4 November 2021
EMA/654291/2021
Veterinary Medicines Division

Committee for Veterinary Medicinal Products

CVMP assessment report for CircoMax (EMEA/V/C/005185/0000)

Vaccine common name: Porcine circovirus vaccine (inactivated recombinant)

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Introduction

The applicant Zoetis Belgium SA submitted on 19 June 2020 an application for a marketing authorisation to the European Medicines Agency (the Agency) for CircoMax, through the centralised procedure under Article 3(1) of Regulation (EC) No 726/2004 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 11 October 2018 as the PCV antigens in CircoMax have been developed using recombinant DNA technology.

The applicant applied for the following indications: Active immunisation of pigs against Porcine Circovirus type 2 to reduce viral load in blood and lymphoid tissues, virus fecal shedding and the lesions in lymphoid tissues associated with PCV2 infection. To reduce body weight gain losses in cases of early PCV2 viremia (before 16 weeks of age).

Onset of immunity: from 3 weeks after vaccination.

Duration of immunity: 23 weeks after vaccination.

The final current proposal for the indication is:

Active immunisation of pigs against porcine circovirus type 2 to reduce viral load in blood and lymphoid tissues, fecal shedding and the lesions in lymphoid tissues associated with PCV2 infection. Protection was demonstrated against porcine circovirus genotypes 2a, 2b and 2d.

Onset of immunity (both vaccination schedules): 3 weeks after (the last) vaccination.

Duration of immunity (both vaccination schedules): 23 weeks after (the last) vaccination.

The active substances of CircoMax are inactivated recombinant chimeric porcine circovirus 1 containing the porcine circovirus 2a open reading frame 2 (ORF2) protein, inactivated recombinant chimeric porcine circovirus 1 containing the porcine circovirus 2b ORF2 protein. CircoMax is an inactivated, emulsified vaccine to induce immunity against PCV2. The target species are pigs for fattening. The product is intended for administration by intramuscular use.

CircoMax emulsion for injection contains 1.5 – 4.9 relative potency (RP) of inactivated recombinant chimeric porcine circovirus type 1 containing the porcine circovirus type 2a ORF2 protein and 1.5 – 5.9 RP of inactivated recombinant chimeric porcine circovirus type 1 containing the porcine circovirus type 2b ORF2 protein and is presented in the following packs:

Cardboard box of 1 vial of 50 ml (25 doses), 100 ml (50 doses) or 250 ml (125 doses).

Cardboard box of 10 vials of 50 ml (25 doses) or 100 ml (50 doses).

Cardboard box of 4 vials of 250 ml (125 doses).

The rapporteur appointed is Niels Christian Kyvsgaard and the co-rapporteur is Paolo Pasquali.

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

On 4 November 2021, the CVMP adopted an opinion and CVMP assessment report.

On 11 January 2022, the European Commission adopted a Commission Decision granting the marketing authorisation for CircoMax.

Marketing authorisation under exceptional circumstances

Not applicable.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Multi-strain dossier

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (dated 28 May 2018) which fulfils the requirements of Directive 2001/82/EC 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 reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the active substances takes place outside the EEA at Zoetis Inc Iowa, United States, and Zoetis Inc Nebraska, United States. The sites have a manufacturing authorisation issued on 03 October 2018 by Unites States Department of Agriculture. GMP certifications, which confirms the dates of the last inspections and show that the sites are authorised for the manufacture and batch release of such veterinary dosage forms, were issued by the Veterinary Medicines Directorate, United Kingdom.

Manufacture of the final product (blending, filling), packaging and batch release within the EU take place at Zoetis Belgium SA, Louvain-la-Neuve, Belgium which holds a manufacturing authorisation issued on 03 March 2018 by the Federal Agency for Medicines and Health Products, BE. GMP compliance was confirmed by the competent national authority Federal Agency for Medicines and Health Products, BE.

Overall conclusions on administrative particulars

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

The GMP status of the active substance(s) and of the finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 – Quality

Chemical, pharmaceutical and biological/microbiological information (quality)

Qualitative and quantitative particulars of the constituents

Qualitative and quantitative particulars

CircoMax is a bivalent vaccine intended for active immunisation of pigs against porcine circovirus type 2 to reduce viral load in blood and lymphoid tissues, fecal shedding and the lesions in lymphoid tissues associated with PCV2 infection.

The finished product is an emulsion for injection. The active substances (antigens) are inactivated recombinant chimeric porcine circovirus (PCV) type 1 containing the PCV type 2a ORF2 protein (PCV2a), and inactivated recombinant chimeric PCV type 1 containing the PCV type 2b ORF2 protein (PCV2b). The product contains (in relative potency (RP) units): PCV2a, 1.5-4.9 RP and PCV2b, 1.5-5.9 RP per dose of 2 ml. The product contains squalane (as SP oil solution, also known as Metastim®, which in addition to squalane contains poloxamer 401 and polysorbate 80) as adjuvant (0,4% v/v). Other ingredients are EDTA tetrasodium, disodium tetraborate decahydrate, buffer salts (monobasic potassium phosphate, disodium phosphate, sodium phosphate dibasic), sodium chloride, and potassium chloride as described in section 6.1 of the SPC. The vaccine does not contain preservative.

CircoMax is available in multidose 50, 100, and 250-ml high density polyethylene (HDPE) plastic vials. The vials are closed with chlorobutyl rubber stoppers and sealed with aluminium caps, as described in section 6.5 of the SPC.

Filling volume overage has been stated and justified. No formulation overage for antigen stability is proposed. The absence of antigen overage was not considered adequately justified and constituted a major objection; however, based on provision of additional stability data and a commitment provided regarding stability of final product, this has been solved.

Container and closure

CircoMax is filled into multidose HDPE plastic vials containing 25, 50, or 125 doses of 2 ml, respectively. The vials are closed with chlorobutyl rubber stoppers (Ph. Eur. 3.2.9) and sealed with aluminium caps. HDPE vials are sterilised by gamma irradiation at ≥ 25 kGy, according to Ph. Eur. 5.1.1. Rubber stoppers are steam sterilised (Ph. Eur. 5.1.1). Certificates of analysis have been supplied for containers and closure demonstrating compliance with the proposed specifications.

Product development

CircoMax is essentially a fall-out product from the parent vaccine CircoMax Myco; CircoMax Myco is based on the predecessor product Suvaxyn Circo + MH RTU which is approved in the EU.

The PCV2a antigen included in the present product is identical to the antigen used in Suvaxyn Circo + MH RTU. The PCV2b antigen is identical to the antigen used in CircoMax Myco and was obtained by recombinant technology using the same porcine circovirus type 1 vector strain backbone as for

the PCV2a antigen, producing a chimera expressing porcine circovirus type 2b protein. As for PCV2a antigen, in this construct the PCV2b capsid gene (ORF2) itself is avirulent and non-infectious and the PCV1 genome backbone is non-pathogenic. By including the PCV2b antigen a broader immune coverage is provided against current and emerging strains of PCV2 compared to vaccines based on a single PCV2 type only.

The PCV2a antigen production process is identical to the one used for the licenced Suvaxyn Circo + MH RTU and the master seed virus is identical. For PCV2b antigen, a new master seed virus (MSV) has been qualified (identical to the PCV2b MSV used in CircoMax Myco), but otherwise the production process of PCV2b antigen is identical to that of PCV2a.

The inactivation procedures are the same as those used for the latter licensed vaccine. Inactivation of the PCV2a and PCV2b is performed by addition of Beta Propiolactone (BPL). Kinetic of inactivation studies demonstrated that the proposed inactivation procedures are capable of inactivating the proposed maximum pre-inactivation titre for PCV2a antigen (9.3 $\log_{10}$ fluorescent assay infectious dose 50% ($FAID_{50}$)/ml) and for PCV2b antigen (8.6 $\log_{10}$ $FAID_{50}$/ml) within less than 67% of the proposed duration of the inactivation process, in accordance with the requirements of Ph. Eur. 0062. Inactivation is terminated by addition of sodium thiosulfate. Test for completeness of virus inactivation is carried out on each batch directly after inactivation. Test for completeness of virus inactivation has been validated for the PCV2a antigen; no specific validation for the PCV2b antigen is needed.

