EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the initial scientific discussion for the approval of Coxevac (as published in July 2010). For information on changes after this date please refer to module 8.

1. Summary of the dossier

Inactivated *Coxiella burnetii* vaccine

On 14 July 2010 the Committee for Medicinal Products for Veterinary Use (CVMP) adopted a positive opinion, recommending the granting of a marketing authorisation under exceptional circumstances for the veterinary medicinal product COXEVAC, suspension for injection, intended for the active immunisation of cattle and goats to reduce infection with *Coxiella burnetii*. The applicant for this veterinary medicinal product is Ceva Sante Animale.

The active substance of COXEVAC is inactivated phase-I *Coxiella burnetii,* strain Nine Mile, an inactivated bacterial vaccine for cattle and goats. The vaccine induces active immunity against Q-fever in cattle and goats.

The benefits of COXEVAC are the active immunisation of cattle to lower the risk for non-infected animals vaccinated when non-pregnant to become a shedder (five-times lower probability in comparison with animals receiving a placebo), and to reduce shedding of *Coxiella burnetii* in these animals via milk and vaginal mucus, and the active immunisation of goats to reduce abortion caused by *Coxiella burnetii* and to reduce shedding of the organism via milk, vaginal mucus, faeces and placenta.

The most common side effects are: in cattle it is very common to see a palpable reaction of maximum diameter of 9 to 10 cm at the injection site, which may last for 17 days. The reaction gradually reduces and disappears without need for treatment. In goats it is very common to see a palpable reaction of 3 to 4 cm diameter at the injection site which may last for 6 days. The reaction reduces and disappears without need for treatment. In goats it is also very common to observe a slight increase of rectal temperature for 4 days post-vaccination without other general signs.

The CVMP considered that due to the current epidemiological situation of Q-Fever and the consequent threat to animal and public health there are objective and verifiable reasons for recommending the granting of a Marketing Authorisation under exceptional circumstances for this product, namely that

- the epidemiological risk for animal health in the EU and the associated zoonotic risk constitute an objective need to have authorised products available for use in the coming months
- vaccination may form an important element of disease control policies at national, regional or Community level
- the quality and safety of the product have been satisfactorily demonstrated as well as key elements of efficacy in cattle and goats
- the applicant has agreed to the necessary post-authorisation specific obligation to further investigate and elaborate the efficacy of the product in goats.

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2. Quality assessment

Table of qualitative and quantitative particulars

Ingredients	Quantity per dose (1 ml)	Function
Active ingredient *Coxiella burnetii* strain Nine Mile, phase I	72 QF Unit*	active ingredient
Excipients Thiomersal PBS**	 ≤ 0.02% w/v qs to 1 ml	 preservative diluent

* Relative ELISA value in comparison with a reference item
** PBS : sodium chloride (9 g), potassium dihydrogen phosphate (0.227 g), disodium phosphate dehydrate (0.8908 g), water for injection (ad 1000.0 ml)

Containers

The containers are low density polyethylene (LDPE) bottles, closed with a silicone-coated bromobutyl stopper and sealed with an aluminium cap.
The stoppers are sterilised by autoclaving. The LDPE bottles are sterilised by irradiation by the supplier. Information on the quality standards for the containers and rubber closures were provided. Compliance with European Pharmacopoeia, where appropriate, was demonstrated.

Development of the product

Justification of the antigen type present in the vaccine
The use of the Nine Mile strain (Phase I) as a vaccine strain is recommended by the World Organisation for Animal Health (OIE). *Coxiella burnetii* has 2 antigenic forms, called Phase I and Phase II. The bacteria in Phase I have longer lipopolysaccharide chains on their surface than those in phase II, and thereby have different antigenic properties. The infective form is phase I, found under natural circumstances. The phase-II form exists only under laboratory conditions, after serial passages on embryonated eggs or cell culture. Administration of phase-II antigen induces the production of antibodies against phase-II antigen only, whereas vaccination with phase-I antigen elicits also the production of antibodies against phase-I and phase-II antigens.

The major antigen which is phase-I specific is the phase-I LPS. There are other proteins which can be different between phase I and phase II but these are not considered as important for inducing protective immune responses.

