinated prior to pregnancy.

Introduction and general requirements

Suvaxyn PRRS MLV is a modified live PRRS vaccine. The Belgian PRRSV strain 96V198 was selected as vaccine strain, because it belongs to genotype 1 and to subtype 1, which is the predominant subtype found in Western Europe.

General guidance on the efficacy testing of veterinary vaccines is provided by Directive 2001/82/EC, Annex I, Title II (as amended 2004/28 and 2009/9). Additional guidance is provided in various relevant EU Directives, Guidelines and Ph. Eur. monographs.

Laboratory trials

In total 11 laboratory studies have been conducted to evaluate the efficacy of Suvaxyn PRRS MLV:

- One study for the assessment of the minimum immunising dose.
- One study for the evaluation of the OOI and the influence of MDA.
- One additional study for the assessment of the OOI.
- Two additional studies to evaluate the influence of MDA.
- Six studies for the assessment of the DOI.

As challenge virus strain the genotype 1 PRRSV isolate Olot/91 has been used. It shares 90.4% nucleotide identity with the vaccine strain 96V198, and 9.4% of the complete genome is divergent. The original virus strain has been isolated in Spain in 1991 from a late-term abortion in sows and published by Plana *et al.,* 1992. The isolate was passaged four times on porcine pulmonary macrophages (PAMs) and this virus was designated PRRSV isolate Olot/91. Ultra-deep next generation sequencing of this strain was published by Lu *et al., 2014* (GenBank accession number KF2031332).

In general, the methods for statistical evaluation are considered acceptable. Previous concerns regarding the effect estimates for the pairwise differences with 95% confidence intervals and p-values were justified. As well as previous concerns regarding the multiplicity adjustment for multiple comparisons of different treatment arms were answered appropriate by using Fisher's Least Significance Difference (LSD) method which in case of statistical significance is followed by pairwise comparison "at the pre-designated alpha level".

Dose determination

One non-GLP immunogenicity study was performed to establish the minimum immunising dose (MID) of Suvaxyn PRRS MLV. 2-week-old seronegative piglets were immunised intramuscularly with three different antigen quantities and received a respiratory challenge with an EU PRRSV isolate 4 weeks later. Upon request previous concerns regarding the statistical evaluation (effect estimates for the pairwise differences, multiplicity adjustment for multiple comparisons) were satisfactorily answered. It is noted that the MID was not evaluated in 1-day-old piglets, the most sensitive target species but other laboratory studies have been performed in 1-day-old piglets with a back-titrated dose of $10^{2.1}$ to $10^{2.2}$ CCID50 per dose via IN and IM route. In summary the results provided support an MID of 2.2 log10 CCID50.

Onset of immunity

To evaluate the OOI of Suvaxyn PRRS MLV the applicant conducted two laboratory studies in piglets. In both studies a challenge infection with an EU PRRSV isolate was administered intranasally 4 weeks after vaccination.

A study was performed to evaluate both, the OOI in seronegative 1-day-old piglets and the influence of MDA in 1-day-old seropositive piglets (see below for MDA). The study was carried out following the guidelines for the Evaluation of efficacy of veterinary vaccines and immunosera, 04/2008:50207 and the Reflection paper on the demonstration of a possible impact of MDA on vaccine efficacy in young

animals (EMA/CVMP/IWP/439467/2007). Seronegative 1-day-old piglets were immunised by IM or IN route with a dose of $10^{2.5}$ CCID50 (target titre, only in this study the vaccine was not re-titrated).

This study supports an OOI of 28 days.

The claim "For active immunisation of clinically healthy pigs in a PRRSV contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRSV (genotype 1)" is supported by the data.

The specific claim "Vaccination of seronegative 2-week-old piglets was demonstrated to significantly reduce lung lesions and oral shedding against challenge administered at 28 days post vaccination" regarding the IM administration is supported by the study results.

