11 September 2014
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Porcilis PCV M Hyo (EMEA/V/C/003796/0000)

Common name: porcine circovirus and *Mycoplasma hyopneumoniae* 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 October 2013 the applicant Intervet International B.V. submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Porcilis PCV M Hyo in accordance with Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the CVMP on 13 June 2013 as the product is produced by means of a biotechnological process (Article 3(1) of Regulation (EC) No 726/2004). The rapporteur appointed is E. Werner and co-rapporteur K. Lehmann.

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

Each dose of 2 ml Porcilis PCV M Hyo contains two active substances: porcine circovirus type 2 ORF2 subunit antigen (PCV2) as at least 2828 AU (antigenic units as determined in the in vitro potency test, ELISA) and inactivated *Mycoplasma hyopneumoniae* (J strain) at least 2.69 RPU (relative potency unit defined against a reference vaccine). Each dose contains 0.268 ml light mineral oil and 2.0 mg aluminium (hydroxide) as adjuvant.

The proposed indication is for the active immunisation of finishing pigs to reduce viraemia, the PCV virus load in lungs and lymphoid tissues, the shedding of PCV2 and to reduce severity of lung lesions caused by *M. hyopneumoniae.* Additionally, the vaccine is also indicated to reduce daily weight loss associated with PCV2 and/or *M. hyopneumoniae* infection during the finishing period. The proposed target species is pigs (for fattening). The proposed route of administration is intramuscular.

The vaccine is presented in a cardboard box with 1 or 10 polyethylene terephthalate (PET) vials of 20 ml (10 doses), 50 ml (25 doses), 100 ml (50 doses), 200 ml (100 doses) or 500 ml (250 doses). The vials are closed with nitrile rubber stoppers and sealed with aluminium caps.

On 11 September 2014 the CVMP adopted an opinion and CVMP assessment report.

On 7 November 2014, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (DDPS) was provided. 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 event occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The manufacturing of active substances takes place at Burgwedel Biotech in Burgwedel (Germany) and at the Intervet International site in Boxmeer (The Netherlands). Batch release takes place in Boxmeer.

Valid manufacturing authorisations and GMP certificates for all sites were provided.

No further inspection of the active substance manufacturing sites, final product manufacturing sites and batch release sites is considered necessary.

Overall conclusions on administrative particulars

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

sites are in line with legal requirements.

Part 2 – Quality

Composition

Porcilis PCV M Hyo is an inactivated vaccine containing PCV2 ORF2 subunit antigen and whole cells of *Mycoplasma hyopneumoniae* (J strain, ATCC #25934). The antigens are adjuvanted with light mineral oil and aluminium hydroxide. No preservative is added. The other excipients are: sorbitan oleate (emulsifier), polysorbate 80 (emulsifier), ethanol 96% (stabiliser), glycerol (stabiliser), and physiological saline solution (diluent).

The product is an emulsion (oil-in-water) for injection.

Container

Porcilis PCV M Hyo is presented in PET vials containing 20 ml (10 doses), 50 ml (25 doses), 100 ml (50 doses), 200 ml (100 doses) or 500 ml (250 doses). The γ-irradiated PET vials are closed with autoclaved type I nitrile rubber stoppers. The vials are sealed with aluminium caps.

The containers and closures are in compliance with the pharmacopoeial requirements and their sterilisation is adequate.

Development pharmaceutics

Vaccines against *M. hyopneumoniae* and PCV2 are administered during the same time period in the life-cycle of pigs, justifying the initiative to develop a combined vaccine against these two pathogens in order to minimise the number of vaccinations.

The development of such a combined vaccine was started based upon an authorised vaccine from the same company containing inactivated whole cells of *M. hyopneumoniae* strain ATCC #25934 as active ingredient and a light mineral oil and aluminium hydroxide as adjuvant. This product is registered in the European Union (EU). Porcilis PCV M Hyo has the same composition as that authorised vaccine except for the PCV2 ORF2 antigen and thiomersal. The PCV2 ORF2 antigen is also authorised in the EU in another vaccine from the same company.

During the development of Porcilis PCV M Hyo, the production process and controls of both antigens and the blending of the final product were slightly modified compared to those described in the dossiers of the above mentioned monovalent vaccines. These modifications were adequately addressed and they are acceptable.

Method of manufacture

The component of *M. hyopneumoniae* is produced by culturing bacteria in liquid growth media (scaling up). The culture is inactivated by addition of binary ethylenimine (BEI) which afterwards is neutralised by addition of sodium thiosulfate. The inactivated harvest is concentrated by using ultrafiltration before the bulk is stored.

Spodoptera frugiperda cell line (Sf-21-CB) is used as the substrate to propagate the recombinant *Autographa californica* multiple nuclear polyhedrosis virus (recombinant baculovirus: BacPCV2-Orf2) expressing the PCV2 ORF2 antigen. The antigen solution, containing baculovirus (remnant of production), is inactivated by BEI. Excess BEI is neutralised by addition of sodium thiosulfate. The antigen harvest is clarified by centrifugation to separate the supernatant which contains the antigen before the bulk is

stored.