The upper and lower specifications for relative potency for each antigen are based on safety and efficacy studies. The clinical studies include both studies on the parent product CircoMax Myco as well as new studies performed for the fall-out product CircoMax. Thus, the formulation of the batches used for clinical trials were not all exactly the same as in those intended for marketing as the CircoMax Myco batches also contained *M. hyopneumoniae* antigen and thiomersal. Batches used in clinical trials are listed and batch records are provided.

No formulation overage is proposed, thus the minimum potency specifications for release are the same as the minimum potency specifications during shelf life based on analyses of decrease of antigen potency in the finished product stability batches; this was not considered adequately justified and a major objection was posed on the determination of the release potency specification for the two antigens; however, based on provision of additional stability data and a commitment regarding stability of final product, this has been solved. Filling volume overage has been stated and justified.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. or internal standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC. The selected container materials are considered standard for this type of product. No preservative is added.

The product development is considered adequately described and the composition and presentation of the vaccine has been explained.

Description of the manufacturing method

PCV2a and PCV2b antigens

The PCV2a antigen production process is identical to the cPCV1-2 antigen used in the approved vaccine Suvaxyn Circo + MH RTU, and the manufacturing process of the new PCV2b antigen is identical to that of the PCV2a antigen. The manufacturing process is a standard virus production in pig kidney PK-15 cells followed by separation of micro carriers and cell material, and concentration,

purification, and inactivation of virus. The manufacturing process is based on a seed lot system.

The production process consists of the following steps: scale up of WCS of PK-15 cells, inoculation of cells with PCV seed, and production cultivation on microcarriers in bioreactors. Multiplicity of infection is defined, and cultivation times and target temperatures are set for the cultivation steps. Gentamycin is used during the cultivation steps. Culture fluid containing both cell-free virions and virus associated to infected cells that have detached from the microcarriers as a result of virus infection, is harvested. Harvest of viral fluids and subsequent replacement with fresh growth media may be accomplished repeatedly and up to four harvests may be collected. Physical agitation may be used to assist in removal of cells from the microcarriers. Initial harvest is based on visual observation of cultures and/or evaluation of bioreactor control parameters *e.g.* dissolved oxygen consumption. The maximum cumulative incubation time from inoculation with frozen seed to final harvest is defined. The maximum passage levels are defined for cells and virus and verified by genetic stability studies. Harvest is followed by removal of microcarriers by screen filtration, concentration by filtration (the harvest stocks may be combined before concentration), and purification by diafiltration. The concentrated antigen stocks can be stored up to 30 days at +2 to +8 °C prior to inactivation. Inactivation of viral fluid is performed by addition of Beta Propiolactone and terminated by addition of sodium thiosulfate after which testing for complete inactivation of virus is performed. The final antigen fluids are stored in polypropylene bags or stainless-steel vessels at +2 to +8 °C; the shelf life is 24 months. The final antigen batch sizes range between 50 and 270 L.

Vaccine Production

Bulk vaccine formulation is done by mixing the appropriate amounts of PCV2a and PCV2b antigens, SP-oil adjuvant, and phosphate-buffered saline. The amounts of antigens added are targeted to meet the release specifications. Details of blending are provided. pH of the final bulk is controlled and adjusted if necessary. The formulated blend may be stored at +2 to +8 °C for up to 3 days; the holding time is validated. The final bulk is filtered through a coarse screen and filled into sterile multidose HDPE vials (25, 50, or 125 doses). The filled vials are closed with the stopper and crimped. The finished product is stored at +2 to +8 °C.

Validation of the manufacturing process is demonstrated by provision of results from three batches of each of the PCV antigens (2a and 2b), and six consecutive finished product batches. The finished product batches were based on three final bulks manufactured with three different PCV2b antigen batches but only one single batch of PCV2a antigen; a concern was posed on this matter, however, based on a commitment provided regarding consistency of final product, this has been solved. The final bulk bathes were filled in 25-doses and 125-doses vials to support also the 50-doses vial presentation. The batch size for the six finished product batches is 10% of the proposed batch size; however, based on the manufacturer's experience with the specific processes and equipment this is considered acceptable.

Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible and consistent manner. The in-process controls are considered adequate for this type of manufacturing process.

Production and control of starting materials

Starting materials listed in pharmacopoeias

All compendial starting materials are listed and their function is described. The starting materials

include glucose (anhydrous), hydrochloric acid, sodium chloride, sodium hydroxide, sodium thiosulfate, gentamicin sulphate, phenol red sodium salt, potassium chloride, potassium phosphate monobasic anhydrous, sodium hydrogen carbonate, sodium phosphate dibasic anhydrous, sodium phosphate dibasic heptahydrate, sodium dihydrogen phosphate monohydrate, disodium tetraborate decahydrate, polysorbate 80, purified water, water for injections, foetal bovine serum and squalane. The quality of the materials must comply with Ph. Eur with the exception of sodium phosphate dibasic heptahydrate and sodium dihydrogen phosphate monohydrate, which comply with USP, and phenol red, which complies with American Chemical Society (ACS). This is acceptable as no Ph. Eur monographs exist. Examples of certificates of analyses are provided for all the listed starting materials.

Starting materials of biological (animal) origin includes foetal bovine serum and shark-derived squalene. For bovine serum, valid European Directorate for the Quality of Medicines (EDQM) certificates of suitability are provided for each of the suppliers.

Specific materials not listed in a pharmacopoeia

Starting materials of biological origin

Master and working seeds

PCV12a:

The PCV2a chimera is already used as one of the components in the authorised vaccines Suvaxyn Circo + MH RTU and CircoMax Myco. As such, the master seed virus Lot # 2117-63-052004 has already been found suitable and approved for use in the manufacture of veterinary viral vaccines. The strategy for generation and testing of future working virus seed (WSV) is included and is considered acceptable.

PCV12b:

The PCV2b chimera is already used as one of the components in the authorised vaccine CircoMax Myco. As such, the master seed virus Lot #1306063 has already been found suitable and approved for use in the manufacture of veterinary virus vaccines. Strategy for generation and testing of future WSVs is included and is considered acceptable.

PK-15 cell line:

The PK-15 cell line is already used for the manufacture of the PCV2a antigen, which is one of the components in the authorised vaccines Suvaxyn Circo + MH RTU and CircoMax Myco. Overall testing of the MCS is in accordance with the current version of Ph. Eur. 5.2.4 Cell cultures for the production of veterinary vaccines as well as EMA/CVMP/IWP/206555/2010/Rev.1. For the PK-15 working cell seed (WCS), the testing is in accordance with current guidelines.

Other starting materials of biological origin

Components of porcine and bovine origin are used for production of seed material and/or during fermentation of pre-cultures and main culture. The starting materials include: Porcine origin: microcarriers (contains gelatine), porcine trypsin powder; bovine origin: Lactalbumin Hydrolysate (LAH) and OptiMEM 50x Salts II Solution (contains transferrin). Raw material specifications, including source and accepted countries of origin, and examples of certificates of analyses are provided for the starting materials.

The animal-based materials are considered in compliance with the requirements of Ph. Eur. 5.2.5 *'Substances of animal origin for the production of immunological veterinary medicinal products (IVMP)'.*
Starting materials from TSE-relevant species, used in routine manufacture, include bovine serum, transferrin (derived from bovine blood), lactalbumin hydrolysate (derived from bovine milk), and porcine trypsin powder (containing lactose derived from bovine milk). The bovine milk used for manufacture of LAH and trypsin is considered fit for human consumption. Valid EDQM certificates are provided for the bovine serum and transferrin materials. The risk of transmitting TSE through the use of animal-based starting materials can be considered negligible.

Starting materials of non-biological origin

Non-compendial starting materials of non-biological origin include Betapropiolactone (BPL), EMEM with phenol red, OptiMEM 50x Acid Soluble Solution, OptiMEM 50x Salts, Poloxamer 401 (adjuvant component, surfactant), sodium phosphate heptahydrate, sodium phosphate monobasic monohydrate, EDTA tetrasodium salt dehydrate, and microcarriers. Examples of certificates of analyses are provided.