The previous proposed specific claim "For active immunisation of clinically healthy seronegative fattening pigs from 1 day of age, to reduce viremia and nasal shedding caused by infection with PRRS virus" regarding the IN administration was supported by the study results. But, as the IN immunisation of 1-day-old piglets in the presence of MDA was found to be not efficacious against respiratory challenge with EU PRRSV isolate the applicant decided to remove the IN route from the SPC and product information.

The non-GLP study was performed in seronegative 2-week-old piglets vaccinated intramuscularly with a dose of $10^{2.2}$ CCID50. This study supports an OOI of 28 days in 2-week-old seronegative piglets. Vaccinated piglets showed reduced viral loads in serum, nasal secretions on day 7 post-challenge and oral secretions on day 4 and 9 post-challenge. Additionally, lung lesions were reduced and rectal temperatures were lower at the day of challenge and 7 days post-challenge. The results of the study support the specific claim "Vaccination of seronegative 2-week-old piglets was demonstrated to significantly reduce lung lesions and oral shedding against challenge administered at 28 days and at 16 weeks post vaccination".

Duration of immunity

To evaluate the DOI of Suvaxyn PRRS MLV the applicant performed six laboratory studies. Four studies were performed in piglets and two studies in gilts. All studies were designed based on the recommendations of the Ph. Eur. monograph 50207 (Evaluation of efficacy of veterinary vaccines and immunosera).

Two studies were performed in 1-day-old seronegative piglets either vaccinated intramuscularly or intranasally with one dose of $10^{2.2}$ CCID50 (minimum dose). In one study animals were challenged 26 weeks post-vaccination and in a second study animals were challenged 18 weeks post-vaccination. Both studies support a DOI of 26 and 18 weeks, respectively. Both studies revealed significantly lower viral loads in serum and nasal secretions and a reduction in lung lesions in vaccinated animals after challenge infection compared to control animals. Additionally, vaccination did reduce lung lesions in vaccinated animals compared to control animals. This supports the specific claim for IM immunisation "Vaccination of seronegative 1-day-old piglets was demonstrated to significantly reduce lung lesions against challenge administered at 26 weeks post vaccination". As the vaccine is recommended to be used in a PRRSV contaminated environment and as it is highly unlikely that seronegative piglets are born under such circumstances the applicant decided to remove the IN immunisation as an administration route from the SPC and product information.

Two studies were conducted in 2-week-old seronegative piglets intramuscularly vaccinated with one dose of $10^{2.35}$ CCID50. In one study challenge infection was performed 26 weeks post-vaccination and in a second study animals were challenged 16 weeks post-vaccination. Both studies support a DOI of 26 weeks and 16 weeks, respectively. Both studies showed significantly lower viral titres in serum and

nasal secretions in vaccinated animals after challenge infection compared to control animals. After 16 weeks vaccinated animals showed also lower viral loads in oral secretions and reduced lung lesions induced by challenge infection compared to unvaccinated controls supporting the specific claim "Vaccination of seronegative 2-week-old piglets was demonstrated to significantly reduce lung lesions and oral shedding against challenge administered at 28 days and at 16 weeks post vaccination".

A study was performed in adult female pigs vaccinated 4 (to 11) weeks before mating and a subsequent challenge infection at day 81 to 89 of pregnancy to evaluate the DOI of 16 weeks induced by a single vaccination with a dose of $10^{2.0}$ CCID50. The results of this study support a DOI of 16 weeks in gilts vaccinated approximately 4 weeks before mating. Vaccinated gilts showed significantly lower viral titres in serum and nasal swabs. The number of stillborn was reduced in vaccinated gilts as well as a reduction transplacental infection as shown by reduced viraemia in piglets at birth and weaning, reduced viral loads in lungs and reduced lung lesions in piglets at weaning.