The final product is produced by mixing the aqueous phase (containing *M. hyopneumoniae* antigen, PCV2 antigen, aluminium hydroxide, ethanol 96%, 50% glycerol solution and physiological saline solution) with the oil phase (containing light mineral oil, sorbitan oleate and polysorbate 80). Subsequently, the mix is emulsified and filled into PET vials.

The production process is considered as standard manufacture for viral and bacterial vaccines. The production process is adequately described.

The validation of the production steps was provided and it was satisfactory.

Control of starting materials

Active substance

Specifications of active ingredients are defined and analytical methods are provided. Additional data are presented, particularly concerning the starting materials of biological origin (e.g. Sf-21-CB cells, BacPCV2-Orf2 virus, *M. hyopneumoniae*).

The approved shelf lives of the PCV2 ORF2 antigen and the *M. hyopneumoniae* antigen are sufficiently substantiated by appropriate data.

Excipients

Specifications of excipients and other starting materials (e.g. materials of biological and non-biological origin, media) are defined and analytical methods are provided.

Where applicable, the starting materials are in compliance with Ph. Eur. or other appropriate monographs. Certificates of analysis where provided and were satisfactory.

Valid EDQM certificates and/or certificates of analysis for substances of biological origin used during production were provided. Certificates of analysis of the starting materials of non-biological origin were provided and are satisfactory.

Details of in-house preparation of media were provided.

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

The starting materials of animal 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.3).

The overall TSE risk associated with this vaccine is considered negligible.

Control tests during production

The applicant presented in-process data for consecutive antigen bulks and batches.

During the manufacture of the PCV2 ORF2 subunit antigen the following tests are carried out: Number of cells infected, test for cell disruption, baculovirus titre determination, inactivation, residual sodium thiosulphate, antigen content and sterility.

During the production of the *M. hyopneumoniae* inactivated antigen the following tests are carried out: Mycoplasma ATP test, purity test of the inoculum and of the harvest, identity, inactivation, excess

thiosulphate, sterility and antigen content.

The filling volume is controlled during the manufacture of the finished product.

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

Control tests on the finished product

The applicant presented data for consecutive finished product batches.

The control on the finished product is performed either on the vaccine bulk or on the filled product and is carried out to assure the quality parameters. The following tests are performed: pH determination, potency and identity for PCV2 ORF2, potency and identity for *M. hyopneumoniae,* aluminium content, stability of the emulsion, viscosity, appearance and sterility (filled product only).

Test descriptions and limits of acceptance are presented. The control methods are satisfactorily validated or clarification is provided in order to confirm that the production and control processes generate consistent vaccine batches.

Stability

Stability studies include 8 final vaccine batches and encompass both the smallest and the largest presentation filled in PET vials. Statistical evaluation of all currently available stability data (at present from 6 batches) demonstrates stability of the final vaccine over a 27 months period. The shelf life of the *M. hyopneumoniae* antigen and of the PCV2 ORF2 antigen was demonstrated.

The results justify a shelf life of 24 months when the product is stored at 2 °C – 8 °C.

The transport stability at elevated temperatures and the in-use shelf life of 8 hours are substantiated by appropriate data.

Overall conclusions on quality

The production process, the control of the starting materials, the in-process controls and 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. Consecutive batches at development and production scale were provided in order to demonstrate batch-to-batch consistency.

The results of the stability studies showed that the vaccine is stable for up to 27 months. The results justify a shelf life of 24 months for the finished product.

The CVMP considers the analytical dossier as fully adequate.

Part 3 – Safety

Porcilis PCV M Hyo is a subunit vaccine containing the ORF2 capsid protein of PCV2 and inactivated whole cells of *M. hyopneumoniae* strain J (ATCC #25934) adjuvanted with aluminium hydroxide and a light mineral oil. The vaccine is intended for intramuscular immunisation of piglets from three weeks of age to reduce viraemia, virus load in lungs and lymphoid tissues as well as virus shedding caused by PCV2 infection, and severity of lung lesions caused by *M. hyopneumoniae* infections. The vaccine is also indicated to reduce daily weight loss associated with PCV2 and/or *M. hyopneumoniae* infection during the finishing period.

In total two laboratory safety studies, two field safety studies, and ten field efficacy studies, in which also

safety data were included, were provided. In the first study, vaccinations were performed in accordance with the proposed vaccination schedule and administration route i.e. a single intramuscular vaccination of a dose of 2 ml from 3 weeks of age. The batches used were blended with a fixed quantity of PCV2 ORF2. The quantity of *M. hyopneumoniae* varied between medium and maximum potency values. In the second study, the safety of 2 x 1 ml was also assessed in piglets from the age of 3 days with an interval of at least 18 days although only a single vaccination of elder piglets is foreseen as the primary vaccination course for Porcilis PCV M Hyo.

Laboratory tests

The laboratory trials have been conducted in accordance with good laboratory practice (GLP) requirements.

The safety of a single dose (2 ml) and a repeated administration (2 x 1 ml) was evaluated in the same study; the results are reported and discussed together.

The antigen content per dose is pointed to:

- PCV2 ORF2 subunit antigen ≥ 2,828 AU (antigenic units as determined in the in vitro potency test via ELISA),
- *M. hyopneumoniae*, inactivated ≥ 2.69 RPU [max. 6.29 RPU] (relative potency unit defined against a reference vaccine).

