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CVMP assessment report
Porcilis AR-T DF (EMEA/V/C/055/X/009)

Common name: Vaccine to reduce atrophic rhinitis in piglets

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

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Introduction

An application for an extension to the Community marketing authorisation for Porcilis AR-T DF was submitted to the EMEA on 5 May 2009 by Intervet International BV in accordance with Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II point 1.iii thereof.

The already authorised Porcilis AR-T DF is an aqueous vaccine (suspension for injection) containing as the active components ≥ 5.9 log2 TN titre Protein dO (non toxic deletion derivative of *Pasteurella multocida* dermonecrotic toxin) and ≥ 4.2 log2 Aggl. titre inactivated *Bordetella bronchiseptica* cells per dose of 2 ml. Protein dO is produced by the genetically modified *Escherichia coli* strain PTO-1. The *Bordetella bronchiseptica* cells belong to strain Bb7. The active substances are mixed with the dl-α-tocopherol based aqueous adjuvant. Formalin is added as preservative.

The indication for Porcilis AR-T DF is reduction of clinical signs of progressive atrophic rhinitis in piglets by passive oral immunisation with colostrums from dams actively immunised with the vaccine.

The vaccine is presented in multidose glass vials containing 20 ml (10 doses of 2 ml) and 50 ml (25 doses of 2 ml). The volume of a single dose is 2 ml by intramuscular injection to pigs of 18 weeks and older. The basic vaccination consists of two doses with a 4 week interval between them. The first injection should be administered 6 weeks before the expected date of farrowing. Revaccination (with a single dose) should be carried out 2 to 4 weeks prior to each subsequent farrowing.

The extension application is primarily to replace the original *E. coli* host with a new *E. coli* host, which results in a new expression system. (The plasmid pSPE857 encoding Protein dO remains unaltered). A slightly different declared strength of the active substance Protein dO is proposed, resulting from re-calculation of release requirements based on a larger number of finished product batches. Several other changes are also proposed, such as changes to starting materials, the addition of larger pack sizes (100 ml and 250 ml PET vials), changes to the preparation of the finished product and changes to the control tests.

Part 1 - Administrative particulars

The pharmacovigilance system in place is considered appropriate.

Part 2 - Quality

Composition

Porcilis AR-T DF is an inactivated aqueous vaccine, where the immunogenic components are mixed in a dl-alpha-tocopherol based adjuvant. The active substances in the vaccine is Protein dO (≥6.2 $\log_2$ TN titre), a non-toxic derivative of *P. multocida* dermonecrotic toxin produced by a genetically modified *E. coli* strain and inactivated strain Bb7 *B. bronchiseptica* cells (≥4.2 $\log_2$ Aggl. titre). Formaldehyde is added as preservative.

Container

Ph. Eur. hydrolytic type I glass (20 and 50 ml) or polyethylene terephthalate (PET) (20, 50, 100 and 250 ml) vials are to be used. Both types of containers are closed with Ph. Eur. halogenobutyl rubber stoppers and sealed with coded aluminium caps.

Development Pharmaceutics

The production process of Porcilis AR-T DF has been changed in order to improve the robustness and consistency of the Protein dO antigen. The expression system was identified as the main problem due to instability of the recombinant Protein dO-encoding plasmid in the *E.coli* host. This could only be solved by replacing the original *E.coli* host with a new *E.coli* host. The plasmid pSPE857 encoding Protein dO remained unaltered. Consequently a new master seed and a new working seed are introduced. During the extensive analysis of the Protein dO production process, the extraction and purification methods used during the down stream processing were identified as critical steps, and these methods were optimised. Furthermore, other changes to the production processes for the Protein dO and *B. bronchiseptica* antigen, preparation of the adjuvant, and to the blending and filling of the final product were introduced.

The comparability studies performed indicate that the Protein dO produced from the original and new master seeds (MSs) are identical with regard to the primary structure of the protein. Furthermore, it is shown that the same toxin neutralizing epitope is present. Supplementary comparative data indicate that the secondary and tertiary structures are identical for the proteins derived from the current and proposed production processes. Based on the comparative studies provided, the Committee considered that sufficient comparative studies have been performed, and that the proteins derived from the current process and the proposed process are comparable.

Method of manufacture

The manufacturing processes for the *B. bronchiseptica* cells, Protein dO, adjuvant and final vaccine are described, including the changes introduced in this line extension. Relevant validation studies are presented.

Control of starting materials

Active substance

The manufacturing process and controls for the *B. bronchiseptica* cells remain unchanged. The production strain for the Protein dO antigen has been changed by replacing the *E. coli* host; the plasmid containing the gene encoding Protein dO is unchanged from the initial application (pSPE857). A new MS and working seed (WS) have been prepared.

