SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

Porcilis PCV is a biotechnology derived inactivated immunological veterinary medicinal product intended to be used for the active immunisation of pigs against Porcine Circovirus Disease (PCVD). First recognised in 1991 in Canada, Porcine Circovirus Type 2 (PCV2) is considered to be associated with a number of disease syndromes which have been collectively named PCVD. In particular, infection by PCV2 is nowadays recognised as the major risk factor in the establishment of the complex syndrome known as Post-weaning Multi-systemic Wasting Syndrome (PMWS) which affects principally piglets at the post-weaning and beginning of fattening stages. Porcilis PCV is administered via the intramuscular route in the neck in the area behind the ear to pigs from three days of age to reduce the virus load in blood and lymphoid tissues and to reduce weight loss associated with PCV2 infection occurring during the fattening period.

The vaccine antigen is the major capsid protein encoded by a specific gene (the Open Reading Frame 2, ORF2, gene) of Porcine Circovirus Type 2 (PCV2). This antigen is recognised to be highly immunogenic. The final product is an oil-in-water adjuvanted vaccine. Gentamicin is present as a remnant of production in the final product. No preservative is added as the product is recommended to be used within a short time period from the first opening of the vaccine vial.

2. QUALITY ASSESSMENT

Composition

Porcilis PCV is an emulsion for injection for pigs. Each dose of 2 ml contains as active substance porcine circovirus type 2 ORF2 subunit antigen to at least 4.5 $\log_2$ ELISA units, being the antibody titre obtained according to the *in vivo* potency test. Adjuvants are dl-alpha-tocopheryl acetate and light liquid paraffin and the excipients are polysorbate 80, simethicone and water for injection.

Container

The vaccine is filled in 20, 50, 100 or 200 and 500 ml capacity polyethylene terephtalate (PET) containers pre-sterilised by gamma irradiation. The containers are closed with a nitryl rubber stopper and sealed with a coded aluminium cap. Information on the quality standards for the containers and rubber closures were provided. Compliance with European Pharmacopoeia, where appropriate, was demonstrated.

II.A.3 Development Pharmaceutics

The development of this subunit vaccine was chosen based upon the scientific evidence that ORF2 is a major immunogenic protein. In addition, the high productivity of the baculovirus expression system was considered essential for the commercial production of an effective subunit vaccine. The active component of the vaccine is the PCV2 ORF2 protein expressed in insect cells after inoculation with a recombinant baculovirus containing the ORF2 gene from a PCV2 virus strain from lung tissue of a feeder pig clinically suffering from PMWS. To support the suitability of the inclusion in the vaccine of the selected PCV2 ORF2, successful heterologous challenge experiments were carried out by using recent European field isolates, thus mimicking field conditions representative of the majority of European countries.

Critical aspects for the demonstration of the efficacy of PCV2 vaccines under laboratory and field conditions were taken into account in order to justify, in particular, the selection of animals included in the efficacy studies and the challenge model. The use of animals with maternally derived antibodies against PCV2 and in some cases also with low amounts of PCV2 was deemed particularly appropriate in order to reflect the current field situation and, as a consequence, to resemble a worst case scenario for evaluation of the efficacy. However, proof of evidence for the suitability of the vaccination in sero-

negative animals was further provided. The complexity of the field situation and the difficulty of reproducing clinical signs of PCV2 associated diseases, namely PMWS, were addressed in order to support the design of the studies carried out to demonstrate the efficacy of the vaccine.

In order to quantify the amount of virus load, a PCV2 specific real time quantitative PCR (Q-PCR) and a PCV2 specific immunohistochemical (IHC) technique were developed. In addition and in support to the efficacy data obtained under experimental conditions, it was considered of crucial importance to evaluate vaccine efficacy under field conditions and, in particular, to investigate the outcome of vaccination in farms with outbreaks of PMWS.

Definition of the optimal immunising dose of ORF2 antigen was described and it was shown that to break through significant levels of maternally derived antibodies (MDAs) a vaccine with a high amount of antigen is required. An *in vivo* potency test was validated by showing its capacity to discriminate between optimal and sub-optimal batches. Experiments were carried out to support correlation with batch release specifications. Vaccine batches will be produced with a fixed ORF2 antigen content and blended with a standard amount of adjuvant to ensure consistency of production, therefore facilitating a standard batch.

Relevant details of batches of vaccines used in the clinical studies were provided.

Method of manufacture

Production of the vaccine is the result of a two phase process: firstly, the production of the ORF2 subunit antigen in the baculovirus expression system and secondly, the formulation/manufacturing of the final product. Flow charts of the different stages of the production process and the control tests performed during each stage and on the final product were presented.

For the initial steps (the construction of the recombinant baculovirus and the production of the ORF2 antigen) the basic technology process used was described. Production of ORF2 subunit antigen is based on the fermentation of *Spodoptera frugiperda* cells infected with the recombinant baculovirus vector. The synthesis of the ORF2 antigen (and assembly into VLPs) takes place in the cytoplasm of the insect cells. The resulting antigen solution is chemically inactivated by binary ethyleneimine (BEI).

Relevant details were provided concerning cells propagation, harvest, re-suspension in production medium and inoculation with working seed virus (WSV). Reference was provided of cell seeding density, T° and incubation time according to the stage of production. For antigen production the cells are separated from the cell production medium using appropriate methods. The inactivation process was described in detail.

Data were provided on stability of the bulk antigen. Sufficient results were provided to demonstrate the batch to batch consistency of final product. Validation of the antigen production method was satisfactory and the consistency of fermentation parameters was also demonstrated through monitoring of growth conditions of the infected insect cells during the fermentation process.

The blending strategy is based on: a) a fixed antigen content per dose and b) a fixed amount of two adjuvants included in a dual adjuvant system developed and patented by the Applicant, and already adopted for different commercial vaccines for swine. Despite the addition of two adjuvants, the pharmaceutical form of the finished product is equivalent to an oil-in-water emulsion. In order to prepare the final vaccine, both components of the adjuvant system are added to the antigenic fraction and stirred until a homogeneous emulsion is obtained. Evidence was provided of satisfactory homogeneity.

To ensure that a batch of vaccine will lead to the claimed efficacy, its relative potency is determined by an *in vivo* assay which has been validated.

Based on the analysis performed the potency test is able to detect sub-potent batches.

Validation studies

Details of a number of validation studies were presented:

- Validation of the sterility test
- Validation of the determination of dl-alpha-tocopheryl acetate in the final product
- Validation of the determination of paraffin in the final product
- Validation of the inactivation steps (including the inactivation control test used in the quality control)
- Validation of the antigenic mass ELISA for quantification of antigen
- Validation of the potency test.

CONTROL OF STARTING MATERIALS

Concerning starting materials listed in a Pharmacopoeia, certificates of analysis were provided for all adjuvants/excipients or their components. The following materials were tested according to relevant Ph.Eur. monographs: Paraffin, light liquid, Polysorbate 80, Gentamicin sulphate, Hydrochloric acid concentrated, Sodium hydroxide, Water for injection (bulk), alpha-tocopheryl acetate, Simethicone, Sodium thiosulphate.