It was demonstrated that phase-I LPS is the main antigen which is responsible for protection induced by vaccination with inactivated phase-I bacteria. Briefly, in BALB/c mice both formalin-inactivated whole-cell phase-I *Coxiella burnetii*, and LPS extracted from phase-I bacteria were equally effective against challenge with *C. burnetii*, while inactivated, whole-cell phase-II bacteria or phase-II LPS did not confer any protection. This indicates also that the common antigens which can be found on both phase-I and phase-II bacteria play no important role in protection against *C. burnetii* infection.
It is not surprising that phase-I LPS is the protective antigen because *C. burnetii* isolated from naturally infected animals is always in phase I and the main phase-I specific antigen is the phase-I LPS. The phase-I LPS makes it possible for the bacterium to avoid the recognition mechanism of the animal's immune system. From the literature it is clear that the long LPS associated with phase-I is the most immunogenic and induces protective immune responses.

Justification for the development of an *in vitro* potency test
A serology test was first tested for potency testing. Neither phase-I nor phase-II antibody test were retained because:

- a potency test based on these antibody ELISA tests would give too variable results (high CV%).
- identical antigen amounts induce different results, making the discriminative power of the potency test becoming too low when these ELISA tests are used.

Instead, a phase-I antigen quantification ELISA test was developed for potency testing.

Antigen phase control in the vaccine
Phase-I bacteria can change to phase II but it takes quite a number of egg or cell culture passages. In the literature it is described that *Coxiella burnetii* Phase-I strain, starts to change from phase I to phase II after numerous (8 or more) egg passages. It has to be noted that the change from phase I to phase II is gradual, which means that during egg or cell culture passages the ratio of phase-II cells gradually increases in the mixture of the phase-I and phase-II cells, until it becomes fully phase II.
The Master Seed (MS) for Coxevac was established in such a way, so the risk of production of Phase-II antigen is negligible. Seed-lot system is applied, using only very limited egg passages up to the Working seed(WS) and to the production of the active ingredient.
In order to confirm that the antigen is indeed in phase I, specific identity tests are also performed.

Method of preparation

Relevant details were provided concerning production of the Working Seed from the master seed and production of the antigen before purification: egg preparation, inoculation with working seed, harvest of yolk sacks and treatment of those prior to inactivation. The inactivation process was described in detail. Treatment of the inactivated material up to the active ingredient was also well explained.

Inactivation
After treatment, the harvested material is then diluted with phosphate buffered saline (PBS) containing formaldehyde and inactivation is carried out under regular stirring. Samples are taken to verify inactivation and sterility. The result of the inactivation test must be known before the antigen is moved out of the high security area. The inactivated antigen is stored at 5±3°C until further processing.

Concentration and Purification
In order to remove useless egg components from the harvest, the inactivated antigen is first concentrated and then purified.

The resulting suspension is stored at 5±3°C until preparation of the bulk vaccine. A sample is taken for sterility testing, antigen content and phase–identification. The purity of the active ingredient from egg-yolk sack derived material is also measured with an ELISA test.

Blending
The active ingredient is diluted with PBS to a final concentration of *Coxiella burnetii* particles of 100µg/ml, and stirred. Thiomersal solution is added to the suspension to obtain a final thiomersal concentration of 0.01% w/V.

Filling, labelling and packaging
The bulk product, maintained at 5±3°C, is filled into the sterile bottles with a filling equipment. Sterile rubbers are inserted and the bottles are then capped. Validation of the filling volumes are provided. The presentations are then labeled and packaged.

Consistency of production
Production data and results from in-process controls are provided on three consecutive batches in order to support the consistency of production.

Production and control of starting material

Starting materials listed in a pharmacopoeia

Satisfactory details were provided for following substances: Disodium phosphate dihydrate; Formaldehyde solution (35%); Potassium dihydrogen phosphate; Sodium chloride; SPF eggs; Thiomersal; Water for injection; LDPE bottle

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

- ***Coxiella burnetii* strain Nine Mile, phase I**

Origin and history : the bacteria was isolated from a tick (*Dermacentor andersoni*) in 1935 in the USA. The passage history although not recent is reasonably detailed .