Safety of the administration of one dose

The safety of a single vaccination was evaluated in 24 *M. hyopneumoniae* seronegative piglets (12 vaccinated animals and 12 phosphate buffered saline (PBS)-controls) at the age of 19 days using a batch of medium *M. hyopneumoniae* potency and a fixed amount of PCV2 ORF2 antigen according to the outline of production. Prior to injection, the general health status of the animals was observed and the rectal temperature recorded. Doses of 1 x 2 ml of the vaccine and 1 x 2 ml PBS, respectively, were administered intramuscularly into the neck.

At four hours after vaccination one vaccinated piglet was less active and only the vaccinated animals developed an average increase of 1.1 °C body temperature which returned to normal levels 24 hours later. Neither the vaccinated animals nor the controls developed any local reactions at any time point. There were no macroscopic abnormalities at the injection site in any group.

On the basis of the above the vaccine was considered safe when given to three-week-old piglets. Only a slight transient increase in rectal temperature is to be expected.

Safety of one administration of an overdose

As an overdose safety testing is not required according to Ph. Eur. the design for the laboratory safety studies followed the single-dose vaccination scheme. No separate overdose study has been conducted. This is acceptable.

Safety of the repeated administration

Safety of repeated vaccinations (2 x 1 ml) were done in approximately three-day-old piglets at an interval of at least 18 days. In the same study a group was included that was vaccinated with the approved posology (i.e. 1 x 2 ml from 3 weeks of age).

The safety of the repeated administration of the vaccine was evaluated in 36 *M. hyopneumoniae* seronegative piglets using a batch of maximum *M. hyopneumoniae* potency and a fixed amount of PCV2 ORF2 antigen according to the outline of production. Prior to injection, the general health status of the animals was observed and the rectal temperature recorded. Twelve piglets were vaccinated with a single dose (1 x 2 ml) at the age of 19–21 days, and twelve piglets received a repeated administration (2 x 1 ml) at the age of 2–4 days and at 19–21 days. Twelve control piglets were injected twice with 1 ml PBS at the age of 2–4 days and at 19–21 days. All injections were given via the intramuscular route.

Neither the vaccinated animals nor the controls developed any abnormalities after injection at the age of 2–4 days. After the injection at the age of 19–21 days, the animals of all groups were found to be less active at 5 to 8 days post vaccination (DPV). This was considered to be caused by the post-weaning diarrhoea. At four hours after vaccination only a minor transient temperature increase occurred in the vaccinated animals lasting 1–2 days after vaccination. Neither the vaccinated animals nor the controls developed any local reactions at any time point. No macroscopic abnormalities at the injection site were found in any of the three groups.

Since the piglets did not show any notable signs of disease attributable to the vaccine except some reduced activity, and the average body temperature increase did not exceed 1.5 °C and no piglet showed a rise more than 2.0 °C, it is concluded that the vaccine complies with the Ph. Eur. requirements.

Examination of reproductive performance

Since the vaccine is not intended for use in pregnant animals, this section is not applicable.

Examination of immunological functions

No studies on the possible impact on the immunological functions were performed. Generally no adverse effects of inactivated vaccines of this kind on the immune system are known and are not to be expected. None of the components of the vaccine is known to have an immunosuppressive effect and there are no data suggesting a negative influence on the immune response of the vaccinated animal. Specific studies to evaluate an adverse influence on the immunological functions were not conducted. This is considered acceptable.

Special requirements for live vaccines

Porcilis PCV M Hyo contains a subunit antigen (PCV2 ORF2) and whole cells of inactivated *M. hyopneumoniae* as active ingredients. Therefore, this is not applicable.

Study of residues

The active substances being principles of biological origin intended to produce active immunity are not within the scope of Regulation (EC) No 470/2009.

The excipients (including adjuvants) listed in section 6.1 of the summary of product characteristics (SPC) are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this veterinary medicinal product.

The proposed withdrawal period of zero days is acceptable.

Interactions

No data concerning interactions with other veterinary medicines were provided and the respective standard warnings are stated in the SPC.

Field studies

All field trials were conducted according to the principles of good clinical practice (GCP). Two studies were provided to assess the safety in piglets under field conditions.

A first study investigated the safety of a single vaccination of piglets (1 x 2 ml) in a placebo controlled clinical study. In total, 172 piglets belonging to three farms (2 in The Netherlands and 1 in Germany) were included. At the end of the trial, 84 vaccinated animals and 85 controls were evaluated. A vaccine batch of medium *M. hyopneumoniae* potency and fixed PCV2 ORF2 content was used. The age of the animals ranged between 17 and 24 days. Vaccine and placebo control were administered intramuscularly into the neck.

The serological data indicated the normal decline of maternally derived antibodies and the absence of any field infection. Both vaccinated animals and controls belonging to one farm developed clinical observations (diarrhoea, apathy) that disappeared within 24 hours after vaccination. There was a significant increase of the rectal temperature in the vaccinated animals compared to the controls. Three piglets showed a transient increase slightly above 2 °C. Examinations of the injection site showed hardness, swelling, redness and warmth. The mean diameter was 0.34 cm (maximum 1 cm) in the vaccinated animals. The local reactions lasted 24 hours. There was no clinically relevant effect of vaccination on weight gain.