Excipients

All the starting materials which are the subject of Ph. Eur. monographs comply with the current requirements, including the dl-α-tocopheryl acetate, polysorbate 80, polysorbate 20, sodium chloride, phosphate buffer, simethicone, formaldehyde solution, ampicillin and water for injections.

All the starting materials of biological origin comply with current TSE legislation and relevant guidelines.

Qualitative and quantitative information are provided for all the media and solutions used.

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

All starting materials of ruminant origin comply with Ph. Eur. monograph 5.2.8, and EMEA guidelines EMEA/410/01 and EMEA/CVMP/019/01. A risk assessment of materials or substances used in the manufacture and preparation of the product, and relevant TSE Certificates of Suitability are provided.

Control tests during production

During the production of the *B. bronchiseptica* antigen the following in-process controls are performed: sterility of medium, purity and identity of inoculum, purity and identity of culture, test on inactivation, determination of antigen content and sterility of the antigen concentrate.

Details of the method used for the determination of the antigen content are provided and assessed as satisfactory.

During the production of the Protein dO the following in-process controls are performed: sterility of medium, purity and identity of inoculum, purity and identity of culture, test on the removal of Protein dO production strain, determination of antigen content, and sterility of the antigen concentrate.

A test on filling volume is performed during filling of the final vaccine.

Justification was provided for the absence of a test for bioburden before sterile filtration. The sterile filtration steps are controlled with regard to filter integrity.

Control tests on the finished product

The methods used for the control of the finished product and the specifications were provided and considered satisfactory.

The following tests are included in the finished product specification: sterility and second inactivation control, safety, appearance, free formaldehyde, endotoxin, dl-α-tocopheryl acetate, pH, potency test for the Protein dO antigen, potency test for the *B. bronchiseptica* antigen, and final inspection.

However, there are now some justified differences from the finished product specification for the original vaccine. These include different limits for the potency test (recalculated based on many batches of both Protein dO and *B. bronchiseptica* antigen). The potency tests are also considered acceptable as identification tests. The lower limit for free formaldehyde is changed (to a limit justified in the preservative efficacy study). Justification was also provided for the sterility test to be the second inactivation test. The limits for the safety test are considered acceptable. The individual safety data of the batch safety test for new batches has been provided to define finally acceptable release requirements for the batch safety test.

The results of the analysis of three consecutive production runs of the vaccine were presented which comply with the required specification. The variability of the antigen content for the new protein dO batches is justified.

Stability

Active substances:

The proposed shelf-life and storage conditions for both antigens were considered justified. Comparability of the new and original Protein dO was demonstrated, the batch release and stability

results indicated that there are no differences between batches produced with the original and new production strain, and therefore it was considered acceptable that the antigen shelf-life is based on original data.

Finished product:

The proposed shelf-life is 60 months for both the glass vials and the PET containers when stored at 2-8°C. A package of stability data was provided to support the claimed shelf-life, and this included real-time data on both pilot scale and production batches stored in both types of containers. Stability studies on batches of the finished product prepared from new batches of Protein dO antigen are still on-going but the applicant has committed to provide the stability results at the end of the study.

An in-use shelf life of 10 hours was justified by data from a broached vial study (with storage of the broached vial at 30°C).

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

Not applicable.

Overall conclusions on quality

The changes introduced in this extension application were described in sufficient detail and considered acceptable by the Committee. The quality data can be considered in compliance with the relevant requirements of the relevant directives, guidelines and monographs of Ph. Eur.

The comparability studies performed indicate that the Protein dO produced from the original and new MS are identical.

The new Protein dO MS and WS are acceptably prepared and described.

The comparability of the stability of the new and original Protein dO was demonstrated, the batch release and stability results indicated no differences between batches produced with the original and new production strains, and the CVMP considered it acceptable that the antigen shelf-life is based on original data, although a new confirmatory stability study is on-going.

Part 3 – Safety

The robustness of the Protein dO (a non-toxic deletion derivative of *Pasteurella multocida* dermonecrotic toxin) production process had been identified as a potential area for improvement in the original application. The expression system PTO-1 was identified as the main problem due to instability of the recombinant Protein dO-encoding plasmid pSPE857 in the original *E. coli* host. Studies demonstrated this stability could only be improved by replacing the original *E. coli* host with a new *E. coli* host, resulting in a new expression system (PTO-W). (The plasmid pSPE857 encoding Protein dO remained unaltered.) The change described above is the main reason for this extension application.

The Committee agreed the change was within the scope of Commission Regulation (EC) 1085/2003, Annex II, Point 1 (iii): "Replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure. Modification of the vector used to produce the antigen/source material, including a new master cell bank from a different source where the efficacy/safety characteristics are not significantly different".