Controls on Master seed bacteria :

- sterility

- bacterial and fungal : in compliance with Eur. Ph. 2.6.1.
- Mycoplasma : in compliance with Eur. Ph. 2.6.7.
  - extraneous agents: for this point, the applicant's approach is based on a risk analysis and testing, according to following steps: after having identified the potential extraneous agents susceptible to be present (step 1), some can be excluded based on geographical and scientific exclusion criteria (step 2 – in the case of missing or contradictory information, the agent was considered as present); others can be excluded because of their pathogenesis or passage properties (step 3).
  - The remaining agents need to be tested for in the MSB - tested in reality on WSB because of practical reasons (step 4). This was however not always possible, either because no reliable test is available, or because a biosafety III level laboratory or a normal PCR laboratory was not found to examine an inactivated nucleic acid extract sample for a given agent. These agents underwent a risk assessment (step 5).

Conclusion on the extraneous agents testing and risk assessment: the applicant concluded that the MSB is free of extraneous agents. The CVMP confirmed that the applicant's approach can be accepted.

Controls on Working Seed Bacteria:
The usual European Pharmacopoeia tests like bacterial and fungal sterility, absence of mycoplasma are carried out along with infective titre.

Starting materials of non-biological origin and in-house media

Satisfactory details were provided for following substances: methyl tert-butyl ether and PBS solution

Specific measures to prevent TSE risk

Coxiella burnetii and SPF eggs are the only raw materials of biological origin involved in the manufacturing process. As they are not of ruminant origin, the TSE risk is negligible.

Control tests during production

The aim of control tests during production is to monitor quality of SPF eggs used in production, infective titre of the harvest material before inactivation, completeness of the inactivation. Antigen content, sterility and bacterial phase status are also controlled on the active ingredient. The various tests carried out as in process control are described, along with relevant details and pass criteria. validation reports were also provided.
Data of in-process control tests on 3 batches of antigen were given in a tabulated form and found to be satisfactory.

Control tests on the finished product

The aim of control tests on the finished product is to confirm the completeness of the inactivation, check physical aspects, sterility, safety and potency, and assay the preservative. The methods used for the control of the finished product and the specifications were provided.

The *in vitro* potency is described. It is based on a phase-I antigen ELISA. All details to replace all key materials involved in this test (reference and control items, positive sera…). The submitted validation studies could show, when analysed in more details, the ability for the ELISA test to detect sub-potent batches. The applicant's approach can be accepted.

Batch-to-batch consistency

Batch release control tests on 4 batches of finished product are provided and are satisfactory.

Stability of the finished product

The different tests carried out (Physico-chemical parameters, sterility and potency) supported the following storage periods:

- Interim products:
    - inactivated antigen: 6 months
    - inactivated concentrated antigen: 6 months
    - purified antigen: 6 months

- Finished product: 12 months

In-use stability

Study results support an in-use shelf life of 10 hours after first opening the immediate packaging.

GENERAL CONCLUSION on Part II

The vaccine is produced in a high containment facility.

The vaccine contains Coxiella phase-I antigen in inactivated form.

A satisfactory control of inactivation is applied twice during the production and the risk of spreading live Coxiella into the environment has therefore been eliminated.

The applicant provided a very detailed and satisfactory extraneous agents risk assessment and vaccine strain testing, which had been the subject of a Scientific Advice request prior to submission of the dossier. The test results and this risk assessment allowed the CVMP to conclude that the risk of the finished product containing extraneous agents is negligible.
Additionally, sterility tests are carried out at different stages of manufacturing such as the seed materials, two times on the antigen itself and finally on the finished product thereby providing additional assurance on the purity profile of the vaccine.
The antigen undergoes a purification process which removes egg yolk material and the vaccine does not contain any adjuvant, all measures resulting in a reduced risk of adverse reactions in the target animals.

The potency test proved to be a sensitive and specific indication of efficacy of the product. The test is capable of distinguishing sub-potent from potent batches by measuring the antigen amount which is linked to efficacy, since the vaccine does not contain an adjuvant.

The potency titres of several finished batches were tested during production and the results showed that the vaccine has an approved shelf life of 12 months.

Overall the CVMP concluded that the quality of the vaccine is satisfactory.

3. Safety assessment

The vaccine does not contain any adjuvant and its antigen is purified (specifically with regard to egg yolk derived material) as well as inactivated. The safety of the vaccine has been tested in all target species in both laboratory tests and field studies.