The following starting materials not listed in the European Pharmacopoeia whether of biological origin (irradiated bovine serum; validation of the irradiation process was provided) or not (2-Bromo-ethylamine-hydrobromide, basal medium), were assessed and found to be satisfactory: bovine serum, 2-Bromo-ethylamine-hydrobromide, basal medium and pimafusine.

Starting materials of biological origin

Active substance

Details of the cell line used for the production of antigen were provided and additional testing for extraneous agents was carried out.

A detailed description of the process (and the controls) leading from initial experiments on construction of a recombinant baculovirus expressing PCV2 ORF2 in insect cells to MSV was provided. Support to the genetic stability of the maximum passage level of both MSV and MCS construct was demonstrated.

Stability in terms of antigen content (antigen mass ELISA) was studied and data provided.

Starting materials of non-biological origin

Bromo-ethylamine-hydrobromide (BEA)

Certificates of Analysis for 2-Bromoethylamine were provided.

Basal medium

Certificates of Analysis for the basal medium were provided.

In house preparation of media

A description was provided for the basal medium for cell production. Relevant media are prepared directly before use and any surplus from use is discarded.

SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

Assessment of starting materials has been conducted in compliance with Commission Directive 1999/104/EC and in accordance with the Note for Guidance on minimising the risk of transmitting agents via veterinary medicinal products (EMEA/410/01-Rev.2). An overall assessment of the risk of transmission of TSE by Porcilis PCV was provided. Certificates of suitability and statements of compliance for cholesterol as a component of basal medium were provided, as appropriate. All starting materials of animal origin (including cell and antigen seed materials) used in the production of the final product were proven to comply with the current regulatory texts related to the TSE Note for Guidance EMEA/410/01-rev.2).

CONTROL TESTS DURING PRODUCTION

The aim of control tests during production is to check antigen mass, sterility and completeness of the baculovirus inactivation. Various tests carried out as in process control were described, including test for cell disruption, baculovirus titre determination, inactivation, residual sodium thiosulphate, determination of the antigen content and sterility, along with relevant SOPs and pass criteria.

The results of in process testing of bulk antigen batches were provided, and found to be satisfactory.

CONTROL TESTS ON THE FINISHED PRODUCT

The aim of control tests on the finished product is to confirm the completeness of the baculovirus inactivation, check physical aspects (e.g. pH and visual appearance), sterility, safety and potency, and assay adjuvants. The methods used for the control of the finished product (either as validated test methods and SOP) and the specification were provided. The various tests carried out on the finished product are described, including inactivation, residual sodium thiosulphate, determination of pH, sterility, *in vivo* potency and identity test, safety test using pigs, visual appearance, identification and assay of adjuvants: dl-alpha-tocopherol acetate and oil content, and filling volume, along with relevant SOPs and pass criteria.

Batch analysis data were provided for several batches of finished product.

STABILITY

Stability of the bulk antigen

Stability in terms of antigen content (ELISA) was studied, with reference to potency when ORF2 antigen was incorporated into final product.
Based on antigen mass ELISA and on data obtained from potency testing, a stability for the bulk of up to 28 months was derived.

Stability of the finished product

The final product is expected to be stored at 2-8°C within a shelf-life of 24 months. Major parameters taken into account in order to support stability specifications for the final product were: potency of the PCV2 ORF 2 component, pH, adjuvants (dl-alpha – tocopherol and liquid paraffin) content and sterility at the end of shelf life.

In order to prove that the final product is completely stable for at least 27 months, thus justifying a shelf life of 24 months, the results were provided respectively on minimum/maximum bracketing presentations of the vaccine. Based on the outcome of stability testing (in terms of antigen content) of ORF2 antigen batches (up to 28 months after storage at 2-8°C), the tests used (potency test) and the results obtained (stable final product) sufficiently guarantee the efficacy of the final product for the maximum period of testing (27 months) allowing a shelf-life of 24 months.

In-use stability

The influence on potency, pH and adjuvants content of broaching and subsequent storage of vaccine at 30°C for 3 days was investigated in order to support the in-use shelf life of 8 hours. The potency remained stable and no change in the other parameters was observed.

OVERALL CONCLUSION ON QUALITY

The analytical part of the dossier is adequately described. A satisfactory description of the production and quality control procedures was provided. The method of manufacture is well described and the specifications for the product are comprehensive and adequate to control the quality of the product. Appropriate validation data were provided. Compliance of starting materials of animal origin used during production with the requirements of the Note for guidance on minimising risk of transmitting animal spongiform encephalopathy agents via human and veterinary products was shown. Based on the stability data provided, a shelf-life of 24 months and in-use shelf-life of 8 h for the finished product is justified. The SPC and other product information include all the necessary information regarding storage and use of the product.

3. SAFETY ASSESSMENT AND RESIDUES

Porcilis PCV is formulated with a standard amount of ORF2 antigen mass per dose (2ml) and blended with a standard amount of adjuvant to ensure consistency of production. The final product is an oil-in-water emulsion. As a consequence of the formulation process, a standard batch can be used in any safety (and efficacy) trial as no minimum/maximum potency would be expected. Porcilis PCV is intended for pigs from 3 days onwards. Vaccination schedule includes an initial 2 ml/dose administered intramuscularly followed by a second 2ml/dose given 2-3 weeks later in a similar way.

Two laboratory and seven field studies were carried out in order to investigate potential risks deriving from the use of Porcilis PCV. The two laboratory studies were carried out under GLP (Good Laboratory Practice) conditions, in target animal species, starting from the youngest age for which the vaccine is intended to be used. The reports of seven field trials carried out on commercial pig fattening farms were provided. With few exceptions, all trials were carried out in full compliance with GCP (Good Clinical Practice), and according to a randomised, blinded and placebo-controlled design.

Relevance of batches and information on production of batches used for general safety studies and field safety trials was provided.

LABORATORY TESTS

General safety of Porcilis PCV to piglets of approximately the intended age for vaccination was demonstrated by the two laboratory studies. Standard parameters were used to assess safety in both laboratory trials. Evaluation criteria took into account clinical reactions including mortality (loss of appetite, reluctance to move, tendency to lie down, listless or drowsy, shivery, bristling and possible oedema, especially around the eyes, vomiting, diarrhoea, respiratory signs, impact on body temperature, clinical examination of injection sites *in vivo* and post mortem examination. The impact of vaccination on growth performance was investigated in the study aiming to demonstrate the safety of repeated administration of one dose of the vaccine. Body weight was measured starting from the day before vaccination, then weekly until the day before the end of the study. Blood sampling was also carried out to measure anti PCV2 ELISA antibody in sows and/or piglets.