On the basis of the above the vaccine was considered safe when given to three-week-old piglets. Only a slight transient increase in rectal temperature is to be expected.

In the second study the safety of a repeated vaccination of piglets (2 x 1 ml) was investigated. In this placebo-controlled clinical study a total of 192 piglets at three farms (2 in The Netherlands and 1 in Hungary) were included. At the end of the trial, 89 vaccinated animals and 90 controls were evaluated. A vaccine batch of maximum *M. hyopneumoniae* potency and fixed PCV2 ORF2 content was used. The age of the animals ranged between 3 and 7 days. Vaccine and physiological saline solution (NaCl 0.9%) were administered intramuscularly into the neck at an interval of 18 days.

The serological data indicated the normal decline of maternally derived antibodies. *M. hyopneumoniae* seroconversion was observed in one farm until the end of the observation period (39 DPV); this is considered indicative for a *M. hyopneumoniae* infection. The incidence of piglets with abnormal general health after the first or second injection was not significantly different between the treatment groups. Within one to two days after vaccination, general health of the vaccinated had returned to normal. There was a significant increase of the rectal temperature in the vaccinated animals compared to the controls. The increase lasted for one day at the most. None of the piglets showed an increase more than 2 °C. There were very similar results on local reactions in the vaccine and control group. The injection site reactions were hardness and swelling of 0.1–2.0 cm in diameter in the vaccinated. The local reactions lasted from four hours up to one day and eleven (1 piglet) days, respectively. There was a statistically significant interaction between farm and daily weight gain during the nursery period. The significant lower weight gain in one farm (HU) in the vaccinated animals compared to the controls is considered to be caused by a concomitant disorder (diarrhoea).

This study confirmed the results of the other specific safety field trial described above that the vaccine was considered safe when given to three-week-old piglets.

Safety data were collected during ten (10) field studies conducted to evaluate the efficacy and safety of the product. The studies were carried out according to a controlled, randomised, and blinded design. Healthy three-week-old suckling piglets were allocated randomly, within litters, to one of two groups. Each group consisted of approximately 300 piglets. Porcilis PCV M Hyo (1 x 2 ml) was administered to pigs of the vaccine group, whereas the control group received sterile phosphate buffered saline. In three of the field trials groups from the age of 3–10 days were included that were vaccinated with Porcilis PCV M Hyo using the repeated vaccination (2 x 1 ml); physiological saline solution was administered to the controls.

The safety data collected in the ten field efficacy studies confirmed the conclusions of the specifically generated field safety studies. Using the recommended single vaccination schedule of 1 x 2 ml mild systemic reactions such as being less active, a tendency to lie down and/or minor signs of discomfort or transient local reactions might occur in individual cases and last in general one day after vaccination. Transient local reactions are in general small (maximum 2 cm) and disappear within 1 day after vaccination.

The adverse reactions are adequately reflected in section 4.6 of the SPC.

User safety

The applicant provided a user risk assessment compliant with the CVMP guideline for user safety for immunological veterinary products (EMEA/CVMP/IWP/54533/2006). Hazard identification and characterisation was adequately addressed. Potential risks were identified, and appropriate advice given in the relevant section of the SPC.

Porcilis PCV M Hyo is a vaccine that contains PCV2 ORF2 subunit antigen and BEI inactivated whole cells of *M. hyopneumoniae*. The vaccine contains as adjuvants aluminium hydroxide and light mineral oil and excipients sorbitan oleate, polysorbate 80, ethyl alcohol, glycerol and physiological saline solution.

Neither the baculovirus construct used for the production of the PCV2 ORF2 antigen nor *M. hyopneumoniae* J strain are zoonotic organisms being able to infect humans.

Only the presence of the adjuvant component light mineral oil may have consequences if self-injected.

The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC. Standard user safety advice warnings are included in the SPC.

Environmental risk assessment

An environmental risk assessment (ERA) in compliance with the CVMP guideline on the environmental risk assessment of immunological veterinary medicinal products (EMEA/CVMP/074/95) was provided.

A Phase I evaluation was provided.

Potential hazards for the environment such as incomplete baculovirus construct used for the production of PCV2 ORF2 antigen or spread of not completely inactivated *M. hyopneumoniae* were listed.

Since the product is used in piglets and administered intramuscularly, direct exposure to the environment does not occur. Any unused product or waste should nevertheless be disposed of by the appropriate channels. As the vaccine is inactivated, excretion of any of the components by vaccinated animals is not to be expected. In conclusion, the overall risk of the Porcilis PCV M Hyo vaccine for the environment is judged to be negligible.

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

Overall conclusions on the safety documentation

All safety trials (two laboratory safety studies and two field studies) were conducted with Porcilis PCV M Hyo and complied with the safety tests as described in the Ph. Eur. None of the animals developed notable signs of disease and no serious adverse reactions attributable to the vaccine were observed. The average body temperature increase for all animals did not exceed 1.5 °C and, in general, no animal showed a rise in body temperature greater than 2.0 °C except three piglets in a field study that developed a transient increase in rectal temperature just above 2.0 °C. Transient mild systemic and local reactions were observed lasting on average one day.

