SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

Nobilis Influenza H5N2 emulsion for injection, is an adjuvanted, inactivated vaccine against avian influenza type A, subtype H5 in chickens.

Avian influenza 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 Notifiable Avian Influenza (NAI) 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.

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. The 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 H5N2 is an inactivated vaccine against Avian Influenza (AI) type A, that contains inactivated whole virus of subtype H5N2 (European strain, A/duck/Potsdam/1402/86). The antigen is incorporated in a water-in-oil emulsion in order to stimulate immunity.

II. QUALITY ASSESSMENT

The application dossier contained information on the production of the H5N2 avian influenza virus antigen from the Master Seed virus. The virus is grown in embryonated chicken eggs using well-established methods. The viral antigen is inactivated with formaldehyde and emulsified with an oil adjuvant. Details were provided on the sources of the starting materials and controls that have been or (in the case of substances produced on a batch basis) will be applied to them. In-process and final product control tests were described and limits of acceptance specified. The vaccine is blended on the basis of the pre-inactivation viral titre of the bulk antigen. The batch potency test consists of measuring the serological response of chickens to a single 0.25 ml dose of vaccine. Basic stability data were provided. The antigen may be produced in one of three manufacturing sites and the final product may be assembled and tested at one of two manufacturing sites.

Since this application was submitted quickly, in response to the major threat from avian influenza virus infections, there were many deficiencies in comparison with what is required for a standard Marketing Authorisation application. It was considered, however, that sufficient information had been

provided in Part 2 of the dossier 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 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. The Applicant accepted these specific obligations, in support of the granting of the Marketing Authorisation in exceptional circumstances.

The Applicant also gave a commitment to provide additional information 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.

3. SAFETY ASSESSMENT

GLP safety studies with the vaccine formulation of the product had not been completed at the time of submission of the application for a Marketing Authorisation in exceptional circumstances so the data presented did not meet the full requirements of Annex I of Directive 2001/82/EC. However, in the meantime, taking into account the minimum data requirements for an authorisation under exceptional circumstances, the Applicant had submitted reports of two GLP safety studies using Nobilis Reo+IB+G+ND. This vaccine contains the same adjuvant as Nobilis Influenza H5N2 but different antigens, two of which (Infectious Bronchitis and Newcastle Disease) are produced in eggs by a similar process to that used for the avian influenza antigen of Nobilis Influenza. These results indicated that the product is safe for chickens, although the birds used for these studies were four weeks old, which is older than the minimum age recommended for Nobilis Influenza. The warnings in the SPC reflect the reactions seen in these GLP studies using Nobilis Reo+IB+G+ND. The results from safety testing of three standard production batches of Nobilis Influenza H5N2 were also presented and add supporting evidence for the safety of the vaccine in chickens.

On the basis of the safety data submitted and the fact that each batch is tested for safety in one-day-old and 2 to 4 week-old SPF chickens it was accepted that use of the vaccine is unlikely to cause significant safety problems when used in the field. This was considered to be sufficient for an authorisation in exceptional circumstances for use in chickens, pending the results of GLP safety studies for Nobilis Influenza H5N2. The batch safety tests are carried out using chickens younger than 2 to 4 weeks vaccinated by the subcutaneous route using two times the dose recommended for young chicks (2 x 0.25 ml). Consequently, section 4.9 of the SPC recommends that a dose of 0.5 ml should not be given to chickens aged less than two weeks of age and vaccination by the intramuscular route is also not recommended for chickens less than this age.

The Applicant gave a specific obligation to provide the reports of the ongoing studies when they are completed.

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

There is no information on safety for other avian species other than general observations from administration of Nobilis Influenza to a large number of zoo birds of multiple species. No safety problems were identified during or after the administration to these zoo birds.

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 normal application for a Marketing Authorisation. The Applicant submitted 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 were supported. Studies were conducted with a number of different Nobilis Influenza vaccines, containing different subtypes and strains of avian influenza viral antigen. Where equivalence between different strains could be deduced the data generated with these other vaccines were taken into account.

In view of the current risk to the EU, particular weight was given to efficacy demonstrated against recent highly pathogenic H5N1 avian influenza virus strains of Eurasian origin.

The vaccine has been shown to be capable of inducing antibodies and protecting vaccinated birds against challenge with a number of appropriate strains.

Several avian species have been used in the efficacy studies presented in the dossier (chickens, ducks, turkeys and pheasants). 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 H5N2 containing vaccines:

H5N2, strain A/duck/Potsdam/1402/86:

- One study in chickens challenged with a recent Asian HPAI isolate three weeks after a single vaccine dose – mortality prevented, reduction of virus excretion.
- One study in ducks challenged with a recent Asian HPAI isolate three weeks after a single vaccine dose – mortality prevented, clinical signs reduced, reduction of virus excretion.
- Studies show equivalence with Mexican H5N2 strain (since similar levels of protection were obtained from challenges and the serological responses induced by the two strains were similar).