The data available are deemed sufficient to establish the safety profile of COXEVAC. The vaccine is globally well tolerated in each of the target species, even if some mild to moderate local swellings (sometimes with redness) are very common in both target species, sometimes quite extended and lasting several weeks.

More rarely pruritus, petechiae, wheals and suffusions could be observed. As these signs were identified only in one trial, it seems to be due to an artifact rather than a real property of the vaccine. Hence, it was not deemed necessary to mention them in the SPC.

Hyperthermia (sometimes above 40.5°C, as observed in young calves) appears to be the only general reaction identified in the target species.

One publication (Guoquan Zhang et al., 2007, Mechanisms of Vaccine-Induced Protective Immunity against *Coxiella burnetii* Infection in BALB/c Mice) mentions that vaccines produced from whole cell antigens can induce severe local or systemic adverse reactions, especially when administered to individuals with prior exposure to the agent.
The situation seems to be quite different for COXEVAC which contains a purified active ingredient: all the clinical signs seen in all 3 target species remained with acceptable limits; they did not have a negative impact on the physiological status of the animals, as the animals continued to behave and eat normally and showed normal weight gain or milk production after vaccination.

Environmental risk assessment

A satisfactory phase I assessment of risk for this inactivated vaccine, in accordance with EMEA/CVMP/074/95, is available. The final product contains no components which may exert a toxic effect and there are no pharmacologically active components included in this vaccine. On the basis of the phase I assessment, a phase II assessment is not required. COXEVAC is judged to present no risk to the environment.

Withdrawal periods

The preservative and excipients used in the product are listed in table 1 of the annex to Commission Regulation (EU) No 37/2010 and a withdrawal period of zero days was therefore accepted by the CVMP.

Overall, the CVMP concluded that COXEVAC is a product with an acceptable level of safety.

4. Efficacy assessment

General remarks
It is beyond the scope of this assessment report to take an exhaustive stock of the clinical signs and epidemiology of Q-fever. However, the following key points are raised, as they are considered useful to properly assess the efficacy data of COXEVAC:

C. burnetii infections are generally asymptomatic, including a lack of fever. When clinical findings are present, Q-fever symptoms are classically divided into acute or chronic phase:

- acute Q fever in mammals can lead to abortions, stillbirths and pneumonia. The abortion rate can range from 3 to 80% of pregnant females. High abortion rates are rarely observed, except in some caprine herds. In cattle, metritis is frequently the unique manifestation of the disease. Aborting

females recover rapidly and generally do not abort during the following gestations, while metritis can persist for several months.

- *C. burnetii* infection often becomes chronic in both humans and animals. Such persistent infections are mostly asymptomatic but may occur in pregnant females in the form of massive contamination of the placenta with *C. burnetii* leading to abortion or low foetal birth weight, mainly in sheep and goats, and lower birth weight and infertility in cattle. The female uterus and mammary glands are primary sites of chronic *C. burnetii* infection.

Shedding of *C. burnetii* into the environment occurs mainly during parturition (at due time, or early during abortion): over 10^9 bacteria per g of placenta are released at the time of delivery. Infected mammals also shed *C. burnetii* in milk, urine and faeces. Aborting females but also females with normal parturition as well as cows suffering from metritis can shed *C. burnetii* in milk for several months, even during several milking periods. Milk shedding is more frequent and lasts longer in cows and goats than in ewes. Ewes shed more and longer in vaginal discharges than goats, and can shed bacteria at subsequent pregnancies. Goats shed *C. burnetii* in faeces before and after kidding.

Shedding is considered intermittent in milk, faeces and urine in chronically infected goats, sheep and cattle.

In naturally or experimentally infected ruminant herds, *Coxiella burnetii* can be excreted in vaginal mucus, milk and faeces for periods from days to months.

From an immunological point of view, early studies suggested that both humoral- and cell-mediated immune responses are important for host defense against *C. burnetii* infection, while cell-mediated immunity probably plays the critical role in eliminating the organisms. T-cell immunity plays a major role in the control of Q-fever.

The intracellular survival of *C. burnetii* and establishment of persistent infection probably correspond to subversion of microbicidal functions of macrophages, as well as impairment of the T-cell immune response. In particular, the receptor used by each *C. burnetii* phase for entry into monocytes and macrophages is probably critical for its survival within these phagocytic cells.

