SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

Poulvac FluFend H5N3 RG is an adjuvanted, inactivated vaccine against avian influenza. This disease occurs worldwide and not only affects domestic poultry, but also infects a wide range of feral birds covering 88 species and 22 families, occurring most prolifically in migratory waterfowl. Type A influenza virus can also infect various species of mammals (including humans). The main reservoir of infection is thought to be wild ducks, gulls and shorebirds. Infections in poultry can be unapparent, i.e. low pathogenic avian influenza (LPAI), or cause mild to severe respiratory disease, decreases in production, decreases in food or water intake, or cause a rapidly fatal systemic disease known as highly pathogenic avian influenza (HPAI). Important economic losses occur as a result of mortality, but also due to egg production loss, to retardation of growth, bad feed conversion, diminished quality and cost of medical treatment for secondary bacterial infections.

Influenza A viruses show a great antigenic diversity; there have been 16 haemagglutinin subtypes (H1 - H16) and 9 neuraminidase subtypes (N1 - N9) recognized. All these subtypes have been isolated from birds and in most possible combinations. Influenza virus identification is based on the H and N subtype present. All HPAI and all H5 and H7 viruses have been classified as Highly Pathogenic Notifiable Avian Influenza (HPNAI) viruses by the OIE (2005). Avian influenza outbreaks involving HPNAI subtype H5 or H7 have been reported from Mexico, USA, Italy and several countries in Asia. The recent spread of a highly pathogenic H5N1 virus from Asia to various countries in Europe and Africa has been a cause of major concern.

Poulvac FluFend H5N3 RG is an inactivated and adjuvanted vaccine against Avian Influenza (Al) type A, based on the use of a reassortant virus, obtained through reverse genetics technology. It shows a low-pathogenicity phenotypic trait.

If the N fraction of the Al subtype involved in an infection differs from the N fraction incorporated in a vaccine, it is in principle possible to differentiate between poultry vaccinated with the vaccine strain(s) and poultry infected with a field strain with another N component. Thus, for Poulvac FluFend H5N3 RG, the N3 subtype was selected for use in construction of the reassortant such that a “DIVA” approach could be used for differentiating infected (H5N1) from vaccinated animals.

The antigen is incorporated in a water-in-oil emulsion in order to stimulate immunity.

In view of the current concern about the spread of highly pathogenic avian influenza the present application has been submitted with a request for accelerated review in accordance with Article 39(8) of Regulation (EC) No 726/2004. In consideration of observed deficiencies in the normally required supporting data as specified in Annex I to Directive 2001/82/EC (see below), assessment has also been conducted taking into account the provisions of Article 39(7) of Regulation (EC) No 726/2004 for authorisation in exceptional circumstances and the recommendations in the CVMP Reflection Paper on Minimum Data Requirements for an Authorisation Under Exceptional Circumstances for Vaccines for Emergency Use in Birds Against H5 and/or H7 Highly Pathogenic Avian Influenza Virus (EMEA/CVMP/IWP/46853/2006).

II. QUALITY ASSESSMENT

The application dossier contains information on the production of the avian influenza virus antigen grown in eggs. The viral antigen is inactivated with formaldehyde and emulsified with an oil adjuvant. Details are provided on the sources of the starting materials and controls that have been applied to them. Proposed in-process and final product control tests are described and limits of acceptance specified. The proposed batch potency test consists of measuring the HI serological response of chickens to a single 0.50 ml dose of vaccine. Although there are currently two manufacturing sites proposed, batch release will only take place at one site.

Since this application has been submitted quickly, in response to the major threat from avian influenza virus infections, there are certain deficiencies in comparison with a standard Marketing Authorisation application.

The major outstanding issues concern the differences of production and control between the manufacturing sites (including the nature of the eggs used), the lack of a validation study for the potency test on finished product and the lack of stability data.

However, the information provided is considered sufficient to meet the minimum requirements for an exceptional Marketing Authorisation. This conclusion has been reached, taking account of the guidance set out in the CVMP Reflection Paper on the minimum requirements for an authorisation under exceptional circumstances for emergency use in birds against H5 and/or H7 highly pathogenic avian influenza virus.

3. SAFETY ASSESSMENT

In chickens:
Laboratory studies show safety of the vaccine after a single dose, an overdose and a repeated dose regimen. They show that the vaccine causes only minor and transient local reactions considered normal for mineral oil adjuvanted vaccines after intramuscular (i.m.) administration. Additional supportive data on laboratory safety are available for a similar vaccine on SPF chickens, formulated in the exact same manner as Poulvac FluFend H5N3 RG (except for the antigens), confirming the safety of this type of vaccine.

The field trial results also support the field safety of Poulvac FluFend H5N3 RG for use in chickens when administered subcutaneously under field conditions.

In ducks:
Laboratory studies show safety of the vaccine after a single dose, an overdose and a repeated dose regimen. They show that after i.m. administration, the vaccine causes reactions comparable to those registered for chickens. If no lesion is present after i.m. injection, it can be assumed that no lesion will be present after subcutaneous (s.c) injection (which is the route of administration retained in the SPC).