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

Media and solutions include: OptiMEM with 0.25% LAH, OptiMEM with 0.25% LAH/FBS/gentamicin, Eagle's medium with 0.05% LAH, 0.01M Phosphate Buffer Saline (PBS), gentamicin sulphate solution, 1M sodium thiosulfate, 10X trypsin solution with EDTA, SP oil solution, PBS No. 10 solution, EDTA tetrasodium and borate solution. Information on the qualitative and quantitative composition, methods of preparation, sterilisation, and storage conditions of the media and solutions is included in the dossier.

Control tests during the manufacturing process

The analytical methods used to test the PCV2 antigens are identical to those used in the already approved vaccines Suvaxyn Circo + MH RTU and CircoMax Myco. In-process controls include analyses of virus titre and identity, sterility, complete inactivation, potency, residual sodium thiosulfate, and relative purity (calculated). Descriptions of test method are provided for all methods.

Virus titre and identity before inactivation is determined by staining virus-inoculated NL-ST cells with a monoclonal antibody specific for PCV2. Upper limits of PCV2a and PCV2b titres prior to inactivation are defined and the method has been validated for both PCV2a and PCV2b. Completeness of virus inactivation is tested by staining virus-inoculated NL-ST cells. The method has been validated for PCV2a antigen; specific validation for PCV2b antigen is not considered necessary.

The virus content in the inactivated final antigen fluid is determined by ELISA using rabbit anti PCV2 serum as capture antibody, monoclonal PCV2 antibody (5D5-5H4) for detection together with a peroxidase-conjugated secondary goat-anti-mouse antibody. In-house reference vaccine and placebo vaccine are used as controls. Validation of the ELISA procedure has been conducted for the PCV2a antigen. Internal verifications have been conducted and confirmed that the same test is applicable to the PCV2b antigen.

Sterility testing is performed as per Ph. Eur 2.6.1 and has been validated for method suitability.

Control tests on the finished product

Control of finished product includes analyses of general characteristics (description, pH, and viscosity), potency/identification of the individual antigens, quantification of adjuvant (squalane), and sterility. Test for inactivation is not performed for batch release; this is acceptable since it is performed for the individual antigens after inactivation. No test is found for residual gentamycin; however, maximum residue limit (MRL) for gentamycin is calculated and the maximal theoretical concentration in the finished product is well below the MRL for porcine muscle. Descriptions of test method are provided for all methods and non-compendial methods are validated. Sterility testing is performed as per Ph. Eur 2.6.1 and has been validated for method suitability. Determination of the squalane is based on HPLC; the method is considered adequately validated.

Potency/identification

The PCV2a content of the finished product is determined by ELISA using a monoclonal antibody specific for PCV2a as capture antibody and a biotinylated monoclonal PCV2 antibody and commercial streptavidin peroxidase for detection. The reference vaccine contains both PCV2a and *M. hyopneumoniae* antigens. A placebo vaccine without PCV2a antigen and a positive control vaccine batch are used as controls. The assay is considered validated and in line with the expectations of VICH GL1 and GL2. Overall, it is considered demonstrated that the PCV2a ELISA for finished product is able to reflect the amount of the PCV2a antigen in the final product with adequate accuracy.

The PCV2b content of the finished product is determined by ELISA using a monoclonal antibody specific for PCV2b as capture antibody and a biotinylated monoclonal PCV2 antibody and streptavidin peroxidase for detection. The reference vaccine is containing PCV2a, PCV2b, and *M. hyopneumoniae* antigens. A placebo vaccine without PCV2b antigen and a positive control vaccine batch are used as controls. The assay is considered validated and in line with the expectations of VICH GL1 and GL2. Overall, it is considered demonstrated that the PCV2b ELISA for finished product is able to reflect the amount of the PCV2b antigen in the final product with adequate accuracy.

A major objection was posed on the determination of the release potency specification for the two antigens; however, based on a commitment provided regarding stability of final product, this has been solved.

Overall, the selection of parameters in the finished product specification covers the aspects that would be expected and are considered sufficient to assure an acceptable and consistent quality of the product.

Batch-to-batch consistency

The applicant presented batch data for three batches of each of the PCV antigens (2a and 2b), and six consecutive finished product batches. The finished product batches were based on three final bulks each manufactured with three different PCV2b antigen batches but with only a single batch of PCV2a antigen. However, as the applicant has committed to provide the authorities with consistency data for the first commercial batch prepared with different PCV2a antigen batch(es) as soon as this becomes available, this has been accepted. A commitment letter has been provided including expected due dates for fulfilment. The final bulk batches were filled in 25-doses and 125-doses vials to support also the 50-doses vial presentation. The batch results submitted fulfil the proposed in-process control specifications and specifications for finished product and demonstrate acceptable consistency of manufacturing process and final product.

Stability

Antigens

PCV2a antigen

The stability testing of the PCV2a antigen include testing of potency; stability of this parameter is considered demonstrated for the proposed shelf life of 27 months at +2 to +8 °C. Sterility of the antigen after long-term storage has been adequately demonstrated and the absence of routine sterility testing of the antigen is considered justified.

PCV2b antigen

The stability testing of the PCV2b antigen include testing of potency and sterility. Sterility testing of the PCV2b antigen is not due to concerns regarding antigen sterility, but the PCV2b antigen stability protocol included sterility testing to support other international marketing authorizations. The results provided support the proposed shelf life of 30 months at +2 to +8 °C.

Finished product

The proposed shelf life of finished product is 18 months at +2 to +8 °C. Twenty-one months stability data are provided for six finished product batches supporting the proposed shelf life.

The finished product batches included three batches of 25-doses and three batches of 125 dose vials were used. The 50-dose presentation is considered supported by the bracketing approach.

The stability batches were based on three different final bulks. The final bulks are based on three different batches of PCV2b antigen but only one single batch of PCV2a antigen; however, as the applicant has committed to conduct an additional stability study on the first commercial batch formulated with different PCV2a antigen fluids and provide the authorities the data generated from the study, this has been accepted. A commitment letter has been provided including expected due dates for fulfilment.

Based on the provided commitment, the proposed shelf life of the finished product can be accepted.

In-use shelf life

No in-use shelf life is claimed as the product is to be used immediately after first broaching.

Overall conclusions on quality

CircoMax is a bivalent inactivated vaccine intended for active immunisation of pigs against porcine circovirus type 2. The finished product is an emulsion for injection presented in HDPE vials containing 25, 50, or 125 doses. The active substances (antigens) are inactivated recombinant chimeric porcine circovirus type PCV2a and inactivated recombinant chimeric porcine circovirus type PCV2b.

The manufacturing processes of the two PCV antigens are identical and comprise standard virus production in pig kidney PK-15 cells followed by separation of micro carriers and cell material, and concentration, purification, and inactivation of virus. The manufacturing process is based on a seed lot system. Based on the data from six consecutive finished product batches, batch-to-batch consistency is overall considered demonstrated, provided that an appropriate justification is given to the concern regarding the use of final bulks based on three different batches of PCV2b antigen but only one single batch of PCV2a antigen; a commitment provided regarding consistency of final product has subsequently been provided. Compliance with Ph. Eur. monographs 0062 *Vaccines for veterinary use* is generally considered demonstrated.

Overall, information on the development, manufacture, and control of the active substances and the finished product has been presented in a satisfactory manner and is considered acceptable. TSE safety is considered confirmed.

The proposed shelf life for the finished product (18 months at 2-8 °C) is considered supported based on a commitment provided regarding stability of final product.

Recommendations:

The applicant is recommended to provide the following data post authorisation:

- The applicant commits to provide the authorities consistency data for the first commercial batch of vaccine prepared with different PCV2a antigen batch(es) as soon as these become available.
A commitment letter has been provided including expected due dates for fulfilment.

- The applicant commits to conduct an additional stability study with the first commercial batch formulated with a different batch of PCV2a antigen and provide the authorities the data generated from the study. A commitment letter has been provided including expected due dates for fulfilment.

Part 3 – Safety

Introduction and general requirements

The active substances porcine circovirus PCV2a and PCV2b antigens (inactivated, recombinant) of CircoMax have been already authorised in the EU. A full safety file in accordance with Article 12(3)(j) has been provided.