A study evaluated the efficacy of a booster vaccination with Suvaxyn PRRS MLV in gilts against a challenge with an EU PRRSV isolate during the 2nd half of pregnancy. Gilts were vaccinated twice at 4 months interval. Mating was performed 4 to 5 weeks after the second vaccination. Animals were challenged at day 79 to 91 of pregnancy, corresponding to approximately 4 months after the second vaccination and approximately 8 months after the first vaccination. The results support the efficacy of a booster vaccination applied 4 months after the primary vaccination against respiratory infection with PRRSV at the 2nd half of pregnancy. Vaccinated gilts had lower viral titres in serum, nasal and oral secretions. Additionally, vaccinated animals showed an increase in reproductive performance as well as a reduction in transplacental infections as shown by reduced viraemia in piglets at birth and weaning, reduced viral loads in lungs of piglets and lung lesions at weaning.

The specific claim for sows and gilts as stated "to reduce the associated negative impact on reproductive performance (reduction of the occurrence of stillborn, of piglet viraemia at birth and at weaning, of lung lesions and of viral load in lungs in piglets at weaning)" and a DOI of 16 weeks is supported by both studies performed in gilts and sows. For fattening pigs from 1 day of age a DOI of 26 weeks is supported by the studies provided and summarised above.

Maternally derived antibodies (MDA)

To evaluate the influence of MDA on the efficacy of Suvaxyn PRRS MLV, three laboratory studies in seropositive piglets were performed. These three studies were designed and conducted based on the Reflection paper on the demonstration of a possible impact of MDA on vaccine efficacy in young animals (EMA/CVMP/IWP/439467/2007) and Ph. Eur. monograph 50207 (Evaluation of the efficacy of veterinary vaccines and immunosera).

A general concern was raised concerning the design of the studies which evaluated the influence of MDA. The Reflection paper (EMA/CVMP/IWP/439467/2007) recommends to use three groups of animals at the minimum age recommended for vaccination, one group containing animals without MDA (group 1) and two groups containing animals with representative MDA titres (group 2 and 3). But the applicant stated that a MDA negative group could not be statistically compared with the MDA positive group due to p-values which could not be generated. As other studies have been performed in seronegative piglets (OOI, DOI) selected parameters (e.g. viraemia, lung lesions, etc.) were compared between the groups of these studies for a negative impact of MDA. This rationale is considered acceptable as the indication for Suvaxyn PRRS MLV only states "to reduce viraemia and nasal shedding" and this was shown in seronegative as well as in seropositive piglets after challenge infection. Other specific claims have only been observed in seronegative piglets which are well reflected in the product information.

One study was performed to evaluate both, the OOI in seronegative 1-day-old piglets (see above for OOI) and the influence of MDA in 1-day-old seropositive piglets. Vaccination of piglets of one day of age was applied by either the IM or IN route with a dose of $10^{2.5}$ CCID50. Four weeks later the challenge infection was performed intranasally with an EU PRRSV isolate. No viraemia was observed in control piglets after challenge. It is concluded that the levels of MDA at challenge were too high and therefore it was not possible to evaluate the effect of vaccination. The study was considered not valid.

A second study was also performed in 1-day-old piglets either vaccinated intramuscularly or intranasally with a dose of $10^{2.1}$ CCID50. Challenge infection was performed at 67 days post-vaccination, when MDA tested by serum neutralisation assay became undetectable in non-vaccinated piglets.

After challenge infection reduced viral loads in serum, nasal and oral secretions were observed as well as lower rectal temperatures (day 3 post challenge) in IM vaccinated piglets compared to non-vaccinated controls. These results are similar to that obtained in 1-day-old seronegative piglets (C/394/13, OOI-study) and therefore are in compliance with the Reflection paper (EMA/CVMP/IWP/439467/2007) which states that “it should be shown that the efficacy of the vaccine in animals vaccinated in the presence of MDA is, notwithstanding normal biological variation, similar to that obtained in animals of the same age but vaccinated in the absence of MDA”.