However, the mechanisms of phase-I vaccine induced protective immunity are not well understood and it remains unknown what components of host defense are responsible for control of *C. burnetii* replication and clearance of the organisms.

Human health concerns:

Q-fever disease is considered as a re-emerging zoonosis in many countries. This could be due to the evolution of its epidemiology or of the agent, which could become more virulent, to modifications of its clinical signs, to an improvement of the sensitivity of diagnostic tests, or because medical practitioners are better informed and look for it more accurately.

C. burnetii in humans causes highly variable clinical manifestations ranging from acute to fatal chronic infections. However, about 60% of the infections are asymptomatic seroconversions.

Q-fever remains primarily an occupational hazard for persons in contact with domestic animals such as cattle, sheep and goats. Persons at risk from Q-fever include farmers, veterinarians, abattoir workers, those in contact with dairy products and laboratory personnel performing *Coxiella burnetii* culture and more importantly working with *C. burnetii*-infected animals.

Q-fever is essentially an airborne disease. *C. burnetii* has been isolated from a lot of different hosts such as amoebae, ticks, birds, mammals and arthropods. Cattle, goats and sheep are considered the primary reservoirs from which human contamination occurs. Infections occur after inhalation of aerosols generated from infected placentas, body fluids or contaminated dust resulting from contaminated manure and desiccation of infected placenta and body fluids. Transmission of *C. burnetii* is mostly associated with parturition and abortion of domestic ruminants and particularly with caprine abortions.

Direct contact with aborted females is not required. People may be infected by handling contaminated wool, manure, or clothes contaminated with faeces. The ingestion of contaminated raw milk or raw milk products is considered as a less efficient route of contamination.

Even if Q-fever as a zoonosis is not questioned, many epidemiological aspects of the disease need further investigations. More data on the bacteria are deemed necessary, in particular on molecular markers and virulence factors in order to precisely identify the origin of each human infection and to better understand the mechanisms leading to various clinical manifestations in humans and ruminants.

COXEVAC as a MUMS vaccine:

According to the MUMS guideline for immunologicals (EMEA/CVMP/IWP/123243/2006), specific provisions are:

- for laboratory studies, no minimum/maximum dose potency requirements wherever formulation of the final product is standardised.
- field efficacy studies may replace laboratory studies, when justified; if sufficient laboratory studies are performed, field studies are not required.
- no expert report needs to be provided (indeed it was not provided for this COXEVAC application).
- literature may be used to support the safety and efficacy claim, provided these data were raised by testing the product, for which the application is made. Bibliographic data should preferably originate from acknowledged scientific literature ideally from peer-reviewed journals.

It is also to note that, given the nature of the disease, the protection necessary for the workers and the environment, the length of pregnancy in cattle, the applicant reported difficulties to carry out challenge tests. This organisation issue had a consequence on the efficacy demonstrations that could be done.

The studies in goats and cattle provided by the applicant were assessed in the light of these points and recommendations.

The applicant provided a goat laboratory efficacy test in a controlled environment with level 3 biosecurity at one of INRA's laboratories. Vaccinated and control goats were challenged with a field strain of Q-fever during pregnancy. *Coxiella burnetii* challenge strain CbC1 was isolated from the placenta of a goat that had Q-fever and aborted.

The challenge was carried out on pregnant animals because the presence and/or intensity of the clinical signs (abortion, vaginal discharge, shedding in milk) of Q-fever during pregnancy or around parturition, allow a clearer differentiation between vaccinated and control animals.

Efficacy laboratory studies in cattle were carried out taking into consideration the recommendation of the EMEA MUMS guideline mentioned above, i.e. field efficacy studies may replace laboratory efficacy studies when justified. The justifications provided by the applicant namely:

- the field efficacy trials verifies efficacy claims for COXEVAC under field conditions by natural exposure to the infective agent.
- due to the long pregnancy in cows, a study with challenge test would last many months in isolated laboratory conditions which are very difficult to find knowing that they need to be BL3 facilities, were accepted by the CVMP.

The field trials in cattle were conducted according to the principles of GCP rules and the field trial and laboratory study in goats were conducted in accordance with good scientific practices. The goat laboratory test was a part of scientific research programme.