The safety documentation is largely the same as provided for the parent vaccine CircoMax Myco. Two additional safety studies were provided, one US laboratory study (B924R-US-19-880) was performed with single dose and repeated dose from three weeks of age; and a US field study (B921R-US-18-809) was performed on at total of 5400 pigs.

Safety documentation

The applicant has provided target animal safety data based on laboratory studies with regard to single dose and split-dose administration and also based on field studies. A user risk assessment is also provided.

No data are provided on reproductive safety nor the effect on lactation and pregnancy as the vaccine is only indicated for the vaccination of piglets.

List of laboratory safety studies:

Study title	*Study reference*	*Batch used*
Repeated dose, 3-day-old piglets	B924N-NL-15-457	L1114LW05
Supportive data Single dose and repeated dose, 3-week-old pigs	B924R-US-17-732	L0517LW20

Study title	Study reference	Batch used
Supportive data Single dose and 10x overdose, 3-week-old pigs	B924R-JP-17-692	193755A
Supportive data 2x overdose 3-week-old pigs	B924R-US-15-524	L1014LW07
		L0215LW06
		L0215LW07
Supportive data 2x overdose 3-week-old pigs	B924R-US-17-733	L0517LW20
		L0517LW21
		L0517LW22
Supportive data Single dose and repeated dose 3-week-old pigs	B924R-US-19-880	L0119LW02

Laboratory tests

The applicant performed one good laboratory practice (GLP)-compliant study to assess single dose safety and split-dose administration safety with CircoMax Myco (study B924N-NL-15-457). Additionally, the applicant submitted the results of two safety studies performed for regulatory authorities outside the EU, study B924R-US-17-732 and study B924R-JP-17-692. These studies provide supportive safety data. Finally, the applicant provided the results of the study B924R-US-19-880 that was carried out with a CircoMax vaccine batch of above maximum potency (6.73 RP for PCV2a and 6.04 RP for PCV2b).

The vaccine batches used in the laboratory safety trials were manufactured according to the manufacturing process described in part 2.B of the dossier with some minor deviation not considered to adversely impact the safety of the product. The batch used in the GLP-compliant EU study was of maximum potency (4.9 [PCV2a], 5.9 [PCV2b] and 4.7 [*M. hyopneumoniae*] RP/dose).

The study represents the intended label vaccination schedule including administration of the product once according to the single dose scheme, and twice according to the split-dose scheme (D0 and D14).

Vaccinations neither caused systemic abnormal reactions nor did they adversely affect growth. Rectal temperature was not statistically different in vaccinated animals compared to negative controls, although transient temperature increases were observed in vaccinated piglets 4 hours and 1 day after vaccination. Injection site swellings of less than 2 cm in diameter occurred in the majority of piglets and lasted up to 9–10 days. Swellings were caused by an influx of inflammatory cells and considered a normal response to vaccination with an adjuvanted vaccine.

In summary, local and systemic adverse reactions such as redness and swelling at the injection site (below 2 cm in diameter for up to 10 days) and transient increase in body temperature during the first 24 hours after vaccination (not exceeding 2.1 °C) were seen and indicated as common and very common, respectively. Adverse reactions from this pivotal study were thus adequately reflected in the product literature.

Safety of one administration of an overdose

The demonstration of overdose safety is not required for inactivated vaccines anymore since Directive 2009/9/EC amending Directive 2001/82/EC came into force. Nevertheless, the applicant submitted the results of three safety studies for CircoMax Myco which were performed for regulatory authorities outside the EU and did therefore not entirely comply with EU legislation and/or regulatory guidance. In two US studies, the safety of a single dose and of repeated administrations of single doses was assessed (B924R-US-15-524 and B924R-US-17-733, with two-fold overdose in both experiments). In the Japanese study, the safety of a single dose and a ten-times overdose was assessed in 3-week-old piglets (B924R-JP-17- 692).

Besides the reactions already mentioned in section 4.6, depression and reduced appetite were observed. The swellings were moderate (up to 7.5 cm diameter up to 13 days). Injection site reactions were found to be caused by local inflammatory response. Transient depression, reduced appetite, lameness and dyspnoea were also sporadically observed, but were not clearly related to vaccination. The findings of the two-fold overdose studies are adequately included in section 4.10 of the SPC (the findings of the Japanese ten-fold overdose study were not included as the conduct of such study was never required in the EU and adding results of a 10-fold overdose study would be unprecedented).

Safety of the repeated administration of one dose

The safety of two doses of CircoMax Myco given with 2 weeks interval was studied in study B924N-NL-15-457 described above. Local reactions and transient increase in body temperature were observed. This was also studied in study B924R-US-19-880 where the animals were immunised with CircoMax batch of above maximum potency and which is seen as supportive only. Transient pyrexia and injection site reactions were observed. The injection site reactions tended to resolve slower after the second injection.

Examination of reproductive performance, lactation and pregnancy

No reproductive studies were provided as the product is only indicated for fattening animals. The safety of the veterinary medicinal product has not been established during pregnancy or lactation, therefore the use of the product is not recommended during pregnancy and lactation.

Examination of immunological functions

A justification has been provided in this section of the dossier, but no specific trials have been carried out. It is not common for inactivated vaccines to have adverse immunological effects that affect the overall safety of the target species. As the laboratory data show that vaccine batches with maximum potency were well tolerated in seronegative pigs of minimum age, it is considered that no further examination of immunological functions is required.

User safety

The applicant provided a user safety risk assessment compliant with the CVMP 'Guideline for user safety for immunological veterinary products' (EMEA/CVMP/IWP/54533/2006). Minor potential risks were identified, which are essentially associated with handling and accidental self-injection, as mentioned in section 4.5. of the SPC. The risk assessment is largely the same as for CircoMax Myco.

CircoMax is an inactivated adjuvanted vaccine intended to be administered by professional users. The vaccine contains two components, which are chimeric PCV strains that have been specifically created using genetic modifications. The two PCV virus components do not infect humans and are inactivated in the product.

The adjuvant is composed of squalane (a naturally occurring material which is considered as not falling within the scope of Regulation No 470/2009). Although polysorbate 80 and poloxamer 401 can rarely induce adverse reactions in humans (hypersensitivity and anaphylactic-type reactions, respectively), none of the substances is included in the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 Rev. 1), and the risk is deemed to be minimal. Polysorbate 80 and poloxamer 401 (both included in Table 1 (allowed substances) of the annex to Commission Regulation (EU) No 37/2010). Squalane incorporated in non-mineral SP oil is also used in other porcine vaccines from the applicant, such as Suvaxyn Circo+MH RTU, which was centrally authorised in 2015 (EMEA/V/C/003924) or CircoMax Myco (EMEA/V/C/005184).

Regarding gentamycin, the maximal theoretical concentration in the finished product would be well below biological activity levels. Gentamycin is used during the manufacturing process of both PCV2 components to reduce contamination risks and is found only in trace amounts in the finished product, thus not likely to pose a risk for the vaccine user.

Based on the above risk assessment, the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Study of residues

No investigation into this aspect is required for this vaccine. The active ingredients being substances of biological origin intended to produce active immunity, do not fall within the scope of Regulation (EC) No 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. The vaccine does not contain adjuvants or any other excipients that require a numerical MRL or fall within the scope of Regulation (EU) No 470/2009 regarding residues of veterinary medicinal products in foodstuffs of animal origin. The consumption of products derived from pigs vaccinated with the present IVMP does therefore not present a risk for consumer (human) health.

Gentamicin used in the cell culture-based production of the PCV-2 components is present at low residual levels in the finished medicinal product. The expected levels of gentamicin at injection site would still be approximately 10 times below the MRL established for porcine muscle.

Consequently, the withdrawal period in section 4.11 of the SPC is set at zero days.

Interactions

The applicant did not provide any safety studies investigating the concurrent use of the IVMP with any other veterinary medical product. Thus, section 4.8 of the SPC includes a standard warning.

