SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

This is an application for 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, poor 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 Notifiable Avian Influenza (NAI) viruses by the OIE (2005). Avian influenza outbreaks involving HPAI 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.

The applicant submitted an application for a centralised authorisation on the basis of the information currently available, to meet a potential emergency situation. In view of the current concern about the spread of highly pathogenic avian influenza, the application was submitted with a request for accelerated review in accordance with Article 39(8) of Regulation (EC) No 726/2004. In addition, assessment has 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).

Nobilis Influenza H5N6 is an inactivated vaccine containing Avian Influenza (AI) type A whole virus of the subtype H5N6. The antigen is incorporated in a water-in-oil emulsion in order to stimulate immunity. Since the serotype involved in an outbreak of Avian Influenza can vary, the Applicant manufactures a range of Nobilis Influenza vaccines, containing different subtypes so that appropriate vaccines can be used according to the epidemiological situation. If the N fraction of the AI 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.

This application is for an authorisation for the monovalent vaccine containing Avian Influenza H5N6 subtype but the Applicant had provided a dossier containing information on 6 antigens. Only data relevant to the vaccine containing the H5N6 strain was assessed and information in the report is restricted to the assessment of this vaccine. However, where it was applicable for the assessment, information generated with other Nobilis Influenza vaccines and their component strains was taken into account as indicated.
2. ANALYTICAL ASSESSMENT

The production process described in the dossier gave information on the production of various avian influenza virus antigens, for blending into a monovalent or bivalent vaccine. The viral antigens are inactivated with formaldehyde and emulsified with an oil adjuvant. Details were provided on the sources of the starting materials and controls that had been or (in the case of substances produced on a batch basis) will be applied to them. Proposed in-process and final product control tests were described and limits of acceptance specified. The vaccine is currently blended on the basis of the pre-inactivation viral titre of the bulk antigen. The proposed batch potency test consists of measuring the serological response of chickens to a single 0.25 ml dose of vaccine. Basic stability data were also provided.

Since this application had been submitted quickly, in response to the major threat from avian influenza virus infections, there are deficiencies in comparison with what is required for a normal Marketing Authorisation application. It was considered, however, that, as far as the analytical particulars were concerned, sufficient information had been provided and it would be acceptable to grant the Marketing Authorisation provided the Applicant agreed to accept specific obligations to supplement the data presented in Part 2, to meet the minimum requirements for an exceptional Marketing Authorisation. This conclusion was reached, taking account of the guidance set out in the CVMP Reflection paper (EMEA/CVMP/IWP/46853/2006). As indicated above, the Applicant accepted specific obligations in support of the granting of the Marketing Authorisation in exceptional circumstances.

The Applicant also gave a commitment to provide additional information at a later date to provide confirmation, reassurances and clarification on a number of points arising from the assessment, such as additional information on the stability of the vaccine.

To provide the information that would be required for an application for a standard Marketing Authorisation, a full data package would be required, in accordance with the requirements of Annex I of Directive 2001/82.
3. SAFETY ASSESSMENT

GLP safety studies have been carried out using several formulations of Nobilis Influenza but the vaccines used did not include Nobilis Influenza H5N6. However, it was concluded that for this application for a marketing authorisation under exceptional circumstances, the GLP studies undertaken with the range of Nobilis Influenza vaccines were sufficient to indicate the safety of a single dose (0.5 ml), an overdose and repeated administration of a single dose of Nobilis Influenza H5N6 for two week old chickens and also of a reduced dose of 0.25 ml for one-day-old chickens. Safety studies for Nobilis Reo+IB+G+ND, also presented in the dossier, provide supporting evidence of safety of another vaccine that contains the same adjuvant. The warnings proposed for the SPC reflect the reactions seen in these GLP studies.

No information was provided on safety for reproductive birds; this is indicated in section 4.7 of the draft SPC.