Taking into consideration the results of all laboratory and field studies, including safety data from ten field efficacy studies, a temperature increase just above the advised monograph criterion was evident in less than 1% of total observations. Since these pigs did not develop any other systemic reactions and their temperature returned to normal within one day, the vaccine should be considered to be safe for the use in three-week-old piglets.

None of the components of the vaccine is known to have an immunosuppressive effect and no negative impact on the immune system is to be expected.

The vaccination did not negatively impact the daily weight gain by the end of the nursery period.

The CVMP concluded that user safety for this product is acceptable when used as recommended in the SPC.

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

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

Part 4 – Efficacy

Introduction and general requirements

Porcilis PCV M Hyo is an inactivated adjuvanted vaccine containing PCV2 ORF2 and *M. hyopneumoniae* strain J (ATCC #25934) which is indicated for the immunisation of pigs from 3 weeks of age. Porcilis PCV M Hyo is used to reduce viraemia, virus load in lungs and lymphoid tissues, virus shedding caused by PCV2 ORF2 infection, and severity of lung lesions caused by *M. hyopneumoniae* infections and to reduce the loss of daily weight gain during the finishing period in face of infections with *M. hyopneumoniae* and/or PCV2 (as observed in field studies).

The product is a further development of an authorised vaccine against *M. hyopneumoniae* from the same company to which PCV2 antigen is added and contains the same *M. hyopneumoniae* strain and adjuvants. Porcilis PCV M Hyo is presented as emulsion for injection including as adjuvants aluminium hydroxide in combination with light mineral oil.

The applicant conducted 10 laboratory vaccination/challenge studies (dose finding, onset of immunity, duration of immunity) and 11 field studies to evaluate the efficacy of Porcilis PCV M Hyo.

In all studies except for one (onset of immunity, *M. hyopneumoniae*, 2 x 1 ml) the recommended application route (intramuscular) and vaccination schedule (1 x 2 ml) were used and an unvaccinated control group was included. In some studies a repeated administration (2 x 1 ml) was tested additionally in pigs from 3 days of age. Pigs of minimum recommended age (3 weeks) were used in all studies with the exception of the PCV2 dose-response study in which pigs were vaccinated at 5 weeks of age. The field trials have been conducted according to the principles of good clinical practice (GCP).

Laboratory trials

Establishment of a challenge model

Efficacy of both components of Porcilis PCV M Hyo was assessed by challenges with heterologous strains. Certificates for the challenge strains were provided.

M. hyopneumoniae

All *M. hyopneumoniae* challenges were performed using a Danish field isolate, *M. hyopneumoniae* strain 98.

PCV2

PCV2 challenges in 4 studies were performed using PCV2 strain I-12/11 or PCV2 strain Baker 02 isolated from farms in the Netherlands.

All animals were challenged with PCV2 intranasally.

The epidemiological relevance of the challenge strains used, the antigenic relationship between vaccine and challenge strains and the rationale for the use of different challenge strains against PCV2 were discussed. The strains chosen for challenge are considered representative of the strains circulating in Europe at present.

The challenge model is acceptable.

Determination of the vaccine dose

M. hyopneumoniae

The vaccine dose for *M. hyopneumoniae* is provided is determined using the same potency test as for the authorised vaccine that was used as basis for the development of Porcilis PCV M Hyo. The minimum protective dose for Porcilis PCV M Hyo was based on a minimum dose batch which has been proven to be efficacious in laboratory studies. Based upon this the minimum criterion for the batch potency test for *M. hyopneumoniae* was set at RP ≥ 2.69. The upper limit of 6.29 RPU was set based on a maximum dose batch tested in several laboratory studies.

PCV2

Porcilis PCV M Hyo is formulated to contain a fixed amount of PCV2 ORF 2 antigen of 2,500 AU (antigenic units)/ml. Further information was provided regarding the determination of the vaccine dose (100%). The 100% vaccine dose was proven to be efficacious and safe in several laboratory and field trials.

Onset of immunity

Onset of immunity has been demonstrated with challenge studies according to the relevant Ph. Eur. monograph 2448 for *M. hyopneumoniae* vaccine; no specific Ph. Eur. monograph for vaccines against PCV2 is available.

M. hyopneumoniae

The applicant submitted two relevant studies to evaluate the onset of immunity of the *M. hyopneumoniae* component of the vaccine using specific pathogen free piglets of minimum age (3 weeks), the recommended administration route (intramuscular injection) and the proposed vaccination schedule (1 x 2 ml).

In both studies one group of pigs was vaccinated and one group received no injection and served as control (the pigs were allocated randomly to the groups). All pigs were challenged at 7 weeks of age (4 weeks post-vaccination) with a *M. hyopneumoniae* strain 98 by intratracheal route.

In the first study the vaccine batch used was slightly above the originally set minimum *M. hyopneumoniae* potency. This is considered not to have an impact on the overall assessment as the applicant also performed the second study using a vaccine batch of minimum potency (most relevant study). The first study was regarded as supportive.

The serological data clearly showed that the pigs respond to the vaccination and to the challenge. A high number of pigs was tested seropositive at 6 weeks of age in the vaccinated groups but not in the control groups). After challenge all animals were tested seropositive except for two inconclusive animals in the control group of the second study.

The post-mortem examination revealed that the median lung lesion scores of the vaccinated groups were significantly lower compared to the control groups in the respective studies.