Field studies (safety)

List of field safety studies:

Study reference	*Study title*	*Batch used*
Intermediate potency	B921C-NL-16-664,	193755D CircoMax Myco

Study reference	Study title	Batch used
	B921C-NL-16-643	
Minimum potency	B826C-ES-16-661, B826C-ES-16-662, B826C-BE-16-663, B826C-ES-16-640, B826C-ES-16-641, B826C-BE-16-642	229878A CircoMax Myco
Supporting evidence	B921R-US-16-609	193748B/193676B CircoMax Myco
Supporting evidence	B921R-US-18-809	237330D, 237330A, 280437A. 280437F, 282997A, 282997D, CircoMax

The applicant performed two field studies with CircoMax Myco in The Netherlands, one for each dosing regimen (single dose B921C-NL-16-643 and split-dose B921C-NL-16-664), to address the safety of the IVMP under field conditions. These studies were performed with vaccine batches of intermediate potency (RPs of 2.5 [PCV2a], 3.9 [PCV2b], 2.9 [*M. hyopneumoniae*]), which is acceptable for field trials with veterinary vaccines.

The findings in the laboratory studies were confirmed by the field studies, as transient increases in mean rectal temperature were observed. The increase was within the range stated in the SPC: 'A transient increase in body temperature, not exceeding 2.1 °C, is very common during the first 24 hours after vaccination'. After single dose vaccination, transient local injection site reactions in 2 of the subsets of 15 vaccinated pigs (13.3%), consisting of a mild swelling of 0.5 to 2 cm in diameter with a maximum duration of 3 days. For the split-dose vaccination none of the piglets presented swellings at the injection site. No notable difference was observed concerning average daily weight gain and average body weight 30 days post-vaccination between control animals and vaccinated piglets. No abnormal clinical signs were observed in either group after vaccination.

Additionally, the applicant submitted the results of six EU field efficacy studies performed with IVMP batches containing the active components at or near minimum potency and a US field safety study (supporting evidence, intermediate potency), involving 3-day-old pigs (split-dose vaccination schedule — 2 doses of 1 ml — 4 studies) and 3-week-old pigs (single dose vaccination schedule — 1 dose of 2 ml — 4 studies).

A US study with the fall-out vaccine CircoMax (B921R-US-18-809) was carried out with a total of 5400 piglets and observed abnormal clinical signs and mortality occurred at similar rates between vaccinates and controls.

In summary, it is agreed that the results did support the safety data already generated in the laboratory studies and indicated that a single label dose of the vaccine was safe in 3-weeks-old piglets under field conditions. Likewise, it was agreed that a split-dose of the vaccine was safe in 3-day- and 3-week-old piglets under field conditions.

Environmental risk assessment

Although immunological products do not require a phase I/II assessment as outlined by VICH GLs 6 and 38, the risks of vaccination with the IVMP to the environment were comprehensively described by the applicant in a phase I risk assessment. The overall risk of the vaccine to the environment, humans and other animals is effectively zero.

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

Not applicable.

Overall conclusions on the safety documentation

The applicant has provided data showing that the IVMP has a safety profile with mainly local reactions and transient temperature increases as possible adverse reactions. The vaccine is safe in minimum age piglets when administered by the recommended route and regimens. The maximum potencies and safety statements of the SPC are considered supported and appropriate.

Based on the data provided, it was concluded that target animal safety is acceptable when the vaccine is administered according to the recommended schedule and via the recommended route.

Reproduction safety was not investigated as the product is only intended for use in piglets.

A user safety assessment in line with the relevant guidance document has been presented.

Based on the assessment presented, the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

The consumption of products derived from pigs vaccinated with the IVMP does not present a risk for consumer (human) health. Consequently, the withdrawal period in section 4.11 of the SPC is set at zero days.

The CVMP concluded that CircoMax is not expected to pose a risk to the environment when used in accordance with the SPC.

The applicant provided satisfactory risk assessments for the user and the environment and included appropriate warnings and guidance in the SPC where necessary.

Part 4 – Efficacy

Introduction and general requirements

The vaccine is intended for the active immunisation of piglets over the age of 3 days against porcine circovirus type 2. Two posologies are proposed, either a single 2 ml dose at 3 weeks of age or a split dose, where the first 1 ml dose is given from 3 days of age and the second 3 weeks later. The proposed indications are to reduce viral load in blood and lymphoid tissues, fecal shedding, the lesions in lymphoid tissues associated with PCV2 infection and reduce the loss of weight gain during the finishing period in the face of early infection with PCV2. Onset of immunity is intended to be established 3 weeks further to the completion of either a single dose or split dose vaccination schedule and lasting for 23 weeks.

A specific Ph. Eur. monograph that outlines the requirements for inactivated PCV2 vaccines does not exist; therefore, efficacy parameters were selected by the applicant. Appropriate challenge models against PCV2a, PCV2b and PCV2d were established.

Efficacy was demonstrated in compliance with the European Directive 2001/82/EC (as amended by 2004/28/EC and Directive 2009/9/EC), and the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7. "Evaluation of efficacy of veterinary vaccines and immunosera". CircoMax is a fall-out vaccine of the CircoMax Myco vaccine and efficacy has largely been demonstrated by the combined vaccine in line with EMA/CVMP/IWP/594618/2010

Challenge model:

PCV2 systemic disease is difficult to induce experimentally, and success depends on the inclusion of colostrum-deprived (CD) piglets, a challenge below three weeks of age and co-infection with other porcine pathogens. Not all these criteria can be controlled in a vaccine efficacy trial, therefore other efficacy parameters such as viral load in blood and/or tissues, viral shedding and characteristic histological tissue lesions in conjunction with the presence of PCV2 in those tissues were included. The applicant developed four challenge models, against PCV2a, PCV2b, PCV2d and PCV2d strain Z12, respectively. The four models are summarised below.

Challenge model against Porcine Circovirus type 2a

- The challenge strain was PCV2, Isolate 40895 Passage 7. The PCV2a was passaged serially in porcine kidney cells (PK15) up to passage 6.
- Challenge volume of 3 ml: 1 ml administered intramuscular and 2 ml administered intranasally
- Evaluated parameters were viremia, fecal shedding, lymphoid tissue microscopic lesions and presence of antigen in lymphoid tissues
- Desired primary outcome was reduction of viremia; secondary outcomes were reduction of fecal shedding, reduction of lymphoid tissue lesions, and reduction of detection of PCV2 antigen within lymphoid tissue lesions.

Challenge model against Porcine Circovirus type 2b

- The challenge strain was PCV2, Isolate FD07 Pass 17. The PCV2b P16 was used to infect PK15cells. The day 9 and 12 harvests were combined to produce the challenge virus.
- Challenge volume of 3-4 ml: 1-2 ml administered intramuscular and 2 ml administered intranasally
- Evaluated parameters were viremia, fecal shedding, lymphoid tissue microscopic lesions and presence of antigen in lymphoid tissues
- Desired primary outcome was reduction of viremia; secondary outcomes were reduction of fecal shedding, reduction of lymphoid tissue lesions, and reduction of detection of PCV2 antigen within lymphoid tissue lesions

Challenge model against Porcine Circovirus type 2d

- The challenge strain was PCV2, Isolate PCV2d DIV P7 Lot# DS047-4-24Apr13. Challenge volume of 4 ml: 2 ml administered intramuscular and 2 ml administered intranasally
- Evaluated parameters were viremia, fecal shedding, lymphoid tissue microscopic lesions and presence of antigen in lymphoid tissues

- Desired primary outcome was reduction of viremia; secondary outcomes were reduction of fecal shedding, reduction of lymphoid tissue lesions, and reduction of detection of PCV2 antigen within lymphoid tissue lesions

Challenge model against Porcine Circovirus type 2d, strain Z12

- The challenge strain was Porcine Circovirus 2, Isolate PCV2d (Z12) P9 Challenge Lot 082218PCVd. DNA sequencing identified PCV2b-divergent, later referred to as PCV2d.
- Challenge volume of 6 ml: 2 ml administered intramuscular and 4 ml administered intranasally
- Evaluated parameters were viremia, fecal shedding, lymphoid tissue microscopic lesions and presence of antigen in lymphoid tissues
- Desired primary outcome was reduction of viremia; secondary outcomes were reduction of fecal shedding, reduction of lymphoid tissue lesions, and reduction of detection of PCV2 antigen within lymphoid tissue lesions

All challenge models were considered adequately validated and therefore appropriate for using in the efficacy trials in order to mimic the natural conditions for infection.