H5N2, strain A/chicken/Mexico/232/94/CPA:

- Several studies in chickens challenged with recent Asian HPAI isolates three to five weeks after single or repeated vaccine doses – mortality prevented, reduction of virus excretion.
- One study in ducks challenged with a recent Asian HPAI isolate three weeks after a single vaccine dose – mortality prevented, clinical signs reduced, reduction of virus excretion.
- Studies show equivalence with European H5N2 strain (since similar levels of protection were obtained from challenges and the serological responses induced by the two strains were similar).

The vaccine is capable of preventing clinical signs and mortality and reducing the excretion of virus in vaccinated chickens challenged with appropriate virulent strains of AI virus. Although the vaccine is capable of reducing excretion of virus, this cannot be directly translated into the amount of reduction of viral transmission between chickens or farms, which is one of the major aims for avian influenza

vaccines intended for emergency use. Supporting data demonstrating a reduction of transmission of virus between vaccinated birds were provided from use of a Nobilis Influenza vaccine containing an H7N1 vaccine strain challenged with a H7N7 isolate, in chickens and ducks.

The challenge studies carried out included vaccination by either the subcutaneous (s.c.) or intramuscular (i.m.) routes with broadly similar results. The serological responses following s.c. or i.m. vaccination were compared in two studies, and similar titres were produced by the two routes. It can, therefore, be accepted that the vaccine induces similar immune responses when given by either route.

The SPC recommends the vaccination of chickens from 8-10 days of age. A dose of 0.5 ml is advised 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. 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 $\log_2$ 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. In a study with a 0.25 ml dose of H5N6, a good serological response and acceptable protection was obtained to the challenge administered. 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, from such use. 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 the vaccine administered with an interval of 4-6 weeks. The SPC reflects these data.

Efficacy in other avian species may be variable, e.g. while excretion of virus from vaccinated ducks and transmission to vaccinated in-contact ducks was reduced, there appeared to be no significant effect on excretion and transmission from vaccinated Golden Pheasants, even though these latter birds were protected from mortality and clinical signs. On the basis of the limited information from vaccination of zoo birds it appears that the serological response following vaccination of the various species may be highly variable.

Correlation of protection to potency test pass limits:

The proposed minimum release titre for the potency test is 6.0 $\log_2$ 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 two reports suggest that protection from clinical disease and mortality is achieved in birds with a HI antibody titre as low as 2 $\log_2$ 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. The degree of protection could also be affected by the degree of homology between the vaccine strain and the challenge strain. In addition, it is by no means certain that the same potency would be equally efficacious in other avian species which, though not target species, could be vaccinated in the event of an outbreak of avian influenza.

Onset of immunity:

The H5N2 vaccine strain has been shown to prevent clinical signs and mortality and reduce viral excretion in chickens challenged three weeks after a single dose. On this basis the onset of immunity mentioned in the SPC refers to ‘3 weeks after vaccination’.

Duration of protection:

Data have been provided demonstrating the persistence of antibodies in chickens for at least 45 weeks following the administration of two doses of Nobilis Influenza H5N2 (Mexican strain) vaccine. The Mexican strain was shown to provide a similar level of protection and antibody response in chickens to that induced with the Nobilis Influenza vaccine containing H5N2 European strain. Data have also been provided on the persistence of antibodies in chickens for 12 months following the administration of two doses of Nobilis Influenza H9N2 vaccine and this provides further supporting data. Taking account of the acceptability of extrapolating data from one vaccinal strain to another, as envisaged in the CVMP 'minimum requirements' paper, a statement has been included in the SPC referring to the persistence of antibodies 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.

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:

- The vaccine has been shown to prevent clinical signs and mortality and reduce shedding in chickens (and ducks).
- 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 N component to the N2 included in the vaccine, it may be possible to differentiate between vaccinated and infected birds by using a diagnostic test to detect 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.
  GLP studies have not yet been completed. However, 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 significantly reduce 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. Vaccinated birds will have antibodies to H5 antigen and could become infected without showing clinical signs.

Conclusions:

The vaccine has been shown to be efficacious in preventing clinical disease in poultry, although it could probably not be relied on to completely prevent the spread of virus. The only significant risk identified is that the virus could be introduced into a vaccinated population and spread without detection. This risk is common to all inactivated avian influenza vaccines and Nobilis Influenza H5N2, 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 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 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.