An onset of immunity for the *M. hyopneumoniae* component after single vaccination with Porcilis PCV M Hyo at 4 weeks after vaccination was supported by the results of the above studies.

PCV2

The applicant conducted two studies to establish the PCV2 onset of immunity. In both studies piglets of the minimum age of 3 weeks were vaccinated with a standard batch Porcilis PCV M Hyo using the proposed vaccination scheme. A non-vaccinated control group was included but obviously no blinding procedure was followed. 2 weeks after vaccination the animals were challenged intranasally. In the first study PCV2 strain I-12/11 of batch with lower titre was used and in the second study the same strain of batch with higher titre was used.

The results of the two studies demonstrate that piglets vaccinated at an age of 3 weeks develop a serological response and that the virus load and shedding of PCV2 are significantly reduced. Virus load in lymphoid tissues and lungs were significantly reduced also.

In conclusion, on the basis of the above an onset of immunity for the PCV2 component after single vaccination from 3 weeks of age with Porcilis PCV M Hyo at 2 weeks after vaccination can be supported.

The claims of "reduced viraemia and PCV2 virus load in lungs and lymphoid tissues and reduced virus shedding" was supported by the results obtained in laboratory studies.

Duration of immunity

Duration of immunity has been demonstrated with challenge studies according to the relevant Ph. Eur. monographs. There is no specific Ph. Eur. monograph for vaccines against PCV2.

M. hyopneumoniae

The applicant submitted two blinded studies to evaluate the duration of immunity of the *M. hyopneumoniae* component of the vaccine using specific pathogen free piglets of minimum age (3 weeks), the recommended administration route (intramuscular injection) and the proposed vaccination schedule (1 x 2 ml).

In both studies some pigs were vaccinated with vaccines of minimum potency or slightly above and one group received no injection and served as control (the pigs were allocated randomly to the groups). All pigs were challenged at 24 weeks of age (21 weeks post-vaccination) with *M. hyopneumoniae* strain 98 by intratracheal route.

The serological data clearly showed that the pigs respond to the vaccination and to the challenge. A high number of pigs was tested seropositive at 13 weeks of age in the vaccinated groups but not in the control groups (all negative except for two inconclusive in the second study). After challenge all animals were tested seropositive except for one negative animal in the control group of the second study.

The post-mortem examination revealed that the median lung lesion scores of the vaccinated groups were significantly lower compared to the control groups in the respective studies.

In conclusion duration of immunity of 21 weeks after vaccination for the *M. hyopneumoniae* component after single vaccination with Porcilis PCV M Hyo can be supported on the basis of the above.

PCV2

The applicant submitted 3 studies to demonstrate the duration of immunity (DOI) against PCV2 in piglets vaccinated at 3 weeks of age (1 study serological data only and 2 vaccination and challenge studies).

In the *M. hyopneumoniae* duration of immunity study (the second), sera from piglets were tested for antibodies against PCV2 and for PCV2 antigen at 23 and 27 weeks. The antibody titres from vaccinated animals were significantly higher than those from control animals (non-vaccinated). A PCV2 field infection could be demonstrated between weeks 23 and 27 in a few vaccinated and non-vaccinated animals.

In the vaccination and challenge studies piglets were vaccinated at the minimum recommended age and challenged intranasally 18 or 22 weeks later. A non-vaccinated control group was included in both studies.

Vaccinated animals had consistently higher antibody titres. The reduction of PCV2 virus load in serum (viraemia), lungs and lymphoid tissues and the reduction of virus shedding are supported by the results obtained in laboratory studies.

In conclusion, duration of immunity of Porcilis PCV M Hyo of 22 weeks in piglets vaccinated once at an age of 3 weeks can be supported on the basis of the above.

Influence of maternal antibody on the efficacy of the vaccine

No specific laboratory studies were conducted regarding the influence of maternal antibodies (MDAs) on the efficacy of the vaccine Porcilis PCV M Hyo. The influence of MDAs against the *M. hyopneumoniae* and the PCV2 component was assessed in the relevant field studies.

A thorough analysis of data generated in piglets with and without MDAs (*M. hyopneumoniae*) and different levels of MDAs (PCV2) was provided. Based on the data from all relevant field efficacy studies there is no indication that the presence of MDA interferes with the *M. hyopneumoniae* or PCV2 efficacy conferred by the vaccination.

A statistically significant reduction of the viral load in serum, organs (mesenteric and inguinal lymph nodes, tonsil and lung) and nasal and faecal swabs was observed in all studies designed to evaluate efficacy against PCV2 challenge when comparing vaccinated groups and the controls as well as the increase in seroconversion in the vaccinated animals. The reduction of the severity of the lung lesions caused by *M. hyopneumoniae* was also statistically significant in all studies designed to evaluate the efficacy against *M. hyopneumoniae* challenge.

The results generated in the laboratory studies clearly support the following efficacy claims:

- Reduction of viraemia.
- Reduction of viral load in lungs and lymphoid tissues.
- Reduction of virus shedding caused by PCV2 infection.

- Reduction of severity of lung lesions caused by *M. hyopneumoniae* infection.

Field trials

Eleven GCP-compliant field studies were performed using three Porcilis PCV M Hyo standard batches in different geographic regions of Europe in order to demonstrate efficacy of vaccination. Three of these trials evaluated a repeated vaccination schedule additionally to the proposed single vaccination scheme.