Efficacy parameters and tests:

The applicant chose viral load in blood (viremia), fecal shedding, lymphoid depletion and PCV2 colonisation of lymphoid tissue as efficacy parameters. Histiocytic replacement was also assessed, because it was a sequela to lymphoid depletion. Thus, in some studies the two parameters were analysed together to evaluate lymphoid lesions. The collection of blood and faeces allowed frequent sampling at multiple time points post challenge in order to study development of viremia and shedding over time.

Efficacy documentation

Studies included in part 4

The below list summarises all the laboratory and field (safety and) efficacy studies that were conducted in support of this MA application and included studies both for the EU-dossier as well as for the US-dossier.

Overview of efficacy studies

Type of study	Dose	Challenge strain	Study number
Dose determination	Single dose	PCV2a	B823R-US-15-550
		PCV2b	B823R-US-15-551
		PCV2b	B823R-US-16-646
	Split dose	PCV2b	B823W-US-15-532
Onset of immunity	**Single dose**		
		PCV2a	B822R-US-14-325 B822R-US-16-583 B822R-US-17-693 B822R-US-17-729 B823R-US-18-782 B827R-US-18-783
		PCV2b	B822R-US-16-582 B822R-US-15-562 B822R-US-17-694 B822R-US-17-744 B82R3-US-18-781 B827R-US-18-784
		PCV2d	B820R-US-17-747
	Split dose	PCV2a	B822R-US-15-556
		PCV2a	B825R-US-16-667
		PCV2b	B822R-US-15-557
		PCV2d	B820R-US-17-747
Effect of maternally derived immunity			
		PCV2a	B828R-US-16-669
	Single dose	PCV2a	B828R-US-18-833
		PCV2b	B828R-ES-15-476
		PCV2b	B828R-ES-16-613
	Split dose	PCV2a	B828R-ES-17-707
		PCV2a	B828R-US-18-797
		PCV2b	B823W-US-15-532
Duration of immunity			
		PCV2a	B824R-US-15-452
	Single dose	PCV2a	B824R-US-17-756
		PCV2b	B824R-US-15-451
		PCV2b	B824R-US-17-755

	Split dose	PCV2a	B824R-GB-16-635
		PCV2b	B824R-GB-16-636
Field studies			
	Single dose		B826C-ES-16-640
			B826C-ES-16-641
			B826C-BE-16-642
	Split dose		B826C-ES-16-661
			B826C-ES-16-662
			B826C-BE-16-663
Field vac + experimental challenge	Single dose	PCV2a at 6w post vac	B826R-US-18-821
		PCV2b at 6w	B826R-US-18-820
		PCV2a at 23w	B826R-US-18-817
		PCV2b at 23w	B824R-US-18-816
		PCV2d at 23w	B824R-US-19-890

Dose determination

The predecessor product of CircoMax Myco and CircoMax is the porcine vaccine Suvaxyn Circo+MH RTU which was authorised by the centralised procedure in November 2015. CircoMax Myco and CircoMax contains the same chimeric PCV2a master seed as Suvaxyn Circo+MH RTU. The potency specification of the PCV2a component differs between the two vaccines with regard to interval range between minimum and maximum potency and with regard to reference strain. Additionally, CircoMax Myco and CircoMax both contain the new chimeric PCV2b strain for which a new master seed was established. The chimeric PCV2b was essentially built the same way as the chimeric PCV2a, using the same PCV1 strain as the backbone for inclusion of a PCV2b ORF2 gene sequence.

The applicant submitted a total of three dose determination studies (one for PCV2a; two for PCV2b) following single dose administration. Additionally, one dose determination study for the PCV2b following the split dose administration (2x1 ml) was submitted. The four studies showed that a potency of 1 RP for the PCV2 components was efficacious in MDA-negative piglets, even though higher potencies performed notably but not significantly better in these studies. However, study B823W-US.15-532 which included MDA-positive and -negative piglets, demonstrated that a potency of 1 RP was not sufficient to overcome interference by MDAs. Therefore, the minimum potency above 1 RP was recommended for the PCV2 components of CircoMax Myco and is also recommended for CircoMax. In the proposed SPC, a minimum RP is defined at 1.5 RP.

Onset of immunity

The applicant submitted nine challenge studies for CircoMax, seven for the single dose and two for the split dose vaccination scheme, in order to determine the onset of immunity of the PCV2a component of CircoMax at or below minimum potency.

Likewise, the applicant performed nine challenge studies, to determine the onset of immunity of the PCV2b, including eight studies with the single-dose scheme and one study with the split-dose scheme, at or below minimum potency. Additionally, the applicant submitted one immunogenicity study with a virulent PCV2d challenge covering both the single dose and split dose vaccination schemes.

Results

Colonisation of lymphoid tissue leading to lymphoid depletion and histiocytic replacement associated with PCV2a infection was more variable following challenge, such that statistical reductions in vaccinated pigs could not be shown in all studies. This would have required more animals to investigate statistical differences. Since numerically less vaccinated pigs than control pigs showed lesions in lymphoid tissue after challenge in all studies and significant differences were achieved in the majority of studies for lymphoid depletion and colonisation then, overall, a reduction in viral loads and lesions in lymphoid tissues caused by PCV2a could be considered demonstrated.

Challenges with a heterologous PCV2b strain consistently induced viremia, fecal shedding and tissue lesions. Vaccination significantly reduced the amount of virus in blood and faeces as well as the frequency of viremic and shedding pigs. Vaccination also reduced the frequency of pigs with lymphoid tissue PCV2 colonisation and lesions. In conclusion, an overall reduction in viral loads and lesions in lymphoid tissues caused by PCV2b was demonstrated.

In one single-dose onset of immunity study (study B822R-US-16-582) including groups challenged with PCV2b, with two different vaccine batches, as well as a placebo and negative control groups, significant differences could not be demonstrated for each parameter between vaccinated and both control groups because numerous piglets were excluded from the analysis due to sero-positivity, resulting in an underpowered study.

An additional immunogenicity study B820R-US-17-747 with a virulent PCV2d challenge demonstrated cross-protection afforded by CircoMax against viremia and fecal shedding caused by a PCV2d infection and confirmed the stimulation of cell-mediated immune responses against PCV2a, PCV2b and PCV2d. The onset of immunity against PCV2d was six weeks following a single dose and three weeks following a split dose scheme of CircoMax.

These studies demonstrated protection against the subtypes 2a and 2b as well as cross-protection against subtype 2d and are thus considered acceptable for protection against the PCV2 subtypes 2a, 2b and 2d.

It was concluded that vaccination with CircoMax by the recommended route with doses as recommended in the SPC was efficacious and met efficacy requirements 3 weeks post vaccination.

Duration of immunity

A total of six duration of immunity studies were submitted. Two studies were performed for each PCV2 fraction of the vaccine after single dose administration, and one study for each PCV2 fraction was submitted after split-dose administration. Virulent challenges for both virus fractions (PCV2a and PCV2b) were performed approximately 23 weeks after vaccination corresponding to the normal production lifespan of commercial pigs.

Vaccine batches used in these studies contained the PCV2 fractions at a potency of approximately 1 RP and below the minimum potency (RP≤ 1.5). All challenges induced sufficient viremia and shedding in non-vaccinated control pigs, whereas PCV2 tissue colonisation and lesions were less frequently observed in non-vaccinated control pigs. There was less PCV2 viremia and virus fecal shedding after challenge at 23 weeks following either vaccination schemes. Protection in terms of reduced tissue colonisation and lesion scores was shown in studies where the challenge was virulent enough. A duration of 23 weeks was accepted for both PCV2 genotypes contained in CircoMax.

Maternally derived antibodies (MDA)

A total of seven MDA studies were submitted in order to reveal the influence of maternally derived antibodies on the efficacy of CircoMax. Four MDA studies were performed in MDA positive piglets to assess the efficacy of the PCV2a component of CircoMax Myco, with an additional three MDA studies for the PCV2b component, according to recommendations from the EMA reflection paper describing the demonstration of MDAs on vaccine efficacy.