Other than general observations on administration of Nobilis Influenza to hundreds of zoo birds of multiple species, where no safety problems were identified, and supporting data for ducks, there was no information on safety for other avian species.

A phase 1 environmental risk assessment was conducted. It was concluded that the risk to the environment from this inactivated vaccine is negligible and a phase 2 assessment was not considered necessary.

4. EFFICACY ASSESSMENT

Efficacy of this vaccine has been supported by scientific papers published in peer reviewed journals and internal Company reports.

The amount of detail available for the studies presented is not fully up to the standard expected in a standard application for a Marketing Authorisation. The Applicant submitted this application on the basis of the information currently available to meet a perceived 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. Where equivalence between different strains could be deduced this was taken into account.

The vaccine has been shown to be capable of inducing antibodies and protecting vaccinated chickens against challenge with a number of appropriate strains, including a virulent H5N1 challenge strain.

Several avian species (chickens, ducks, turkeys and pheasants) and other Nobilis Influenza vaccines have been used in the efficacy studies presented in the dossier. It was concluded that while species other than chickens could not be included in the SPC as target species, it would be useful to provide relevant information on these species as they might be vaccinated in the event of an outbreak of avian influenza. In particular, it was considered that the SPC had to be clearly worded to indicate that the claims reflecting the efficacy demonstrated in chickens would not necessarily be applicable to what could be obtained in all species.

Efficacy demonstrated with Nobilis Influenza H5N6 vaccine:

The vaccine has been tested against challenge with H5 HPAI isolates as follows:

Chickens:
- One study in 2 to 3-week-old chickens in which challenge was with a recent H5N1 HPAI isolate 2 or 3 weeks after vaccination, showing prevention of mortality and clinical signs. When challenged at 2 weeks after vaccination virus was excreted at low levels by only 6/10 vaccinates for a limited time (1-3 days) and virus was recovered from the trachea only. Control birds (10/10) died within 24 hrs and excreted virus at a higher level and via both the tracheal and cloacal route.
• One study in 3-week-old chickens in which challenge was with an older H5N2 HPAI isolate from the USA showing prevention of mortality and clinical signs.

Turkeys:
• One study in 1-week-old turkeys challenged with a recent H5N1 isolate 4 weeks after a single vaccination or 2 weeks after a second dose, showing prevention of clinical signs and mortality. Almost all of the vaccinated and challenged birds excreted virus for up to 5 days. The unvaccinated control birds died quickly, therefore a comparison between virus excretion in the vaccinated and control birds was not possible.

Some studies also give information on the serological responses of chickens, turkeys and ducks vaccinated with H5N6. HI titres of the order of 4-5 log₂ were achieved in chickens by 2 weeks after a single dose, while after 3 weeks titres exceeded 6 log₂. In turkeys, titres of the order of 5-7 log₂ were achieved by 18 days after a single vaccination, although they were higher (at least 8-9 log₂) after a second dose. In ducks, titres in excess of 10 log₂ were achieved by four weeks after two vaccinations four weeks apart and titres in excess of 8 log₂ were maintained for at least 28 weeks.

It was concluded that the vaccine is capable of preventing clinical signs and mortality in vaccinated chickens and turkeys and reducing the excretion of virus from vaccinated chickens challenged with virulent AI virus, subtype H5N1. However, in the absence of specific data supporting the safety of the vaccine in turkeys it was considered that these could not be included as a target species in the SPC.

Only serological data are available to support the efficacy of the H5N6 vaccine in ducks. In the absence of data on protection against challenge it was considered that ducks could also not be included as target species in the SPC. It was agreed, however, that since supportive safety data for ducks are available to provide information to the user. Therefore, reference to the limited data available could be included in section 4.4 of the SPC.