The Applicant used piglets with a low level of PCV2 specific MDA. Overall, the use of piglets from herds not totally free of antibodies to PCV2 was mainly justified by the difficulty to find sero-negative animals (due to the ubiquitous presence of PCV2 in the field), by animal welfare aspects regarding the use of CD/CD piglets, and finally by the relevance to mimicking field conditions using sero-positive animals. The impact of varying levels of MDA transferred to progeny on the assessment of the safety of the vaccine was mainly derived from a pivotal efficacy study presented in the dossier. Data provided from this study indicated that piglets may have relatively high levels of anti-PCV antibodies. These levels of antibody were shown to not interfere with an active immune response elicited by Porcilis PCV, thus allowing, in principle, to consider piglets born from sows with high antibody levels, suitable to be used for assessment of the safety of the vaccine**.** Moreover, additional data were provided as generated from a study carried out outside Europe in three day old colostrum deprived-MDA negative piglets (animals were either monitored for local reactions at injection site and for the occurrence of any adverse systemic reactions). Overall, supportive evidence was provided that no difference in the overall safety profile of the vaccine is expected when this will be administered to piglets with no, low or high levels of MDAs.

General safety of one and double dose, and of repeated administration of a dose of Porcilis PCV was assessed through data gathered from observation of clinical and local signs, from measurement of body T°, and weight gain, from post mortem examination. Clinical reactions were absent and general and local reactions appeared to be limited in extension and severity. Based on the results of laboratory studies, the conclusions on the impact of vaccination on individual body T°, and on growth performance were reviewed, and included in the relevant sections of the SPC.

Safety of the administration of one dose and overdose

A detailed description was provided of the relevant study where piglets were vaccinated with a (single)-2ml or (double)-2x2ml dose(s) of Porcilis PCV, administered i.m at the right side of the neck. Animals were observed daily following the administration of the vaccine for clinical signs of disease, systemic and local reactions and anomalies in rectal temperature. Animals were submitted at various time points to necropsy to examine the injection site macroscopically. Sites showing any macroscopically detectable local reactions were excised and histopathological investigation was carried out. None of the piglets belonging to group 1 underwent post mortem examination. None of the test animals died during the whole duration of the study.

No systemic reactions were recorded. An increase in the average body T° of 0.8°C and 1.0°C was recorded in piglets vaccinated with one dose and a double dose of Porcilis PCV, respectively, at one day after vaccination. The temperature increase subsided within 48 hours. Local reactions were limited in extension and severity. Only one animal of the group vaccinated with a double dose of the vaccine showed a minor, transient swelling.

On three time points after the administration of a single dose of vaccine post mortem examination of injection site of 3 animals of the group vaccinated with one dose of the vaccine, revealed local reactions in all animals considered to be consistent with an oil-in-water vaccine. Microscopic lesions consisted of confluent granulomatous inflammation associated with few small optically empty vacuoles within and intermuscularly. The histopathological findings were recognised to be histologically consistent with lesions normally induced by oil containing vaccines.

Overall, it was demonstrated that the administration of a double dose and single dose to 1 week old piglets is well tolerated. The results of this laboratory trial demonstrate a transient impact of vaccination on body T°, justifying the inclusion of a specific warning in section 4.6 of SPC.

Safety of the repeated administration of one dose

A detailed description was provided of the relevant study where piglets were vaccinated with a repeated administration of one dose. Piglets were vaccinated i.m. with a (single)-2ml dose of Porcilis PCV administered into the right hind leg; a 2nd dose was administered 15 days later into the left side of the neck; a 3rd dose was administered 14 days later into the right side of the neck. A control group consisting of piglets selected from the same sows as vaccinated animals was mock-vaccinated in the same manner. Animals were observed daily following the administration of the 3rd dose of the vaccine for clinical signs of disease, systemic and local reactions and anomalies in rectal temperature. The impact of vaccination on growth performance was also considered in this study. Body weight of the vaccine and control animals was determined at weekly intervals over the trial period. Weight gain was calculated as the weight increase compared to D-1 of the beginning of the vaccination trial. Two weeks after the last vaccination all animals were submitted to necropsy and right hind legs and both sides of the neck, examined macroscopically. Only sites showing any macroscopically detectable local reactions were excised and histopathological investigation was carried out.

No major systemic or local reactions were recorded at the injection site throughout the whole study. Following the second and third vaccination a transient and limited increase of rectal T° was recorded in the vaccinated animals which subsided within 48 h. The body temperature of the vaccinates stayed within normal limits after each vaccination.

Repeated administration of one dose of vaccine might result in an impairment of body weight gain in the immediate period after vaccination (approaching statistical significance when overall weight gain was considered). Post mortem examination did reveal macroscopically evident local reactions mainly at the site of the last (third) injection site (8/11 animals). The reactions consisted of homogeneous areas of pale tissue of normal or harder consistency, with or without oedema and haemorrhages. Microscopic lesions consisted of confluent granulomatous tissue in the fatty and/or connective tissue, with in some cases a (limited) extension into the adjacent muscular or intermuscular tissue. No vaccine

remnants were found. The histopathological findings were recognised to be histologically consistent with lesions normally induced by oil containing vaccines. Results gathered from PCV2 ELISA antibody testing demonstrated a statistically significant difference between vaccinated and control piglets confirming the vaccine take.

Overall, it was demonstrated that the repeated administration of a single dose is well tolerated. The results gathered from this study, and further confirmed by those obtained from field trials, lead to the inclusion in section 4.6 of SPC of an additional warning relating to the transient impact of vaccination on growth rate.

Examination of reproductive performance

No study has been performed in any category of breeding animals. However, Porcilis PCV is not intended for use in breeding pigs (this is reflected in section 4.7 of SPC), therefore the absence of any specific safety study carried out in these animals is justified.

Examination of immunological functions

No specific study has been carried out. However, due to the nature and composition of the vaccine, there is no reason for suspecting an impairment of the immune system under the claimed conditions of use of the vaccine.

Study of residues

The absence of any specific study of residues was justified and found acceptable due to the nature of the product. In particular, liquid paraffin, polysorbate 80, dl-alpha-tocopherol acetate, and simethicone are on the annex II list of EC Regulation 2377/90. Traces of gentamicin may be present as a remnant for antigen production. Although gentamicin is classified in Annex III, it is not expected an exposure following the vaccination (≤40µ/dose) posing any problem, therefore a withdrawal period is not considered necessary. As a matter of principle, due to the nature of the vaccine components, and the absence of any residue at injection site, withdrawal period is set to zero days.

Interactions

Since interactions with other veterinary medicinal products have not been investigated, a recommendation for not mixing the vaccine with other parenterally administered vaccines appears in the relevant section of SPC.