For the PCV2a studies, one study with the single dose vaccination scheme (B828R-US-16-669, Relative Potency PCV2a and PCV2b were 1.5-2.0) confirmed reduced viremia and fecal shedding when administered to MDA positive piglets. Infection and depletion of lymphoid tissue was also reduced, although a significant difference was not shown because the challenge was not virulent enough to induce sufficient tissue lesions. A second study (B828R-US-18-833, PCV2a and PCV2b RP 1.69 and 1.54 respectively) was underpowered as too many pigs had to be excluded from the analyses, because they did not possess any MDAs before vaccination. Nevertheless, results showed a significant reduction in fecal shedding and lymphoid depletion of the vaccinated pigs, that were available for analysis. A third study with MDA positive piglets using the split dose vaccination scheme (B828R-ES-17-707, PCV2a and PCV2b RP 1.5) was invalid because the PCV2a challenge was not virulent enough. This study could only be regarded as supportive. In the repeated split dose study (B828R-US-18-797, PCV2a and PCV2b RP 1.5), protection against viremia, shedding, lymphoid tissue infection and tissue lesions caused by PCV2a could be demonstrated in MDA positive pigs following vaccination.

For the PCV2b studies, results of the first study with the single dose vaccination scheme (B828R-ES-15-476, PCV2a and PCV2b RP 1.0-1.5) did not show any protective effect of vaccination in the presence of MDAs. MDA titres before vaccination were very high in this study because dams were vaccinated during pregnancy. A repeated study (B828R-ES-16-613, PCV2a and PCV2b RP 1.5-2.0) with piglets that had moderate MDA levels between 0.5 and 1.3 S/P demonstrated a significant reduction in viremia and lymphoid colonisation and a numerical reduction in fecal shedding, lymphoid depletion and histiocytic replacement caused by PCV2b. Thus, vaccination could overcome adverse effects of MDAs as long as MDA levels were not very high. Consequently, an SPC warning is included in section 4.9 to postpone vaccination when very high MDA levels are expected. A third study was performed using the split dose scheme (B823W-US-15-532, titration with relative potencies of PCV2a and PCV2b from 1.0 to 5.0) and showed, that PCV2b potencies of >1 RP were required to overcome the adverse effects of MDAs, as already discussed in the dose determination section. An additional SPC recommendation is included in section 4.9 of the SPC to use the split dose vaccination scheme in piglets with moderately high levels of MDAs. The two vaccination schemes were never compared in MDA positive piglets in the same study design. Comparing the efficacy results of all MDA studies demonstrated that the split dose vaccination scheme provided notably better protection against PCV2 infection than the single dose scheme in the presence of MDAs.

It was concluded that vaccination by the recommended route with doses of the minimum content recommended in the SPC were efficacious and met the Ph. Eur. efficacy standard including MDA positive animals.

Interactions

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

Field trials

In support of the efficacy of CircoMax under field conditions, six studies conducted with the parent product CircoMax Myco were conducted in two different EU countries and involving 3-day-old pigs (split dose: 3 studies) and 3-week-old pigs (single dose: 3 studies). The studies conducted in Spain were designed to confirm the claims for PCV2; protocol amendments reflect the applicant's decision to change the intended claim for this vaccine to PCV2-related claims only and not PCV2 genotype specific claims. The studies conducted in Belgium were designed to confirm the claims for *M. hyopneumoniae* relevant to the parent product CircoMax Myco.

Study reference	Study title	Batch used
B826C-ES-16-640	Evaluation of the safety and efficacy of a Porcine circovirus Type 1-Type 2 chimera, killed virus - *Mycoplasma hyopneumoniae* vaccine when administered to piglets at 3 weeks of age under field conditions in Spain.	229878A
B826C-ES-16-641	Evaluation of the safety and efficacy of a Porcine circovirus Type 1-Type 2 chimera, killed virus - *Mycoplasma hyopneumoniae* vaccine when administered to piglets at 3 weeks of age under field conditions in Spain.	
B826C-BE-16-642	Evaluation of the safety and efficacy of a Porcine circovirus Type 1-Type 2 chimera, killed virus - *Mycoplasma hyopneumoniae* vaccine when administered to piglets at 3 weeks of age under field conditions in Belgium.	
B826C-ES-16-661	Evaluation of the safety and efficacy of the flexible dose of a Porcine circovirus Type 1-Type 2 chimera, killed virus - *Mycoplasma hyopneumoniae* vaccine when administered to piglets at 3 days and 3 weeks of age under field conditions in Spain.	
B826C-ES-16-662	Evaluation of the safety and efficacy of the flexible dose of a Porcine circovirus Type 1-Type 2 chimera, killed virus - *Mycoplasma hyopneumoniae* vaccine when administered to piglets at 3 days and 3 weeks of age under field conditions in Spain.	
B826C-BE-16-663	Evaluation of the safety and efficacy of the flexible dose of a Porcine circovirus Type 1-Type 2 chimera, killed virus - *Mycoplasma hyopneumoniae* vaccine when administered to piglets at 3 days and 3 weeks of age under field conditions in Belgium.	

The same vaccine batch no.: 229878A containing antigens at (or close to) minimum levels (PCV2a at 1.5 RP, PCV2b at 1.7 RP and *M. hyopneumoniae* at 1.5 RP) was used in all six studies.

All six studies were randomised, negatively controlled, good clinical practice (GCP) compliant studies aimed to assess the safety and efficacy of the 'single dose' and 'split dose' vaccination schemes under field conditions. Studies were performed at two different locations in Spain and in a farm in Belgium.

Results

An overview of the main results with CircoMax Myco is given in the table below:

	Single dose			**Split dose**		
Study site	ES B640	ES B641	BE B642	ES B661	ES B662	BE B663
Mortality % (Con vs Vac)	9.6_9.3	23.2_21.6	6.5_6.1	12.5_12.1	36.2_32.1	9.6_7.6
Mortality difference	ns	ns	ns	ns	ns	ns
Body Weight gain	ns	+	ns	+	ns	ns
PCV parameters						
PCV strains detected	2b	2a 2d	2a	2b 2d	2a	2a
Viremia	+	+	+	+	+	+
Fecal shedding %	ns	ns	ns	ns	ns	ns
Fecal shedding amount	+ 5 mpv	+ ≥3 mpv	ns	+ ≥4 mpv	+ ≥3 mpv	ns
PCV2 colonization	+	+	ns	+	ns	ns
Lymphoid depletion	(ns)	ns	ns	ns	+	ns
Histiocytic replacement	+	+	ns	ns	ns	ns
Systemic PCV2 disease	ns	ns	-	ns	ns	-
Subclinical PCV2 infection	+	+	-	+	ns	-
Mycoplasma parameters						
MH serology	vac+	-	ns	vac+		vac+
MH lung lesions	+	ns	ns	ns	ns	ns

Legend	+	Significant difference in favour of the vaccinated group
	ns	No significant difference
	(ns)	Borderline significant difference
	-	No reactions observed in neither group
	mpv	months post vaccination

In general, no significant differences between vaccinated and non-vaccinated groups with regard to mortality were observed in any of the studies.

The efficacy claims regarding PCV2- infection were generally supported by the field efficacy data. Thus, all study sites confirmed an effect of vaccination against PCV viraemia. At the two study sites in Spain the results showed effect of vaccination on fecal shedding (amount), PCV2 colonisation, histiocytic replacement and subclinical disease. The natural challenge at the study site in Belgium was apparently lower and no effect was seen on the secondary efficacy parameters.

In conclusion the field studies consistently confirmed the protective effect of the PCV2 viraemia and for the secondary PCV indicators for subclinical disease. The positive effect was seen both under the single dose and the split-dose vaccination schemes.

The field studies carried out with the parent trivalent vaccine CircoMax Myco on six farms showed beneficial body weight effects on two of the six study herds (B826C-ES-16-641 and B826C-ES-16-661) and the applicant initially suggested to extrapolate these findings to the bivalent vaccine CircoMax.

The CVMP concluded that a claim for reduction of body weight gain loss could not be granted for CircoMax based on the provided data. Data on body weight gain was exclusively based on studies with

the parent three-component vaccine, and extrapolation was not possible to the bivalent CircoMax vaccine for this parameter.