Data in support of the recommended schedule: The various studies described in the dossier included vaccination by either the s.c. or i.m. routes with similar results. Although Nobilis Influenza H5N6 was not specifically studied, the serological responses following s.c. or i.m. vaccination were compared in two studies with Nobilis Influenza vaccines and in a study of the response to four antigens in a different adjuvanted poultry vaccine. In each case, similar titres were produced by the two routes. It was concluded that, overall, the information and justification provided was sufficient to support the recommendation that either route of administration can be used for this vaccine.

Safety and efficacy were demonstrated in chickens from the following ages:

Safety – One day old
Efficacy – H5N6 – 2-3 weeks old; H5N2 8 days old.

The SPC recommends the vaccination of chickens from 8 days of age. While there were no specific data on the efficacy of Nobilis Influenza H5N6 when administered to birds of this age, the information on the efficacy of other formulations of Nobilis influenza in young birds was sufficient to give an expectation that Nobilis Influenza H5N6 would also be efficacious at the minimum age indicated.

A dose of 0.5 ml is advised for chickens but this dose should not be given to chickens aged less than 2 weeks of age and the dose of 0.25 ml can be used up to an age of 6 weeks. In the challenge studies, a 0.25 ml dose of H5N6 given to chickens 2-3 weeks of age induced a good serological response and acceptable protection to the H5N1 challenges administered. Results from three studies are presented in support of the effectiveness of vaccination of 8 day-old chickens with a 0.5 ml dose of Nobilis Influenza H5N2 (Mexican strain) vaccine and a single dose was shown to be sufficient to prevent mortality and decrease excretion after challenge, 3 weeks post vaccination. A single dose of 0.25 ml H5N2 containing vaccine was administered to 3 week-old chickens in one study and mean HI titres of 5.5 and 5.9 log₂ were obtained after 3 and 4 weeks, respectively. The dose of 0.25 ml has also been used in a study with a vaccine containing an H7N7 strain and this provided satisfactory levels of protection to challenge. It was noted too that the batch potency test is conducted with administration of a 0.25 ml dose to chickens and all batches of vaccine will need to comply with the acceptance criteria for the test. It was concluded, therefore, that, overall, there were sufficient data to support the recommended vaccination schedules in the SPC.
Data have also been presented supporting the efficacy of two doses of vaccine administered to chickens with an interval of 4-6 weeks. The SPC reflects these data.

Efficacy in other avian species may be variable and, on the basis of the information from vaccination of zoo birds, it appears that the serological response following vaccination of the various species may be variable.

Correlation of protection to potency test pass limits:

The proposed minimum release titre for the potency test is 6.0 log₂ HI. Chickens with titres similar to or lower than this at the time of challenge were protected from developing clinical signs and mortality and showed reduced viral shedding following HPAI challenge. Analysis of the results from reports, in which H5 vaccines were used, suggest that protection from clinical disease and mortality may be achieved in birds with a HI antibody titre as low as 2 log₂ at the time of challenge, so the proposed minimum release titre appears to allow a significant safety margin. These data, however, give no indication of the antibody titres required to reduce or prevent viral shedding. In addition, it is by no means certain that the same potency would be equally efficacious in other avian species which could be vaccinated in the event of an outbreak of avian influenza.

Onset of immunity:

Nobilis Influenza H5N6 vaccine has been shown to prevent clinical signs and mortality as well as reduce viral excretion in chickens challenged two weeks after a single dose. On this basis the onset of immunity in chickens mentioned in the SPC refers to ‘2 weeks after vaccination’.

Duration of protection:

Data have been presented that demonstrate the persistence of antibodies for about 7 months following the administration of two doses of Nobilis Influenza H5N6. Supporting data have also been provided on the persistence of antibodies in chickens for at least 45 weeks following the administration of two doses of Nobilis Influenza H5N2 (Mexican strain) vaccine and the persistence of antibodies in chickens for 12 months following the administration of two doses of Nobilis Influenza H9N2 vaccine. Taking account of the similarity of response shown to formulations of Nobilis Influenza containing different vaccine virus strains, a statement has been included in the SPC referring to the persistence of antibodies in chickens for 12 months.