No field trial is available for this target species. This is acceptable because of the current political and epidemiological situation in Europe with regard to avian influenza.

In turkeys:
Although one study is available, the protocol used and the data provided are not sufficiently convincing to include turkeys as a target species.

No data are available for any of the species on safety on the reproductive performance and when the vaccine is administered together with other medicinal products. The SPC provides appropriate warnings on these points.

Environmental Risk Assessment

No hazards can be identified with regard to the environment:

- the vaccine contains no infectious particle or dangerous component. The only ingredient of environmental concern is the mercury in thiomersal. The maximum environmental exposure to mercury is the 10 mg that would be released in the event of a bottle break. As the mercury is part of an organic molecule, it will be easily dispersed by water and will not reach significant concentrations in the environment.
- the administration is individual and done by intramuscular or subcutaneous injection. Thus, the product will never be in direct or indirect contact with environment.
- any unused or waste material will be disposed of by appropriate channels.

4. EFFICACY ASSESSMENT

Efficacy of this vaccine has been supported by several studies. The amount of detail available for the studies presented is not up to the standard usually expected in a normal application for a Marketing Authorisation, as the Applicant was invited to submit this application on the basis of the information currently available to meet an emergency situation. The approach taken during assessment was, therefore, to recognise that individual studies would not, in general, meet the requirements of Annex I of Directive 2001/82/EC but to evaluate the available data as a whole to determine the extent to which the claims made in the draft SPC could be supported.

In particular, limited information is currently available about the challenge strains used in the efficacy trial. It is admitted that recent H5 European viruses are broadly antigenically homogeneous, but that they can clearly be distinguished (in HI tests for instance) from their counterparts in Asia and North America. Thus, the relevance of the challenge strains used with regard to those currently circulating strains in Europe (or those present in recent past in Europe) is of outmost importance to assess efficacy adequately.

Despite this, several studies are available to support the current claims of the SPC:

In chickens:

- when the vaccine was used at 3 weeks of age, administered by intramuscular route in the breast muscle, 2 doses of 0.5 ml given 3 weeks apart, a reduction of mortality and a reduction of viral excretion were shown. No real data are available about the clinical signs.
- onset of immunity is of 3 weeks after the last injection; no data are available about the duration of immunity.
- the fact that SPF chickens only were used gives insufficient information about the vaccine uptake in the presence of antibodies prior to vaccination. Although it is unlikely that this will be an issue for an inactivated vaccine, the SPC reflects on the lack of information when the vaccine is administered to conventional chickens.

In Pekin ducks:

- when the vaccine was used at 1 day of age, administered by subcutaneous route in the neck, 1 dose of 0.2 ml at 1 day followed by 1 dose of 0.5 ml at 3 weeks of age, reduction of clinical signs and reduction of viral excretion were shown. Reduction of mortality was not retained as this stage, because the data were not felt sufficiently strong to support this claim.
- onset of immunity is of 3 weeks after the last injection; no data are available about the duration of immunity.
- it should also be noted that the safety trials were performed in mallard ducks, and not Pekin ducks. Nevertheless, the safety data generated on mallard ducks can reasonably be extrapolated to Pekin ducks as adverse reactions to this type of vaccine can be expected to be similar. On the other hand, it is quite questionable to extrapolate the efficacy data of Pekin ducks to mallard ducks (and other types of ducks) which explains why only Pekin ducks were maintained as the target duck species in SPC.

In turkeys:
No claim would be proposed at this stage, as only serological results are available, with no relationship between serological titres and protection.

5. BENEFIT RISK ASSESSMENT

Poulvac FluFend H5N3 RG is an inactivated and adjuvanted vaccine against Avian Influenza. In the event of an Avian Influenza outbreak in Europe, the common prophylactic measures might involve vaccination in some circumstances, to avoid as much as possible the spreading of the field virus.
Given the fact that:

- the analytical part provides sufficient relevant details to conclude that the manufacturing process is under control, with appropriate controls on raw materials, during production and on the finished product,
- sufficient guarantees are available on the extraneous agents testing for the raw materials of biological origin and on the inactivation process,
- the adjuvant used is a standard adjuvant used in many other vaccines,
- the main expected side effect would be the persistence of oily droplets at the injection site,
- reduction of excretion (shedding) was shown for each target species when challenged, leading to the conclusion that this vaccine could help usefully to restrain field viruses in the case of an outbreak,

The CVMP considered that due to the current epidemiological situation of avian influenza and the consequent threat to both human and animal health there are objective and verifiable reasons for recommending the granting of a Marketing Authorisation under exceptional circumstances for this product.

The CVMP also considered that the Applicant could not reasonably be expected to provide the results from certain trials on the target species for duly substantiated reasons, in particular trials which may not be conducted due to the European Community legislation on the control of avian influenza.

Based on the data presented the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be acceptable