Supportive US studies with field vaccination followed by experimental challenge

Five US studies were presented to support efficacy against PCV2a, PCV2b and PCV2d. In these studies, the pigs were kept under field conditions until four to six weeks post vaccination.

At three weeks of age, which was Study Day 0, pigs were randomised and given either saline as placebo (T01) or vaccinated with 2 ml of one of three commercial batches of CircoMax (T02, T03, T04, batches 237330A, 280437F and 282997D, respectively) intramuscularly.

Challenge was carried out either six weeks after vaccination (PCV2a in B826R-US-18-821, PCV2b in B826R-US-18-820) or 23 weeks after vaccination (PCV2a in B824R-US-18-817, PCV2b in B824R-US-18-816, PCV2d in B824R-US-19-890).

For the studies with challenge six weeks after vaccination, 120 pigs were enrolled, whereas for the duration of immunity studies 160 pigs were included.

Euthanasia and necropsy were carried out three weeks after challenge.

The table shows post-challenge results as number out of three vaccine batches showing significant reduction in percent ever-positive or ever-abnormal for each parameter:

Study	Challenge	Viremia	Fecal sheeding	Lymphoid Depletion	Histiocytic Replacement	Lymphoid Depletion OR Histiocytic Replacement	Virus infection in lymphoied tissue – Immnuno-histochemistry
B826R-US-18-821	PCV2a 6 weeks	3	3	3	3	3	3
B826R-US-18-820	PCV2b 6 weeks	3	3	3	3	3	3
B824R-US-18-817	PCV2a 23 weeks	3	1	1	0 (Control group was also negative)	1	3
B824R-US-18-816	PCV2b 23 weeks	3	3	3	3	3	3
B824R-US-19-890	PCV2d 23 weeks	3	3	3	0 (also low values in control group)	3	3

The post challenge results support the reduction of the primary efficacy parameter viremia, and reduction of the secondary parameters: fecal shedding, lymphoid depletion, histiocytic replacement, lymphoid depletion OR histiocytic replacement, and virus infection in lymphoid tissue – immnuno-histochemistry. For challenge with PCV2a and PCV2b, these findings are generally consistent between batches, and for challenge at both 6 weeks and 23 weeks after vaccination. It is noted that an "onset" study is missing for PCV2d challenge.

Overall conclusion on efficacy

The laboratory studies have generally supported the 3 weeks claim for onset of immunity against PCV2a and PCV2b after the completion of either the single-dose or the split-dose vaccination schemes.

With regard to duration of immunity, the 23 weeks claim was supported for PCV2a and PCV2b components for both the single dose vaccination scheme and the split-dose vaccination scheme.

The field studies generally supported the claims of protection against PCV2a and PCV2b. Cross-protection against PCV 2d was demonstrated in three US studies with CircoMax Myco and five studies with CircoMax.

The applicant updated the PCV type 2 indication in the SPC in order to specify the subtypes against which efficacy has been demonstrated in line with the phrasing for the parent product. The point reads "Active immunisation of pigs against porcine circovirus type 2 to reduce viral load in blood and lymphoid tissues, fecal shedding and the lesions in lymphoid tissues associated with PCV2 infection. Protection was demonstrated against porcine circovirus types 2a, 2b and 2d''.

Comparing the efficacy results in all MDA studies demonstrates that the split dose vaccination scheme provides notably better protection against PCV2 infection than the single dose scheme in the presence of MDAs.

The EU field studies – which were carried out with the combined circovirus and mycoplasma vaccine CircoMax Myco - did not provide substantial evidence on reduction of PCV2 disease-induced losses of body weight as a potential direct or indirect impact of the *Mycoplasma hyopneumoniae* component on body weight gain could not be ruled out.

Part 5 – Benefit-risk assessment

Introduction

CircoMax is a vaccine containing porcine circovirus antigen (inactivated, recombinant), based on chimeric virus strains (PCV type 1/2a and PCV type 1/2b, respectively).

The product is indicated for the "Active immunisation of pigs against porcine circovirus type 2 to reduce viral load in blood and lymphoid tissues, fecal shedding and the lesions in lymphoid tissues associated with PCV2 infection. Protection was demonstrated against porcine circovirus types 2a, 2b and 2d."

The dossier was submitted in line with requirements of Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

In well-conducted laboratory studies, the vaccine was shown to induce active immunisation of pigs against PCV2 subtypes 2a and 2b and reduce viral load in blood and lymphoid tissues and fecal shedding caused by infection with PCV2; cross-protection against PCV 2d was demonstrated in three US studies with CircoMax Myco. Five new US field studies were provided with the fall-out vaccine dossier and these confirmed protection against PCV2a and PCV2b six weeks and 23 weeks after vaccination. Cross-protection against PCV2d was demonstrated 23 weeks after vaccination.

The product was shown to have an OOI at 3 weeks after vaccination with DOI of 23 weeks after vaccination.

The efficacy of the vaccine was adequately confirmed in the presence of MDA.

The applicant proposed a claim for reduction of body weight losses, but this was not consistently confirmed in the field studies. Furthermore, data on body weight gain was exclusively based on studies with the parent three-component vaccine, and extrapolation was not possible to the bivalent CircoMax vaccine.

Additional benefits

Not applicable.

Risk assessment

Quality

Information on the development, manufacture and control of the active substances and the finished product has been presented in a satisfactory manner.

The manufacturing processes of the two PCV antigens are identical and comprise standard virus production in pig kidney PK-15 cells followed by separation of micro carriers and cell material, and concentration, purification, and inactivation of virus. The manufacturing process is based on a seed lot system. The manufacturing processes are considered adequately controlled. Based on the data from six consecutive finished product batches, acceptable batch-to-batch consistency is overall considered demonstrated. Compliance with Ph. Eur. monographs 0062 *Vaccines for veterinary use* is generally considered demonstrated.

The applicant has committed to provide the following data post-marketing in order to further support the release specifications and the shelf life specifications:

- The applicant commits to provide the authorities with consistency data for the first commercial batch of vaccine prepared with different PCV2a antigen batch(es) as soon as these become available. A commitment letter has been provided including expected due dates for fulfilment.
- The applicant commits to conduct an additional stability study with the first commercial batch formulated with a different batch of PCV2a antigen and provide the authorities the data generated from the study. A commitment letter has been provided including expected due dates for fulfilment.

Safety

The applicant provided satisfactory risk assessments for the user and the environment and included appropriate warnings and guidance in the SPC where necessary.

In summary, the applicant has provided data showing that the IVMP has a safety profile with mainly local reactions and transient temperature increases as possible adverse reactions. The vaccine is safe in minimum age piglets when administered by the recommended route and regimens. The maximum potencies and safety statements of the SPC are considered supported and appropriate.

Based on the results it was concluded that the safety of the target animals was acceptable when the vaccine is administered according to the recommended schedule and via the recommended route.

Reproduction safety was not investigated as the product is only intended for piglets.

A user safety assessment in line with the relevant guidance document was presented. Based on that assessment, the potential health risk of the product to all users is considered low and acceptable when used in accordance with the SPC. The worst-case scenario for user safety is self-injection. Appropriate safety advice/warning statements are included in the SPC to mitigate the risks.

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

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 be efficacious to reduce viral load in blood and lymphoid tissues, fecal shedding and the lesions in lymphoid tissues associated with PCV2 infection. The applicant proposed a claim for reduction of body weight losses, but this was not consistently confirmed in the field studies. Furthermore, data on body weight gain was exclusively based on studies with the parent three-component vaccine, and extrapolation is not possible to the bivalent CircoMax vaccine.

CircoMax is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended and appropriate warnings have been included in the SPC. The withdrawal period is set at zero days.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for CircoMax approvable for the proposed claims:

Active immunisation of pigs against porcine circovirus type 2 to reduce viral load in blood and lymphoid tissues, fecal shedding and the lesions in lymphoid tissues associated with PCV2 infection. Protection was demonstrated against porcine circovirus types 2a, 2b and 2d.

Onset of immunity (both vaccination schedules): 3 weeks after (the last) vaccination.

Duration of immunity (both vaccination schedules): 23 weeks after (the last) vaccination.