The field studies were performed in pigs with MDAs against the respective antigen. The farms were selected based on the infection history of PCV2 and *M. hyopneumoniae* as well as detection of PCV2 and *M. hyopneumoniae* induced lung lesions. In some selected farms herds routinely had been routinely vaccinated against PCV2 and/or *M. hyopneumoniae* until start of the study.

The studies were randomised and blinded using an appropriate number of commercial pigs. Healthy suckling piglets were allocated randomly, within litters, to one of two groups of each approx. 300 piglets. In each study, one group was vaccinated with Porcilis PCV M Hyo (1 x 2 ml) and one group (control) was injected with sterile buffered saline. In three studies mentioned above a third group was included that was vaccinated with Porcilis PCV M Hyo using the repeated vaccination scheme (2 x 1 ml). The study design itself is considered acceptable.

Out of 11 studies in total, 2 studies evaluated the efficacy of Porcilis PCV M Hyo vaccination against PCV2 field injections only, in 1 study the efficacy was evaluated against *M. hyopneumoniae* field infection only and in 7 studies the efficacy of Porcilis PCV M Hyo vaccination against both PCV2 infection and *M. hyopneumoniae* field infection were assessed. One study was designed to evaluate PCV2 serology in MDA positive pigs.

The following parameters were statistically evaluated in the field studies except in the one where only serology was tested:

- Primary parameters: Average daily weight gain (ADWG) during finishing period, PCV2 viral load in serum (except one study) and lung lesion score (except two studies).
- Secondary parameters: ADWG during whole study period, PCV2 shedding (nasal, except two studies), faecal (except one study), pleurisy score, mortality, morbidity, one study: PCV2 viral load in serum.

In addition some supportive parameters were checked without statistical evaluation: PCV2 antibody titre, PCV2 specific IgM and IgG titre, *M. hyopneumoniae* serology and co-infections.

The safety data gained in the field studies were evaluated in part 3 of this assessment report.

Significant reduction in PCV2 viraemia was observed in all respective field studies designed to evaluate efficacy against PCV2 field infections; reduction of viral shedding caused by PCV2 infection was observed in all but one study. Significant reduction of severity of lung lesions caused by *M. hyopneumoniae* infection was seen in 5 out of 8 field studies designed to evaluate efficacy against *M. hyopneumoniae*. These results support the findings in the laboratory studies.

The additional claim in section 4.2 of the SPC 'reduction of loss of daily weight gain associated with PCV2 and/or *Mycoplasma hyopneumoniae* infection' is based on the results from the field studies.

Concerning reduction of loss of daily weight gain, it could be shown that the vaccination has a positive effect on the ADWG during the finishing and the whole study period (up to +67 g/day and up to +34 g/day, respectively). This effect could be demonstrated in 9 out of 10 field studies, but only in five studies a statistical significance was detected for the entire vaccinated group compared to the controls. In three studies there was an effect of gender, production batch or farm on the ADWG during the finishing

period and/or during the complete study. In these studies the ADWG was statistically significantly increased only in a part of the sub-groups. Therefore, overall the ADWG parameters in these studies should be assessed as not significant.

In conclusion a statistically significant increase of the ADWG could be detected in 50% of the field studies. Bearing in mind the clear tendency to a higher ADWG also in the other studies except for one the CVMP concluded that the product was effective for a re-worded indication to reduce the loss of daily weight gain during the finishing period in face of infections with *Mycoplasma hyopneumoniae* and/or PCV2 (as observed in field studies).

Overall conclusion on efficacy

The efficacy claims were evaluated in several well designed and well-conducted laboratory and field efficacy studies.

The information regarding the challenge strains used in the laboratory studies was provided and the epidemiological relevance of the challenge strains used (including origin of strains), the antigenic relationship between vaccine and challenge strains and the rationale for the use of different challenge strains against PCV2 was discussed.

Onset of immunity was established against PCV2 infection at 2 weeks after vaccination and against *M. hyopneumoniae* infection at 4 weeks after vaccination.

Duration of immunity was established against PCV2 infection at 22 weeks after vaccination and against *M. hyopneumoniae* infection at 21 weeks after vaccination.

Regarding MDAs there is no hint that the presence of MDA interferes with the *M. hyopneumoniae* or PCV2 efficacy conferred by the vaccination.

The studies clearly support the claims specific for the PCV2 or *M. hyopneumoniae* component that were all evaluated in well conducted laboratory studies and supported by field study results: Reduction of viraemia, virus load in lungs and lymphoid tissues, virus shedding caused by PCV2 infection and reduction of severity of lung lesions caused *by Mycoplasma hyopneumoniae* infection. To reduce the loss of daily weight gain during the finishing period in face of infections with *Mycoplasma hyopneumoniae* and/or PCV2 (as observed in field studies).

Based on the laboratory and field studies it can be concluded that the minor differences between the efficacy profiles of the single vaccination and the repeated vaccination schedule do not justify the recommendation of the repeated vaccination schedule from an animal welfare or user convenience perspective. The vaccination scheme as recommended in section 4.9 of the SPC to administer a single dose of 2 ml in pigs starting at 3 weeks of age is supported by results of relevant studies and therefore considered acceptable.