IN immunisation of 1-day-old piglets in the presence of MDAs was found to be not efficacious against respiratory challenge with EU PRRSV isolate. Therefore the applicant decided to remove the IN route from the SPC and product information. A GLP-certified study was performed in seropositive 2-week-old piglets which were vaccinated intramuscularly with one dose of $10^{2.2}$ CCID50. Challenge infection was performed on day 63 post-vaccination when MDA, tested using a serum neutralisation assay, became undetectable in control animals. The results support the efficacy of the vaccine applied intramuscularly into 2-week-old piglets. The vaccinated piglets showed reduced viral loads in serum and nasal secretions, as well as lower rectal temperatures on day 5 and 7 post-vaccination. The applicant highlights that results are similar to the OOI study performed in 2-weeks old piglets which additionally could show a reduction of viral loads in oral secretions and a decrease in lung scoring after vaccination. For IM administration the claim “For active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus” is supported by the data obtained in seropositive and seronegative 2-week-old piglets.

Prevention of transplacental transmission

The evaluation of the prevention of transplacental transmission was assessed in two DOI-studies (see above). Both studies did only support a reduction of transplacental infection by vaccination with Suvaxyn PRRS MLV. Briefly, a single vaccination of gilts 4 weeks before mating in the first study showed reduced transplacental infection as piglets had lower viral titres in serum at birth and at weaning. Additionally, lower viral titres in bronchoalveolar lavages and lung exudates as well as reduced lungs with lesions were observed in piglets at weaning compared to piglets of unvaccinated controls. In the second study gilts were vaccinated twice at a 4-months interval and challenged at day 79–91 of pregnancy. Results also showed a reduction in transplacental infection shown by lower viral titres in serum of piglets at birth and weaning. At weaning viral titres in bronchoalveolar lavages were reduced as well as lung lesions in piglets at weaning compared to piglets of unvaccinated controls.

Because the data provided do not support prevention of transplacental infection the claim for sows and gilts was changed as follows: “pre-pregnancy vaccination of clinically healthy sows and gilts, either seropositive or seronegative, was demonstrated to reduce the transplacental infection caused by PRRS virus during the third trimester of pregnancy”.

Field trials

Six (6) field studies performed in UK, Germany and the Netherlands were conducted under field condition. The studies were done according to guidance EMEA/C/825/99 (Field trials with veterinary vaccines) and VICH GL9 (GCP). All animals were originated from a farm with history of disease caused by PRRSV.

The first study (United Kingdom) was performed in 358 1-day-old piglets vaccinated either intramuscularly or intranasally with a dose of $10^{4.8}$ CCID50. As no field virus exposure was detected in control animals the study did not allow an assessment concerning efficacy of the vaccination in the field.

The second study (Germany) was performed in 406 1-day-old piglets either vaccinated intramuscularly or intranasally with a dose of $10^{4.8}$ CCID50. Two peaks of viraemia were observed in control animals. The first peak was observed at day 14 and was concluded to be probably induced by the vaccine strain. The second peak on day 83–84 post-vaccination was concluded to be a mixture of spreading of the vaccine strain with the circulation of a wild type virus. The results show that vaccine virus may spread to unvaccinated control up to day 84 post-vaccination. Induction of antibody response after vaccination was observed in vaccinated animals. Comparison of back transformed mean percentages of days viraemic were not biologically different between control and vaccinated groups and therefore no conclusion on the efficacy of the vaccine under field conditions could be drawn.

The third study (United Kingdom) was performed in 200 2-week-old piglets which were vaccinated intramuscularly with a dose of $10^{4.8}$ $CCID_{50}$. Also in this study a transient viraemia was observed at day 68–69 post-vaccination. The percentage of animals which were ever viraemic during the whole study was 20.8% in the vaccinated group and 66.7% in the control group. No differences were observed in lung lesions at slaughter between groups. Therefore no conclusion can be drawn from the results of this study on the efficacy of the vaccine in the field.