FIELD STUDIES

The reports of seven field trials (field studies 1 to 5 were also planned to evaluate field efficacy of Porcilis PCV) carried out on commercial pig fattening farms were provided. Farms were selected in order to be representative of different production systems such as farrow to finishing, and all-in all-out systems, and of mixed systems including farrowing to weaning and associated fattening system, and multi-site commercial system. PMWS was confirmed in 4 of these farms, whereas PMWS was suspected in two of them. Four farms were reported to be negative or without clinical signs of PMWS. The farms were carefully evaluated with respect to the levels of PCV2 antibodies. Pre-screening tests were carried out on sows as representative serological herd profiles at different times before study initiation, and on suckling piglets, revealing that none of the selected farms had a PCV2 negative antibody status.

In order to support the standard safety profile of Porcilis PCV under the conditions mentioned above, field trials were homogeneously planned (with only minor variations among the protocols) by investigating main parameters accounting for the assessment of the safety of such a type of vaccine (under field conditions). Local and systemic reactions, including general health and feed intake,

impairment of body T° and of growth rate (in all trials where weight was monitored, the average daily weight- ADWG)-was calculated by dividing the weight difference by the number of days corresponding to that period), mortality (in this case, a post mortem examination was also carried out to determine the cause of the death), culling, diseases and additional treatments, were monitored at pre-determined time points, as well as blood samples for determination of PCV2 ELISA antibody titres. Scoring systems (based on description of increasing severity of local reactions and quantitative scoring of systemic reactions) were adopted for recording the size and nature of local reactions and the nature of any anomaly in general health and rate of feed intake (systemic reactions). The results of two additional field studies carried out outside the EU were also provided in order to confirm the safety (and efficacy) of the vaccine. Here, special attention was paid to the impact of vaccination on growth performance.

Field study 1: Safety assessment in 3-7 day old piglets on farms without clinical signs of PWMS

A detailed presentation of the design and of the results of this study was provided. Pigs were monitored for local and systemic reactions from two days before up to 14 days after second vaccination carried out at weaning.

No local or systemic reactions were reported other than a transient systemic reaction in some piglets shortly after first vaccination, which was attributed to the low temperature of the vaccine at administration. These piglets fully recovered the next day. No significant differences in body temperature were observed between the Porcilis PCV vaccinated group and the placebo injected control piglets, but both groups showed a limited temperature increase both after first and second vaccination. In three cases a temperature of ≥40.5 °C was observed (Tmax 40.7°C) which returned to normal within 48 h after vaccination. No significant difference was observed with respect to overall mortality. Vaccination resulted in a minor decrease in weight gain in the period just after weaning but this decrease was fully compensated for during the fattening period and no difference in daily weight gain was observed at slaughter.
Overall, the mean ELISA antibody titres of the selected sows sampled before the start of the study can be considered as low. Two weeks after second vaccination,the mean ELISA antibody titres recorded in the control and vaccinated piglets confirmed the vaccine take.

As a whole, it was demonstrated that when firstly administered to 1 week old piglets followed by a booster vaccination 14 days later, the vaccine is well tolerated. The results of this field trial demonstrate a transient impact of vaccination on body T°, and of an impairment of growth rate limited to the weeks immediately following vaccination.

Field study 2: Safety and efficacy assessment in 3-7 day old piglets on a PWMS suspected farm

A detailed presentation of the design and of the results of this study was provided. Piglets were monitored for local and systemic reactions from the day before up to 14 days after second vaccination carried out at weaning.

No local or systemic reactions were reported. The temperatures remained low overall both after the first and second vaccination (T_{max} of 40.2°C). No significant difference was observed in respect to overall mortality. By contrast, a statistically significant difference was calculated between the treatment groups (in favour of the vaccinated animals) when comparing ADWG of all animals from the first vaccination to slaughter. The difference between the mean ELISA antibody titres measured two weeks after second vaccination, was statistically significant in favour of the vaccinated group which confirmed the vaccine take.

Overall, it was demonstrated that when firstly administered to 1 week old piglets followed by a booster vaccination 14 days later, the vaccine is well tolerated. Similarly to the laboratory studies, on an individual basis, higher rectal temperatures were recorded, thus further justifying the inclusion of a specific warning in section 4.6 of SPC.

Field Study 3: Safety and efficacy assessment in 3-7 day old piglets on a PWMS positive farm

A detailed presentation of the design and of the results of this study was provided. Piglets were monitored for general health, feed intake or local reactions from two days before vaccination up to 14 days after second vaccination carried out at weaning.

Seven days after primary vaccination, a small number of piglets in the vaccinated group exibited local reactions of limited size at the injection site. After booster vaccination, a higher number of piglets exibited local reactions at the injection site resulting in all the cases, in soft to hard swellings of 0.5-5cm diameter. The size and the nature of these lesions were shown not to affect the general health and behaviour of piglets, including feed intake. At day 7 after booster vaccination, pigs were removed for post mortem and histological examination of the injection site. The histopathological findings were recognised to be histologically consistent with lesions normally induced by oil containing vaccines. The swellings had disappeared within 3 weeks post booster vaccination except in 6 animals (including two control animals). Four of these pigs were deeply investigated at slaughter. In only one case (control group), a small spot of scar tissue was found confirming that no significant traces of local reactions can be observed at slaughter. Peak temperatures were observed at 4 hours both after the first and the second vaccination in the vaccine group which had returned within 48 hrs to physiological levels. Mortality as well as the number of treatments was less in the vaccinated group although not statistically different. However, a statistically significant difference in favour of vaccinated piglets was observed in the overall (from 1st vaccination to slaughter) average daily weight gain (ADWG). The difference in ADWG was most prominent during the fattening period. The mean ELISA antibody titres of the selected sows sampled pre-trial can be considered as low. The difference between mean ELISA antibody 2 weeks after second vaccination, was statistically significant in favour of the vaccinates as compared to the controls. The overall picture from these field trials suggests that local reactions are somewhat more pronounced after the booster vaccination, but no plausible explanation could be given rather than hypothesising the involvement of an incidental secondary factor (e.g. the circulation of other pathogens). This is also supported by the fact that local reactions after booster vaccination were not observed in the next field trial or in laboratory safety study of repeated administration of one dose of the vaccine.

On an individual basis, higher rectal temperatures (up to 2.5°C) either after primary and booster vaccination, were recorded, thus further justifying the inclusion of a specific warning in section 4.6 of SPC.

Field Study 4: Safety and efficacy assessment in 3 week old piglets on a PWMS suspected farm

A detailed presentation of the design and of the results of this study was provided. Following the vaccination schedule, the second dose of the vaccine was administered 14 days after the initial vaccination. The piglets were monitored for local and systemic reactions starting two days before and until 14 days after each vaccination.

Prior to the trial the PMWS suspected status of the farm was confirmed. However, based on virological findings during the trial period, the farm was considered as PWMS positive rather than PMWS suspected.