Part 5 – Benefit-risk assessment

Introduction

Porcilis PCV M Hyo is an inactivated adjuvanted vaccine containing PCV2 and *M. hyopneumoniae* strain J (ATCC #25934) (inactivated), which is intended for the immunisation of pigs from 3 weeks of age. The vaccine is used to reduce viraemia, virus load in lungs and lymphoid tissues as well as virus shedding caused by PCV2 infection, and for the reduction of severity of lung lesions caused by *M. hyopneumoniae* infections and to reduce the loss of daily weight gain during the finishing period in face of infections with *M. hyopneumoniae* and/or PCV2 (as observed in field studies).

The product is a further development of an authorised vaccine against *M. hyopneumoniae* to which PCV2 antigen is added. This new product contains the same *M. hyopneumoniae* strain and adjuvants. Porcilis PCV M Hyo is presented as emulsion for injection including as adjuvants aluminium hydroxide in combination with light mineral oil.

Porcine circovirus diseases include primarily PMWS, but also a number of other disorders, e.g. porcine respiratory disease complex (PRDC), enteritis and reproductive disorders. PMWS in post-weaned pigs is characterised by progressive weight loss, respiratory signs, jaundice and a marked increase in mortality. PRDC is characterised by severe coughing and dyspnoea, growth retardation, and increased mortality. Subclinical PCV2 infections are also characterised by reduced weight gain. Almost all commercial pigs are subclinically infected with low levels of PCV2 without developing clinical signs of disease. PCV2 is transmitted by direct pig-to-pig contact or through airborne transmission.

Infection with *M. hyopneumoniae* is associated with respiratory disease ("enzootic pneumonia") and reduced productivity in pigs. Affected swine often have a chronic non-productive cough. Typical is a high morbidity: 30-80% of slaughtered swine show lesions typical for *M. pneumoniae* of swine. Usually the mortality is low unless secondary infections occur. *M. hyopneumoniae* is transmitted by direct contact with respiratory tract secretions from infected swine or through airborne transmission (less frequently). In many herds the pathogen is maintained permanently by transmission from sows to pigs.

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

Benefit assessment

Direct therapeutic benefit

Porcilis PCV M Hyo is a combination vaccine containing two well-known active substances.

Well conducted controlled clinical trials demonstrated that the product is efficacious in the reduction of PCV2 viraemia, reduction of virus load in lungs and lymphoid tissues, reduction of virus shedding caused by PCV2 infection, reduction of severity of lung lesions caused by *M. hyopneumoniae* infection and reduction of loss of daily weight gain during the finishing period in face of infections with *M. hyopneumoniae* and/or PCV2 (as observed in field studies).

The onset of immunity is:

- PCV2: 2 weeks after vaccination.
- *M. hyopneumoniae*: 4 weeks after vaccination.
- The duration of immunity is:
- PCV2: 22 weeks after vaccination.
- *M. hyopneumoniae*: 21 weeks after vaccination.

Additional benefits

Porcilis PCV M Hyo is given to pigs once, intramuscularly, from 3 weeks of age. This single vaccination scheme covering two important pathogens is easy to handle for the veterinary surgeon and of importance to animal welfare.

Porcilis PCV M Hyo is the first vaccine to combine PCV2 and *M. hyopneumoniae*, which is beneficial in order to minimise the number of vaccinations given to pigs regularly. The duration of immunity lasts for the whole fattening period when the pigs are most susceptible to infection.

An additional beneficial effect is seen on herd level. Overall, the pigs are in better condition after vaccination in case of infection with PCV2 and/or *M. hyopneumoniae*.

Prevention of infectious disease caused by *M. hyopneumoniae* reduces the need for antimicrobial treatment.

Risk assessment

Main potential risks:

Quality:

No potential serious risk is raised from the quality part. The formulation and manufacture of Porcilis PCV M Hyo is well described and specifications set will ensure that product of consistent quality will be produced.

For the target species*:*

The product is well tolerated by the target species when used as recommended.

Adverse reactions observed were transient increase of rectal temperature and reduced activity, tendency to lie down and slight discomfort; local reactions after vaccination were transient within one day and at maximum 2 cm in diameter. The vaccination did not negatively impact the daily weight gain until the end of the nursery period.

For the user*:*

The product does not pose an unacceptable risk to the user when used in accordance with the SPC.

For the environment*:*

The product is not expected to pose any risk to 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 consumer, and the environment 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.

Porcilis PCV M Hyo was shown to be efficacious for the active immunisation of pigs to reduce viraemia, virus load in lungs and lymphoid tissues, virus shedding caused by PCV2 infection, severity of lung lesions caused by *M. hyopneumoniae* infection and reduction of loss of average daily weight gain.

Porcilis PCV M Hyo is well tolerated by the target animals and presents a low risk for users, consumer and the environment. Appropriate warnings have been included in the SPC. The withdrawal period is set at zero days.

The formulation and manufacture of Porcilis PCV M Hyo is well described and specifications set will ensure that product of consistent quality will be produced.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete product information.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP concluded that the quality, safety and efficacy of Porcilis PCV M Hyo 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 recommends the granting of the marketing authorisation for Porcilis PCV M Hyo.