All studies were conducted according to detailed trial protocols and the results were presented in sufficiently precise details to be assessed by the CVMP. The techniques involved in the trials were checked and validated.

The CVMP could agree to the following positive effects:

- a field study showed that in farms where Q fever is present, non-infected cows vaccinated when non-pregnant had about 5 times lower probability of becoming a shedder than cows receiving a placebo.
- a laboratory study showed protection of goats against abortion and a considerable control of shedding in faeces, placenta, milk and vaginal secretions was demonstrated in terms of duration and intensity. This last study was reported as a publication.

The following remarks can be made:

- the use of COXEVAC in males is questionable, as no study could be carried out to demonstrate a beneficial effect of vaccination. However, in goats, reduction of shedding in faeces was shown, which could make COXEVAC useful even in males.

- the results obtained in the cattle field trials led to re-assessment of shedding results in milk, vaginal discharge and faeces. From this, it can thus be concluded that a decrease in shedding (number of shedders, level of shedding) can be seen in vaginal mucus and milk when cows are vaccinated with COXEVAC.

- the impact of maternally derived antibodies was not fully investigated in goats and cattle (data from publications). As the vaccine is not intended for very young animals, this is acceptable.

- the reasons why it is difficult or even impossible to challenge (or follow-up in a contaminated environment) non-pregnant animals (like young or males), brought by the applicant would need further discussions.

- the reasoning behind the difficulty to establish an onset of immunity needs to be reassessed; the commitments on additional efficacy data in goats, will be the occasion to do so. Meanwhile, 'not applicable' can be proposed.

- the data presented do not allow to establish a specific booster vaccination programme, at this stage.

- with regard to duration of immunity: it was established in cows, considering that the vaccinated animals were kept permanently in a contaminated environment during the whole period of follow-up. In goats, the time of challenge (15 weeks after vaccination) was considered, but formally no duration of immunity was set.

With regard to these considerations, an authorisation for cattle and goats could be proposed, on the following basis:

Cattle:
Indication: For active immunisation of cattle to lower the risk for non-infected animals vaccinated when non-pregnant to become shedder (five-time lower probability in comparison with animals receiving a placebo), and to reduce shedding of *Coxiella burnetii* in these animals via milk and vaginal mucus.

Onset of immunity: not established.
Duration of immunity: 280 days after completion of the primary vaccination course.

→ vaccination scheme :
Cattle from 3 months of age:
Volume of the vaccine dose: 4 ml

Primary vaccination:
Two doses should be given subcutaneously with an interval of 3 weeks. Under normal conditions the timing of vaccination should be planned so that the primary course is completed by 3 weeks before artificial insemination or mating.

Re-vaccination:
Every 9 months, as described for the primary vaccination.

Goats:
Indication: For the active immunisation of goats to reduce abortion caused by *Coxiella burnetii* and to reduce shedding of the organism via milk, vaginal mucus, faeces and placenta.

Onset of immunity: not established.
Duration of immunity: not established. Protection has been demonstrated by challenge 15 weeks post-primary vaccination

→ vaccination scheme :
Goats from 3 months of age:
Volume of the vaccine dose: 2 ml

Primary vaccination:
Two doses should be given subcutaneously with an interval of 3 weeks. Under normal conditions the timing of vaccination should be planned so that the primary course is completed by 3 weeks before artificial insemination or mating.

→ Special warnings for each target species:
Vaccination of animals already infected at the time of vaccination will have no adverse effect. Also, in safety laboratory trials, the use of Coxevac in males proved to be safe. But no efficacy data are available concerning the use of Coxevac in male animals and the benefits of the vaccine (as described in the indications), when used in infected animals and/or pregnant animals have not been demonstrated. However, in the case that it is decided to vaccinate the whole herd, it is advisable to vaccinate these categories at the same time.
The biological significance of the level of reduction shown is not known.

Coxevac claim in sheep: although CVMP agreed that a laboratory study showed that vaccination reduces significantly bacteria shedding in vaginal discharge and milk in ewes and that a field study showed that vaccination can protect against fertility losses in ewes, it finally concluded that these findings were not supportive enough to include sheep as a target species for this product at this stage.

In conclusion, the CVMP concluded that the product is proven to be efficacious as detailed in the SPC claim for goats and cattle.

5. Benefit risk assessment

The vaccine is produced in a high containment facility.