In less than 2% of piglets, local reactions were observed between day 7 and 14 after the first vaccination, consisting of a swelling of a limited size (0.5-2.0 cm). No local reactions were recorded after the second administration of the vaccine. Both the control and vaccinated group (<2% of the animals) showed a limited reduction in feed intake up to 5 days both after the first and second vaccination. Both groups also showed a deviation from the normal general health status (mainly resulting in inactivity and depression) both after the first and second treatment (not significant different between the vaccinated and control animals). After the second treatment, 4% of the vaccinated animals and 3% of the controls controls experienced a systemic reaction characteristic of an anaphylactic shock (the piglets fell down immediately after administration with tremors and/or

excitation), which was resolved, uneventfully within few minutes. A limited increase in rectal temperature was observed at 4 hours after the first vaccination both in the Porcilis PCV vaccinated group and the placebo injected control piglets. After the second vaccination a more pronounced increase in rectal temperature was observed (T_{vacmax}=42.1). Both after the first and second vaccination the temperatures returned to normal the next day.

These reactions (increased temperature and anaphylactic shock) were basically referred to the adjuvant component of the vaccine in association with other factors. In this context it was noted that a severe bacterial infection was present among the pigs which hindered the interpretation of the safety parameters obtained.

A higher number of pigs died in the vaccinated group. The majority of the deaths could be attributed to bacterial infections. In relation to this it was noted that 80% of all treatments administered were given for the control of bacterial infection or meningitis (not being significantly different between the groups).

The ADWG, both overall and during the fattening period, was higher in the vaccinated group. This was statistically significant for the fattening period. The mean ELISA antibody titres of the selected sows sampled pre study can be considered as moderate. Fourteen days after the second vaccination of piglets, the mean $\log_2$ titres in the vaccinated piglets were significantly higher compared to the control group confirming the vaccine take.

The results of the trial indicated that also when Porcilis PCV is administered to older piglets, an individual increase of T° up to 2.5°C may occur, thus further supporting the inclusion of a warning in the SPC. Based on the specific observation of anaphylactic reactions, details of the clinical manifestations are mentioned in section 4.6 of the SPC. It was however noted that the presence of a severe bacterial infection among the pigs hindered the interpretation of the safety parameters obtained.

Field Study 5: Safety and efficacy assessment in 3 week old piglets on a PWMS positive farm

A detailed presentation of the design and of the results of this study was provided. Following the vaccination schedule, the second dose of the vaccine was administered 14 days after the initial vaccination. The piglets were monitored for local and systemic reactions starting two days before and until 14 days after each vaccination.

No local reactions were observed after initial treatment. During the first week after the booster vaccination, a local reaction consisting of a soft swelling reaching a maximum of 5 cm in diameter was observed with low frequency in the vaccinates. One week after vaccination swellings were no longer present in any of the animals. No systemic reactions were observed after the first vaccination. After the second vaccination 5% of the vaccinated piglets experienced an anaphylactic reaction which was resolved within a few minutes without requiring any treatment of the piglets. Also 1 animal in the vaccinated group showed a reduced feed intake and deviation from the normal health status.

No significant differences in body temperature were observed between the Porcilis PCV vaccinated group and the placebo injected control piglets, but both groups showed a transient temperature increase after first and second vaccination. The T_{max} of the vaccine group after first and second vaccination was 40.9°C and 42.1°C, respectively. Body temperatures returned to normal within 72 hours.

No statistical difference between the two treatment groups was observed with respect to the overall mortality and number of treatments. The average daily weight gain over the complete period was however significantly higher in the vaccinated group. The difference in daily weight gain between the groups was most prominent during the fattening period. The mean ELISA antibody titres of the selected sows sampled pre-trial can be considered as moderate. Fourteen days after the second vaccination of piglets, the mean $\log_2$ titres in the vaccinated piglets was significantly higher which confirmed the vaccine take.

The study confirmed that the vaccine is well tolerated when administered following the recommended vaccination scheme in 3 week old conventional piglets. The results of the trial confirmed also the occasional finding of individual increases of rectal T° > to 2.0°C. The clinical manifestations following anaphylactic shock further supported the need for the inclusion of specific reference in section 4.6 of the SPC.

Field Study 6: A field trial to assess the safety of Porcilis PCV in piglets

The results were presented of an ongoing field trial which evaluated the safety of Porcilis PCV up to 14 days after second vaccination of piglets from four farms. Piglets were monitored daily from the day before until 14 days after each treatment for local and systemic reactions. The aim was to demonstrate the safety of a vaccination with Porcilis PCV in piglets of various ages reared, housed and vaccinated on two PMWS positive farms and two PMWS negative farms.

Most local reactions occurring after first and second administration of the vaccine were reported as soft/hard, warm and sometimes painful swelling (up to 5 and 10 cm in diameter, respectively after the first and second vaccination). At the end of the study, i.e. two weeks after second vaccination, the reactions had disappeared in most of the vaccinated animals. A systemic reaction of anaphylactic type was recorded in 1% of the vaccinated piglets. The piglets recovered in a few minutes without any medical intervention. No significant difference was observed between the vaccinated and control groups with respect to feed intake, deviation from the normal health status, and mortality. Bacterial infections were mainly suspected in farms A, B, C and in some cases arthritis or diarrhoea were also noted. In farm D in most cases respiratory problems were reported. Four hours after each treatment, a statistically significant average increase of rectal T° was recorded in vaccinated animals. Within 24 h the rectal T° was completely restored. Weighing indicated an initial statistically significant impairment of the growth rate in vaccinated animals compared to control animals.

In general, the results of this field trial confirm previous findings of a transient impact of vaccination on body T°, and of an impairment of growth rate limited to the weeks immediately following vaccination. Local and systemic reactions were similar in intensity and duration to the ones recorded in other field trials.

Field Study 7: A field trial to assess the safety of Porcilis PCV in piglets in a non-EU country

The preliminary results of an ongoing field study (primarily aiming to demonstrate efficacy of the vaccine) carried out in a multi-site commercial pig herd (reported and confirmed to be heavily affected by PCV2 related diseases) were presented. In this study piglets were allocated to two treatment groups (vaccinated intramuscularly twice at an interval of 2-3 weeks or served as controls and vaccine was replaced by sterile water for injection). For both groups the local and systemic reactions were monitored for up to 14 days post vaccination. Local reactions at injection site occurred exclusively in the vaccinated group following both vaccine administrations. The swellings were in the majority of cases of limited size; only occasionally swellings up to 5 cm in diameter were monitored. The local reactions were recorded in a higher number of pigs after the second administration of the vaccine. Systemic reactions in the form of anaphylactic shocks were recorded in a limited number of vaccinated pigs following the second vaccination. All the pigs recovered maximally in ten minutes without any intervention. No other systemic reaction was further recorded.

The study confirmed that the vaccine is well tolerated when administered following the recommended vaccination scheme in 2-3 week old conventional piglets. The clinical manifestations following anaphylactic shock confirmed the need for the inclusion of specific reference in section 4.6 of the SPC.

ENVIRONMENTAL RISK ASSESSMENT

A satisfactory Phase I assessment of risk for this vaccine, in accordance with EMEA/CVMP/074/95, was provided. On the basis of the phase I assessment, a phase II assessment is not required. Porcilis PCV is judged to present no risk to the environment.