The forth study (United Kingdom) and fifths study (Germany) were performed in pigs of breeding age which were either non-pregnant or at different stages of pregnancy and allocated to six treatment groups. Groups T01 and T02 were non-pregnant, group T03 and T04 were in the first half of pregnancy and T05 and T06 were in the second half of pregnancy at vaccination. Group T01, T03 and T05 served as controls and were vaccinated intramuscularly with a competitor product (Porcilis Ery or Porcilis PRRS). Groups T02, T04 and T06 were vaccinated intramuscularly with Suvaxyn PRRS MLV. In both studies blood sampling was done on 25% of pigs of each treatment group, a defined safety/observation group. The reproductive performance was evaluated for all pigs. No differences were observed in reproductive performance and serology. No viraemia was observed during the study. Therefore no conclusion can be drawn on the efficacy of Suvaxyn PRRS MLV in gilts either non-pregnant or at different stages of pregnancy at vaccination under field conditions.

The sixth study (The Netherlands) was performed in 201 2-week-old piglets which were vaccinated intramuscularly with a dose of $10^{4.8}$ $CCID_{50}$. A transient viraemia was observed on day 49 in 26.1% of the vaccinated and 91.7% of the control animals indicating a field virus exposure. No animal was viraemic at the end of the study. As only mild lung lesions were observed in 16.7% of the control animals and 0% of the vaccinated animals and all other animals did not have any lung lesions, also this study is considered as informative only.

Overall conclusion on efficacy

Suvaxyn PRRS MLV is intended to be used in pigs for fattening from one day of age, gilts and sows in a PRRS virus contaminated environment. The applicant presented several studies to support the

minimum infectious dose, OOI, the DOI for all target species and routes of administration.

The minimum immunising dose is $10^{2.2}$ CCID50/2 ml.

Regarding the use of Suvaxyn PRRS MLV in 1-day-old piglets a justification for the use of the volume of 2 ml applied intramuscularly was provided which is considered acceptable.

Evidence was provided that a single immunisation is efficacious in 1-day-old and 2-week-old piglets after IM immunisation. Efficacy of Suvaxyn PRRS MLV has been shown to reduce viraemia and nasal shedding even in the presence of MDA. This feature is a great advantage of a vaccine intended to be applied to piglets with MDA in a PRRS virus contaminated environment as established through reliable diagnostic methods.

Results of the studies also support the efficacy of a single immunisation applied to gilts 4 weeks before mating. Vaccination reduces viral load in serum and nasal secretions and the number of stillborn in vaccinated sows. Furthermore, transplacental transmission is reduced because piglets born from vaccinated sows did show reduced viraemia at birth and weaning, as well as reduces viral loads in lungs and lung lesion at weaning compared to control animals. Booster vaccination of sows after 4 months did reveal similar results. The reproductive performance of a revaccination additionally showed significant higher numbers of born alive and born healthy piglets as well as a higher number of weaned piglets.

In conclusion, for IM administration the following indications are supported by the data provided: For active immunisation of clinically healthy pigs in PRRS virus contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1). The OOI is 28 days after vaccination.

For fattening pigs vaccinated from 1 day of age; DOI of 26 weeks was confirmed. Vaccination of seronegative 1-day-old piglets significantly reduces lung lesions after challenge administered at 26 weeks post vaccination. Vaccination of seronegative 2-week-old piglets significantly reduces lung lesions and oral shedding after challenge administered at 28 days and at 16 weeks post vaccination.

For sows and gilts; DOI of 16 weeks was demonstrated when vaccinated intramuscularly approximately 4 weeks prior to breeding.

Vaccination of clinically healthy sows and gilts, either seropositive or seronegative prior pregnancy reduces the transplacental infection caused by PRRS virus during the third trimester of pregnancy, and reduces the associated negative impact on reproductive performance (reduction of the occurrence of stillbirths, of piglet viraemia at birth and at weaning, of lung lesions and of viral load in lungs in piglets at weaning).

Part 5 – Benefit-risk assessment

Introduction

Suvaxyn PRRS MLV is an immunological veterinary medicinal product that is developed by means of a biotechnological process

Suvaxyn PRRS MLV is a modified live vaccine containing porcine reproductive and respiratory syndrome (PRRS) virus, strain 96V198, as active component. It is presented as ‘lyophilisate and solvent for suspension for injection. The solvent (liquid fraction) contains sodium chloride and water for injections.