The vaccine contains Coxiella phase-I antigen in inactivated form.

A satisfactory control of inactivation is applied twice during the production and the risk of spreading live Coxiella into the environment has therefore been eliminated.

The applicant provided a very detailed and satisfactory extraneous agents risk assessment and vaccine strain testing, which had been the subject of a scientific advice request prior to submission of the dossier. This risk assessment allowed the CVMP to conclude that the risk of the finished product containing extraneous agents is negligible.

Additionally, sterility tests are carried out at different stages of manufacturing such as the seed materials, twice on the antigen itself and finally on the finished product thereby providing additional assurance on the purity profile of the vaccine.

The antigen undergoes a purification process which removes egg yolk material and the vaccine does not contain any adjuvant, all measures resulting in a reduced risk of adverse reactions in the target animals.

The potency test proved a sensitive and specific indication of efficacy of the product. The test is capable of distinguishing sub-potent from potent batches by measuring the antigen amount which is linked to efficacy, since the vaccine does not contain an adjuvant.

The potency titres of several finished batches were tested during production and the results showed that the vaccine has an approved shelf life of 12 months.

The safety of the vaccine has been tested in all target species in both laboratory tests and field studies. The data available are deemed sufficient to establish the safety profile of COXEVAC. The vaccine is as expected, globally well tolerated in each of the target species, even if some mild to moderate local swellings (sometimes with redness) are common in both target species, sometimes quite extended and lasting several weeks. The risk of ecotoxicity following the use of COXEVAC vaccine was confirmed as negligible.
Overall, the CVMP concluded that COXEVAC is a product with an acceptable level of safety.

The efficacy studies provided for all initial 3 target species were subject to further questions by the CVMP in particular with regard to the reduction of bacteria shedding in vaginal discharge and milk in ewes and the probability for non-infected non-pregnant cows to become shedders

The CVMP also concluded from the data that while COXEVAC reduces bacteria shedding in vaginal discharge and milk and may increase fertility in comparison with non-vaccinated sick animals, there is not enough supportive data to include sheep in the target species for this product at this stage.

In goats COXEVAC protects against abortion; considerable control of shedding in faeces, milk, placenta and vaginal secretions was demonstrated in terms of duration and intensity.
In cattle, non-infected animals vaccinated with COXEVAC when non-pregnant had about 5 times lower probability of becoming a shedder than an animal receiving a placebo in a contaminated environment. Reduction of shedding of *Coxiella burnetii* was also shown in these animals, via milk and vaginal mucus

Due to difficulties to carry out challenge or field experiments with Q fever, and the nature of the discuss itself, onset of immunity and booster vaccination program could not be established.

Conclusion on benefit risk balance

It can be concluded that the benefits provided to the target animals by the vaccination using COXEVAC, outweigh the risks for the target animals, the user, the environment and the consumer.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for COXEVAC for the active immunisation of cattle and goats to reduce infection with *Coxiella burnetii* can be approved under exceptional circumstances.

The CVMP considered that due to the current epidemiological situation of Q-Fever and the consequent threat to animal and public health there are objective and verifiable reasons for recommending the granting of a Marketing Authorisation under exceptional circumstances for this product, namely that

- the epidemiological risk for animal health in the EU and the associated zoonotic risk constitute an objective need to have authorised products available for use in the coming months
- vaccination may form an important element of disease control policies at national, regional or Community level
- the quality and safety of the product have been satisfactorily demonstrated as well as key elements of efficacy in cattle and goats
- the applicant has agreed to the necessary post-authorisation specific obligation, to further investigate and elaborate the efficacy of the product in goats.

The specific obligation to be fulfilled by the marketing authorisation holder is that an efficacy confirmatory study in goats under laboratory or field conditions should be performed, establishing a duration of immunity, based on a reduction of abortions and/or a reduction in shedding (duration, intensity, frequency) in milk (which seems to be the main route of bacterial shedding), and/or faeces, and/or vaginal excretion. The corresponding claim would then be established in compliance with the parameters tested, and the results obtained (when satisfactory). This trial should be conceived in a way showing consistency with the vaccination scheme (time and number of injections, minimum age at vaccination). The maximum time allowed to prepare the report should be 1 year after the claimed duration of immunity.

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.