User safety

User safety has been addressed: a specific warning related to the risk to the user of the self injection of a vaccine containing mineral oil being included in the SPC.

RESIDUE ASSESSMENT

MRL

Liquid paraffin, polysorbate 80, dl-alpha-tocopherol acetate, and simethicone are on the annex II list of Council Regulation (EEC) No. 2377/90. Traces of gentamicin may be present as a remnant for antigen production. Although gentamicin is classified in Annex III, exposure is not expected following the vaccination, therefore a withdrawal period is not considered necessary.

Withdrawal period

Zero days.

OVERALL CONCLUSION ON SAFETY AND RESIDUES

Overall findings from laboratory and field studies provided supportive evidence for an acceptable safety profile of Porcilis PCV. Safety studies were well described, and in compliance with current requirements. The two laboratory studies were GLP compliant. The field trials were mostly conducted in accordance with GCP. Laboratory data were deemed to be satisfactory to support the final formulation used, as well as the proposed vaccination scheme. In the field trials, the overall safety profile of standard vaccine batches of Porcilis PCV was demonstrated under the expected conditions of use. The SPC reflects the conclusions regarding the temperature increases arising from use of the product, the frequency and the extent of local and systemic reactions, the impact of vaccination on general health and the potential impairment of the growth rate in the immediate period after administration of the vaccine.

No safety data were generated in breeding animals, however, this is clearly reflected in the SPC. No study was performed to investigate the potential adverse effects of the vaccine on the immunological functions, but this is acceptable due to the nature of the vaccine. No information is presented on the safety and use of this vaccine with any other product which is adequately reflected in the SPC. As a matter of principle, due to the nature of the vaccine components, and the absence of any residue at injection site, withdrawal period is set to zero days. The risk to the user posed by the inclusion of an oil adjuvant in the vaccine is clearly reflected in the SPC. A phase I environmental risk assessment was conducted. It was concluded that the vaccine presents a negligible risk to the global environment.

In conclusion, the safety of Porcilis PCV was adequately demonstrated given its current indication.

4. EFFICACY ASSESSMENT

Based on scientifically sound evidence, it can be concluded that, at present, only one PCV2 genotype is associated with different forms of PCV2 infection worldwide and that field isolates show similar antigenic properties (minor variations in the sequence of different PCV2 may occur in the field, but these seem to be without any antigenic relevance). Proof of concept was provided that the vaccine is effective against heterologous challenge, in particular against recent European PCV2 field isolates. Based on this evidence the choice of the vaccine strain/antigen is sustainable.

PCV2 ORF2 antigen in Porcilis PCV is contained in the aqueous phase of the oil-in-water-emulsion, and is formulated with a constant amount of antigen mass per dose and a constant amount of adjuvant. As a consequence of the formulation process, a standard batch can be used in any (safety and) efficacy trial as no minimum/ maximum potency would be expected.

Relevance of batches and outstanding information on production of batches used for efficacy trials was provided. Porcilis PCV is intended for pigs from 3 days onwards. Vaccination schedule includes an initial 2 ml dose administered intramuscularly followed by a second 2ml dose given 2-3 weeks later in a similar way.

Claims attributed to this vaccination regimen was the capacity to induce an active immunisation in pigs from 3 days of age resulting in the reduction of viral load of Porcine Circovirus (PCV) type 2 associated with Porcine Circovirus (PCV) type 2 -related diseases (PCVAD). These claims were tested under experimental conditions using piglets of minimum age as well as 3-4 week old animals. The use of the vaccine was also claimed to result in an increased daily weight gain of pigs if affected by PCVD during the fattening period. This claim was challenged under experimental conditions and supportive evidence was provided by field trials. The proposed onset of immunity of 2 weeks and duration of immunity of 22 weeks have been investigated in experimental challenge studies. The vaccine is not intended to be used in any breeding animals of the target species.

Initially, the results of six GLP laboratory studies and five GCP field trials carried out in order to support the indication for the use of Porcilis PCV were presented.

Laboratory trials

Six laboratory studies were carried out in order to demonstrate the efficacy of the vaccine in reducing the PCV2 load both in lymphoid tissues and in blood, these parameters are proven to be correlated with the occurrence of clinical manifestations of PCVAD. The contribution of vaccination in reducing viral shedding and weight loss caused by PCV2 infection was investigated.

The laboratory studies were characterised by the homogeneity of the experimental conditions, including standardised vaccination scheme, challenge model, observation parameters, test methods, and evaluation of the results.

The animals used in the laboratory studies were in the majority of cases conventional piglets with varying levels (from low to high) of MDAs obtained in the majority of cases from sows of farms free of PMWS. Piglets from SPF sows but with PCV2 specific MDAs were also used. The selection of animals used for the efficacy studies and the challenge model were thoroughly addressed. Justification for the use of animals with MDAs against PCV2 and in some cases also with small amounts of PCV2 virus was provided. Selection of these animals would indeed reflect the current field situation and as a consequence would resemble a worst case scenario for evaluation of the efficacy. The experimental challenge did not consistently induce a clinical expression, including an impairment of growth performance. The difficulty of reproducing clinical signs of PCV2 associated PCVD, namely PMWS, in a laboratory situation was substantiated, also making a reference to the most recent published literature. Basically, the challenge model used in the laboratory studies was functionally set in order to support the intended claims of the vaccine: reduction of virus replication in target body districts, namely in fluids and lymphoid tissues, thus leading to a final reduction of virus load in these organs,

this circumstance known to correlate with the development of clinical signs of PMWS. Following an experimental challenge, the amount of PCV2 antigen load is measured in blood serum, in nasal and/or faecal swabs and in lymphoid tissues is measured by quantitative PCR (Q-PCR) or by immunohistopathology. In order to quantify the amount of virus load, a PCV2 –specific real time quantitative PCR (Q-PCR) and a PCV2 specific immunohistochemical (IHC) technique were developed. A validation study of the Q-PCR was provided, as well as the corresponding standard procedure. Moreover, a detailed description of IHC technique was made available.

A heterologous challenge has been carried out in all experiments. In one challenge study a list of recently isolated field virus strains belonging to both group 1 and 2 PCV2 viruses was further used to assess the efficacy of Porcilis PCV in overcoming the variability of different strains circulating among the pig population. Important aspects of vaccine efficacy were also investigated in order to establish onset and duration of immunity and the level of immunity obtained after vaccination. Clinical evidence of PCV2 infection was absent in all laboratory studies.

All laboratory studies had generally the same design. In each of them, the following parameters were investigated:

Daily observation for clinical signs of disease
The amount of challenge virus in nasal and/or rectal swabs
Body weight measurements
Blood sampling at regular intervals in order to measure the kinetics of PCV2 antibody development- and the amount of challenge virus by Q-PCR
Post mortem examination at necropsy
Selection of samples for IHC and Q-PCR.