Suvaxyn PRRS MLV is intended be administered as a single IM injection (dose of 2 ml) to fattening pigs from 1 day of age. Specifically for breeding females a single dose of 2 ml is given intramuscularly to

gilts and sows prior to introduction into the sow herd approximately 4 weeks prior to breeding. A single booster dose is given every 4 months. Newly introduced PRRS virus-naïve animals should be vaccinated prior to pregnancy.

This vaccine is intended for active immunisation of clinically healthy pigs in a PRRS virus contaminated environment, to reduce viraemia and nasal shedding caused by infection with European strains of PRRS virus (genotype 1). The proposed OOI is 28 days after vaccination. A DOI of 26 weeks (pigs for fattening) or of 16 weeks for sows and gilts is supported.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The benefit of Suvaxyn PRRS MLV is its efficacy for the active immunisation of clinically healthy pigs in an environment contaminated with European strains of the PRRS virus (genotype 1), which was investigated in a large number of laboratory studies and field studies which were generally well-designed.

As demonstrated in conducted controlled clinical trials Suvaxyn PRRS MLV is of value in a prophylaxis of PRRS virus infections. The objective of the vaccine is to induce sufficient immunity to reduce viraemia and nasal shedding in pigs, either seropositive (including MDA positive) or seronegative pigs.

Specific claims concern the reduction of lung lesions in seronegative 1-day-old piglets (pigs for fattening) as well as the reduction of lung lesions and oral shedding in seronegative 2-week-old piglets.

For seronegative and seropositive gilts and sows only a reduction of transplacental infection during the 3rd trimester of pregnancy has been shown. In addition, the reduction of the negative impact on the reproductive performance including the reduction of stillborn, of viraemic piglets at birth and at weaning, of viral load in lungs in piglets at weaning and of lung lesions is demonstrated.

Additional benefits

Suvaxyn PRRS MLV increases the number of available vaccines (prophylaxis possibilities) for the active immunisation of pigs against infections with PRRSV.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use

Safety:

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

For the target species (pigs) there is a risk of a slight rise in temperature which lasts no longer than 4 days. Temporary swellings at the injection site may occur following vaccination. These swellings may

last for over 3 days. General adverse reactions like vomiting, tremors or depression resolves within few hours. The SPC wording is adequate to this matter.

The vaccine is contraindicated to be used in herds where European PRRS virus has not been detected, in boars producing semen and in seronegative pregnant sows in the 2nd half of gestation.

Even if reversion to virulence could generally be possible as the vaccine contains live attenuated virus which has replicative or integrative characteristics, at least no indication is given that after serial passages the vaccine virus reverted to virulence.

Risk for the user:

The user safety for the product is acceptable when used according to the SPC recommendations.

Risk for the environment:

The product is not expected to pose any risk to the environment when used as recommended.

However, care should be taken to avoid the introduction of the vaccine strain into an area where PRRS virus is not already present.

Unintended spread of vaccine strain can occur as it is a vaccine containing live attenuated virus and live organisms can be introduced into the environment. But no clinical signs were observed in pigs with lung lesions assuming sufficient attenuation of the PRRS vaccine strain.

As vaccinated pigs may excrete the vaccine strain for more than 16 weeks following vaccination and thus the vaccine strain can be spread to unvaccinated pigs via direct contact, via contaminated objects or also via the air, special precautions should always be taken to avoid spreading of the vaccine strain to unvaccinated animals such as seronegative pregnant sows in the second half of gestation that should remain free from PRRS virus.

Risk for the consumer:

The product is not expected to pose any risk to the consumer when used as recommended. 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

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animal and presents an acceptable risk for users, the environment and consumers, when used as recommended. Appropriate precautionary measures, including withdrawal period, have been included in the SPC and other product information.

Conclusion

Based on the data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Suvaxyn PRRS MLV is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the marketing authorisation for Suvaxyn PRRS MLV.