The duration of protection in other avian species is likely to vary. For example, antibody levels in some vaccinated zoo birds declined considerably within 6 months.

Effect of maternally derived antibodies:

There is no information on whether the presence of maternally derived antibodies could affect the efficacy (although data indicates that high levels can occur in the progeny of vaccinated hens) – this is indicated in the SPC.

Conclusions

It was concluded that, overall, the information provided was sufficient to support granting of a Marketing Authorisation in exceptional circumstances. The SPC reflects the available data.
5. BENEFIT RISK ASSESSMENT

Benefits:

- Various formulations of Nobilis influenza have been shown to prevent clinical signs and mortality and reduce shedding in chickens, turkeys and ducks. The H5N6 vaccine is not recommended for turkeys because of the lack of safety data for this species. Although supporting safety data for ducks were available these could not be included as target species in the absence of data from challenge studies using the H5N6 vaccine.
- The vaccine is able to induce antibodies in a wide range of birds, (although the response may be variable and the degree of efficacy likely to depend on species and degree of homology between the haemagglutinin components of the field and vaccine strains).
- If the circulating avian influenza field virus has a different H or N component to the H5 and N6 included in the vaccine, it may be possible to differentiate between vaccinated and infected birds by using a diagnostic test to detect Haemagglutinin and/or Neuraminidase antibodies.

Risks:

The risk assessment on the use of this vaccine includes the safety for the target species, the safety for the person administering the vaccine, safety for the consumer and safety for the environment. Highly pathogenic avian influenza is a notifiable disease and the risk of vaccination interfering with disease control measures also needs to be considered.

- Safety for the target species. The vaccine contains an inactivated virus and by comparison with other vaccines of similar composition (containing viral antigens grown in eggs) it has been concluded that it is unlikely that there would be any major safety concerns from the use of this product with antigen produced in eggs. There were no reports of significant reactions in batch safety tests or in any of the efficacy trials and no reports of problems during use in a wide range of avian species in the field.
- Safety for the person administering the vaccine. This vaccine, containing egg-grown antigen, is a conventional vaccine which differs in composition from many other authorised products only in the nature of the inactivated virus antigen included. There is, therefore, no significant risk associated with the active ingredient. In common with many other vaccines it contains a mineral oil adjuvant with the associated risk that might arise from accidental self injection. However, this risk is no greater than with other similar vaccines and appropriate precautions are detailed in the product literature.
- Safety for consumers. The vaccine does not contain any ingredients that are likely to pose a risk for consumers of vaccinated birds.
- Safety for the environment. The vaccine contains no ingredients likely to pose a risk to the environment. In addition, the vaccine is administered by injection so environmental contamination is unlikely.
- Risk of interference with disease control measures. Although the vaccine can be expected to provide a high degree of protection from the clinical effects of disease and to reduce significantly the risk of spread between vaccinated birds, especially in poultry, total prevention of infection and shedding of virus by infected birds may not be achieved.
OVERALL CONCLUSIONS

The vaccine has been shown to be efficacious in preventing clinical disease in chickens and reducing viral excretion in chickens and would probably contribute to a reduction in the spread of virus. The risk of unnoticed introduction of virulent virus into a vaccinated population is common to all inactivated avian influenza vaccines and Nobilis Influenza H5N6, in common with other such vaccines, could be useful in limiting the excretion and spread of AI virus when used appropriately.

Overall, the vaccine could be a useful tool in controlling an outbreak of AI subtype H5 infection or where the risk of infection occurring is considered to be high. In this situation, as long as the vaccine strain is relevant to the disease situation, vaccination would be expected to provide significant benefits in terms of reduced mortality and clinical signs, reduced excretion of virus, and hence, reduced transmission.

The CVMP considered that due to the current epidemiological situation of Avian Influenza and the consequent threat to both human and animal health there were 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.