Laboratory study 1: *Efficacy after basic vaccination of piglets at 3-5 days of age with MDA against PCV2, as determined by challenge at 6 weeks of age*

The objective of this study was to demonstrate the efficacy of basic vaccination of Porcilis PCV in conventional 3-5 day old piglets (from farrow-to-finish farm) in presence of moderate to high levels of MDAs. According to current legislation, the trial has been designed in target animals of the youngest age recommended for vaccination. The groups (vaccinated and control piglets) were compared for serum antibody titres to demonstrated uptake of vaccine. Challenge was carried out 2.5 weeks after completion of the basic vaccination scheme. The main parameter of efficacy was set in the amount of PCV2 in lymphoid tissues measured 3 weeks after challenge. Further indicators of efficacy were weight gain and the amount of PCV2 in sera and nasal swabs at different time points. No clinical signs of disease were observed throughout the study. Serology studies clearly indicated that in the face of moderate to high levels of MDAs, active immunity can be induced following the basic vaccination scheme. Vaccination led to a significant decrease in cumulative virus quantities in mesenteric and inguinal lymph nodes, tonsils, spleen, and serum after challenge. No significant difference in the amount of virus detected in nasal swabs was observed between vaccinated and control groups. Vaccination, however, resulted in a significantly higher ADWG post challenge in the vaccinated animals compared to the control animals.

Laboratory study 2 : *Field efficacy: protection against PCV2 challenge 2 weeks after basic vaccination under field conditions*

This study was aimed to support the claimed 2 weeks onset of immunity of the vaccine. Challenge infection was carried out under controlled conditions of a basic vaccination in conventional piglets raised and vaccinated under field conditions (Field safety study 1) in a farm regarded as PMWS negative (free of disease, no history of PMWS, low MDA). Uptake of vaccine was demonstrated after the administration of the second dose of vaccine. Vaccination resulted in a significant reduction of PCV2 (antigen) in tonsils, mesenteric lymph nodes, and in blood. No PCV2 antigen was ever detected in faecal swabs of the vaccinated animals while at one week after challenge a significant higher

amount of viral antigen was found in faecal swabs taken from control animals. In this study no beneficial effect of vaccination on growth performance was demonstrated after challenge.

Laboratory study 3: *Efficacy of vaccination when used to vaccinate SPF piglets with antibodies against PCV2, as determined by challenge at 18 weeks of age*

The objective of the study was to demonstrate the efficacy of a full (100% antigen content) and of a quarter (25% antigen content) dose batch of Porcilis PCV, in piglets born from SPF sows in presence of high levels of MDA. Three-four day old and one week old piglets were vaccinated with the sub-optimal vaccine batch using the recommended route of administration and vaccination schedule. Efficacy after challenge was compared to the efficacy in a group of piglets which were vaccinated with a full dose of vaccine at one week of age and in a non-vaccinated control group. The results of this study would also support a duration of immunity of 15 weeks. In presence of high levels of MDA, vaccination with 100% and with 25% of a dose of Porcilis PCV resulted in significantly higher levels of antibodies up to the challenge in comparison with those recorded in control animals. The ADWG post challenge was shown to be significantly higher in vaccinated animals. Vaccination also resulted in a significant lower cumulative amount of virus in lymphoid tissues and sera. Moreover a significantly lower amount of viral DNA was found in nasal swabs of vaccinated animals compared to controls. No differences among vaccinated groups were recorded for all the efficacy parameters taken into account in this study.

Laboratory study 4: *Safety and efficacy after single or double vaccination of commercial piglets via the i.m. route as determined by challenge at 10 weeks of age*

This study was aimed at supporting the safety and efficacy of a vaccination scheme consisting of a double vaccination of an initial dose administered at 4 weeks of age followed by the administration of a second dose 2 weeks later and of a one dose vaccination carried out at 4 weeks of age. The study was carried out in conventional piglets in the face of low to moderate PCV2 specific MDA levels. Challenge was performed 4 weeks after the second vaccination. The general safety of the vaccine was evaluated by comparing the results obtained from vaccinated animals to those obtained from unvaccinated and placebo treated animals (incidence and severity of local and systemic reactions and post mortem observations including injection site reactions were taken into account). Efficacy was evaluated through the results of PCV2 serology and the detection of virus load in target organs, and blood and virus shedding (faecal swabs). One or two shots of Porcilis PCV were well tolerated by 4 week conventional pigs with low to moderate levels of MDA. Uptake of vaccine was demonstrated 2 weeks after the administration of the first dose of vaccine. A significantly reduced virus load in serum and in lymphoid organs was recorded after challenge in all vaccinated groups. Also faecal shedding was significantly reduced after challenge. In this study a one shot vaccination regimen was comparable to a two shot vaccination when applied to older pigs (e.g. 4 week old) with low to moderate MDA levels.

Laboratory study 5: *Efficacy of Porcilis Circo inac in conventional piglets, as determined by challenge with recent isolates*

The objective of the study was to demonstrate the efficacy of Porcilis PCV in conventional piglets with moderate MDAs, following a two shot vaccination regimen starting at 3-4 weeks of age. An experimental challenge was carried out 2.5 weeks after completion of the recommended vaccination scheme using 4 different isolates of PCV2 representative of both group 1 and 2 of PCV2 (as recently classified). At the time of challenge, the average antibody titres against PCV2 were comparable in the animals of all vaccinated groups, and significantly higher compared to those of the non-vaccinated animals. The presence of PCV2 antigen was not detected in blood of vaccinated animals at any time during the trial, while it was detected at one or more time points in non vaccinated-challenged pigs. The results of the Q-PCR data in serum, nasal cavity and faeces show that Porcilis PCV is effective in reducing viraemia and virus shedding, following an experimental challenge with four recent isolates.

Differences in histopathological and IHC scores were evident when pigs from all treatments were taken into account, non vaccinated piglets showing more severe PMWS-like lesions and higher amount of PCV2 DNA in lymphoid tissues than vaccinated animals.

Laboratory study 6: *Efficacy of when used to vaccinate SPF piglets with antibodies against PCV2, as determined by challenge at 25 weeks of age*

The objective of this main DOI study was to demonstrate the efficacy of Porcilis PCV in piglets with moderate to high MDAs born from SPF sows, following a two shots vaccination regimen starting at 4-5 days of age or, alternatively, a one shot vaccination regimen at 3 weeks of age. Three weeks after challenge all animals were necropsied. In presence of moderate to high levels of MDA, vaccination with either a single or repeated dose of Porcilis PCV stabilised the level of antibodies up to the challenge at statistically significant higher values in comparison with those recorded in control animals. Following challenge, PCV2 DNA load in serum, faecal and nasal swabs of vaccinated animals were significantly reduced as compared to the controls. The PCV2 DNA load was significantly reduced in tonsils, spleens and inguinal lymph nodes of vaccinated animals. The reduction was not significant in the mesenteric lymph nodes. The cumulative viral antigen quantities detected by IHC were significantly reduced in the vaccinated groups. Challenge did not result in any clinical expression of PCV2 infection and no significant difference among groups was recorded after challenge with respect to the ADWG.