Safety documentation

Two new studies (from 2008), supplementing the original safety studies have been performed with vaccine produced with the new manufacturing method, including the new *E. coli* host.

The CVMP agreed that, in general, the data presented from these studies showed that Porcilis AR-T DF could continue to be considered sufficiently safe with regard to local and systemic reactions after vaccination. Mild and transient local or systemic reaction after vaccination may continue to occur (as with the original product). A double dose of Porcilis AR-T DF had resulted in no unacceptable adverse effects on target animals. Porcilis AR-T DF was considered by the Committee to be safe regarding reproductive performance when administered to pregnant gilts and sows.

The overall risk to the environment of Porcilis AR-T DF was still considered to be negligible.

There was no evidence that the new vaccine would be less safe than the currently approved vaccine.

The SPC and package leaflet were updated to current standards with regards to advice and warnings regarding adverse reactions, overdose symptoms, etc.

Overall conclusions on safety

Data were provided from safety studies with both the original and the new vaccine.

The data presented from these studies showed that Porcilis AR-T DF could be considered sufficiently safe with regard to local and systemic reactions after vaccination. Safety of the new vaccine was at least as good as for the original vaccine. A mild and transient local or systemic reaction after vaccination may occur (as with the original vaccine). It was noted that a double dose of Porcilis AR-T DF had no unacceptable adverse effects on the target animals. Porcilis AR-T DF is considered as safe regarding reproductive performance when administered to pregnant gilts and sows.

The overall risk to the environment of Porcilis AR-T DF is still considered as negligible.

There is no evidence that the new vaccine is less safe than the currently approved vaccine.

The Committee agreed the authorisation requires an increased PSUR reporting frequency (for all presentations with data lock points based on the original birth date of the product) in line with article 49(3) of Regulation (EC) No. 726/2004 with 6-monthly intervals for the first two years, yearly for the next two years and thereafter at 3-yearly intervals for the following reasons: pivotal parts of the production process have been radically changed; new follow-up measures regarding safety data have been agreed; and therefore new data concerning safety and stability will be obtained which could impact on the benefit-risk balance on the product and therefore an increased PSUR reporting frequency is proposed.

Part 4 – Efficacy

Porcilis AR-T DF is administered to female pigs (sows and gilts) for the passive immunisation of their progeny against clinical signs of progressive atrophic rhinitis via the colostrum of vaccinated dams. Therefore, piglets of the vaccinated sows can be regarded as the target animal for the vaccine.

Data were provided from two new efficacy studies performed with the new vaccine produced according to the new manufacturing method, including the new *E. coli* host. These data supplement

the existing efficacy studies. The marketing authorisation holder provided data to prove equal efficacy between the original and the new vaccine by means of comparative serology, i.e., antibody levels, between the original studies and new studies. No challenge studies were performed with the new vaccine.

Overall conclusion on efficacy

The marketing authorisation holder submitted a number of studies with the original vaccine in order to document the efficacy, and these can be compared with the two studies for the new vaccine, for which serology in sows and colostrums are provided.

A new safety and efficacy trial performed with the new vaccine should be the basis for comparison of the serological levels between the original and the new vaccine, however it was somewhat deficient in that no serum sample was taken after the second vaccination for comparison of antibody levels in the sows, and no serum samples were collected from the piglets. Moreover, it was a clear necessity that a correlation between serology and protection could be established, i.e., between the antibody titres in serum and colostrum (or a cut-off value) and protection against disease. However, an additional study did show such a correlation and the Committee accepted that the new Porcilis AR-T DF vaccine induced antibody levels in sows and their offspring against the *P. multocida* toxin and *B. bronchiseptica* at or above the levels measured in earlier challenge experiments in which vaccination with Porcilis AR-T DF was shown to induce protection against atrophic rhinitis.

Challenge studies in 6 weeks old piglets were made in the original dossier according to the Ph. Eur monograph. As no further studies in pigs up until slaughter were provided, no meaningful duration of immunity could be established, so no reference is made in the SPC, section 4.2.

Part 5 – Benefit Risk Assessment

The benefit-risk balance for the original vaccine has been positive since its authorisation. The manufacturing process is now being changed in a number of areas, including the used of a new *E. coli* host for production of the deleted *P. multocida* toxin. The safety of the new vaccine is acceptably documented, but the efficacy documentation rests on serology data from vaccinated sows, therefore no duration of immunity for their piglets could be assigned. The immunogenicity, and thereby the protective capacity of the new vaccine, has been demonstrated to be the same or higher than the levels measured for the original vaccine, therefore the Committee concluded that the benefit-risk balance remains positive.

Conclusion

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