IV.D. Field Trials

Efficacy was evaluated under field conditions in five trials (also carried out to supplement laboratory safety data; see field trial 1 to 5). Field trials were considered of particular importance to assess the efficacy of Porcilis PCV against PMWS as no laboratory challenge model exists which consistently induces the multifactorial PMWS. Therefore the best way to assess the effect of vaccination with Porcilis PCV on PMWS is in field trials on farms with outbreaks of PMWS. Therefore, farms were selected on the basis of compatible clinical symptoms, i.e. increased number of dead born piglets, high percentage return to oestrus, increased mortality in piglets, especially during the second half of the fattening period. These farms were considered PMWS suspect. To definitely confirm the PMWS status of these farms, pigs with compatible clinical symptoms were examined for microscopic lesions in lymphoid tissues and detection of PCV2 within these lesions according to criteria as described by the European consortium on PCV2 (http://www.pcvd.org).

However, no clear evidence for an active circulation of PCV2 during the trial period was provided. This circumstance was justified in several occasions, by the difficulty to stage a “natural” challenge infection at a predetermined moment in time due to the ubiquitous nature of PCV2. Major issues arising from the assessment of field trials were the relevance of the selected farms as representative of the epidemiological situation all over Europe; the absence of data from field trials to support the claim for reduction of virus excretion (the impact of vaccination on growth performance represented the main parameter investigated under field conditions); and the impact of varying levels of MDAs on the efficacy of the vaccine.

Although the geographical area selected to evaluate field efficacy gave rise to some criticisms, the relevance of field studies was considered sustainable taking into account the proposed indications for the use of the vaccine.

In laboratory studies only the effect of vaccination to reduce virus load in blood and in lymphoid tissues, and to reduce virus shedding was investigated as no laboratory challenge model exists which consistently induces the multifactorial PMWS. Therefore, it was considered of crucial importance to evaluate vaccine efficacy under field conditions, and in particular to investigate the outcome of vaccination in farms with outbreaks of PMWS based on progressive weight loss, number of treatments and increased mortality considered as relevant clinical signs of PCV2 associated diseases.

Evidence was provided for a significant beneficial effect of vaccination to reduce weight loss induced by PCV2 infection which was most prominent during the fattening period. Other clinical and production parameters such as mortality and number of additional treatments did not provide additional information on the beneficial effects of vaccination. In contrast, a transient impairment of the growth rate was shown to occur in vaccinated animals in the weeks immediately following the administration of the vaccine, which was, however, compensated during fattening. It should be noted that that reduction of virus excretion was considered an important parameter. However in field studies reduction of nasal or faecal shedding was not studied.

Uptake of the vaccine antigen was clearly demonstrated not to be affected by the presence of MDAs, which would likely result in the capacity of the vaccine to overcome the negative impact of these antibodies on vaccination, and to initiate the development of an active immunity. Overall, from the data presented, demonstration was provided that a full dose regimen of vaccination breaks through medium to high levels of MDAs. Final evidence was provided of the epidemiological relevance of the range of values set by the Applicant to allocate categorisation of MDAs as low, medium, and high antibodies.

OVERALL CONCLUSION ON EFFICACY

A thorough analysis was provided to justify the selection of sero-positive animals in experimental studies. Also evidence was provided for a beneficial effect of vaccination of sero-negative pigs on the reduction of virus load in blood and lymphoid tissues following an infection with PCV2. The need for flexibility in the vaccination schedule, and in particular for initiating vaccination at 3 days of age was justified. In this respect, the influence of varying levels of MDAs (at vaccination) on the effectiveness of the vaccination was analysed in depth. Evidence was provided for the vaccine to be able to break through medium-high levels of MDAs, this range of values likely representing a more extensive field situation in European Countries. This is achieved before the most critical period for clinically apparent PCV2 associated diseases (e.g. before 10 weeks of age, this age likely corresponding to the beginning of fattening period). However, it was also concluded that, in order to support the relevance of efficacy parameters investigated under experimental conditions, additional testing (e.g. duration of viraemia, and virus shedding) under field conditions would have certainly provided a clearer picture of the efficacy of Porcilis PCV.

The results of field trials were satisfactory to support the claim for a beneficial effect of vaccination on the weight loss(es) consequent to PCV2 infection.

Overall, based upon results obtained from laboratory and field studies, it was concluded that the efficacy of Porcilis PCV vaccination to reduce virus load in lymphoid tissues and blood and to reduce weight loss caused by PCV2 infection occurring during fattening was demonstrated. Conversely, the claim for reduction of viral shedding (thus resulting in a lower exposure to PCV2 in field situations), was considered not to have been supported. Satisfactory data were provided for substantiating an OOI of 2 weeks and a DOI of 22 weeks; such a DOI is considered to sufficiently cover the majority of pig industry production systems in Europe. From preliminary results, it also appeared that initial (and single) vaccination carried out in older piglets may provide comparable results compared to a two vaccination regimen initiated at 3 days of age.

V. RISK-BENEFIT BALANCE

Porcilis PCV is a ready to use liquid adjuvanted vaccine containing baculovirus-expressed PCV2 ORF2 to be used in pigs from 3 days of age.

Efficacy of the vaccine is expected to reduce PCV2 load in blood and lymphoid tissues, and to reduce weight loss associated with PCV2 infection occurring during the fattening period. These claims were demonstrated under laboratory or field conditions, following administration of the vaccine, as recommended, to piglets from a minimum age of 3 days, and in the face of medium-high levels of maternally derived antibody. Onset of protection occurs as early as 2 weeks post vaccination and lasts for at least 22 weeks.

The quality profile of the vaccine was satisfactorily demonstrated in terms of robustness and consistency of the production process. Overall, the final product is expected to be free of any component exhibiting deleterious effects in vaccinated animals, to the environment, to the end users and consumers of food derived from vaccinated animals.

Major evidence for the safe use of the product in target animals has been provided. Safety trials have been carried out in the most susceptible category of pigs intended to be vaccinated, e.g. piglets from 3 days of age. Field studies have confirmed the safety profile of the vaccine. Transient local reactions at the injection site may occur after vaccination mainly in the form of a hard, warm and sometimes painful swelling. A transient increase in body temperature, normally not exceeding 1°C, may occur until 2 days after vaccination. Vaccination may result in an impairment of growth rate in the immediate period after administration of the vaccine. Considering the low risk of the consequence and the likelihood of the occurrence, the level of risk associated with this event can be considered as minor. No specific safety (and efficacy) studies have been carried out to assess the impact of vaccination on the reproductive performance. A warning for the absence of any data generated in breeding animals is reflected on the SPC.

It may be concluded that the benefits provided to the target animals by the vaccination with Porcilis PCV, outweigh the risks for the target animals, the environment, the user and the consumer.

Based on the data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product was considered to be in accordance with Directive 2001/82/EC as amended.