I. INTRODUCTION

Nobilis Influenza is an inactivated viral vaccine which is intended to induce immunity to avian influenza. Avian influenza occurs worldwide and affects domestic poultry and wild birds, including migratory waterfowl. The severity of the disease ranges from mild respiratory disease to a more generalised and rapidly fatal disease. Exposure of poultry to migratory waterfowl and international movement of poultry, poultry equipment and people are all important means of spreading the disease around the world. The strategy for dealing with an outbreak therefore needs to include biosecurity and sanitary measures, although vaccination may also play an important part in controlling the disease.

Influenza (in birds, animals and people) is caused by a group of viruses called orthomyxoviruses and these viruses contain substances known as haemagglutinins (H) and neuraminidases (N). There are several different types of H and N (H1, H2, N1, N2, etc) and they may combine in different ways to create numerous virus types. The virus which is currently causing serious problems in various parts of the world is of the H5N1 type, but other types may circulate as well, e.g. H7 types. The types in circulation change frequently and this is why it is not possible to develop vaccines well in advance of an epidemic; a vaccine produced last year may not be effective against this year's virus.

This causes a problem because of the length of time it takes to develop a new vaccine, including the full range of tests that are required before the VMD can issue a marketing authorisation. Under exceptional circumstances such as this the VMD may grant a provisional authorisation, and the authorisation for Nobilis Influenza is a provisional authorisation.

For a provisional authorisation, the company must demonstrate that the quality of the product is adequate, that the major safety questions have been answered and that there is some evidence that the product will work. The authorisation is valid for one year and may be renewed if the exceptional circumstances continue and the company has not yet been able to gather all the information which is needed for a full a marketing authorisation.

Nobilis Influenza may contain up to two types of Avian Influenza Type A, which will be chosen from an agreed short-list, depending on which viruses are in circulation when the product is manufactured. The product is a water-in-oil emulsion and is presented in bottles made of glass or plastic (polyethylene terephthalate or PET). It is intended for subcutaneous or intramuscular injection.

II. QUALITY ASPECTS

Product Development and Composition

Nobilis Influenza has been developed for the active immunisation* of susceptible birds against avian influenza virus of subtypes H5, H7 and/or H9. It is intended to prevent clinical signs of disease and to reduce excretion and transmission of the virus.

* This means that it will cause the vaccinated birds to produce antibodies to the viral antigens.

It may contain up to two of the following five avian influenza type A viruses:

- subtype H5N2, strain A/duck/Potsdam/1402/86
- subtype H5N6, strain A/duck/Potsdam /2243/84
- subtype H7N1, strain A/CK/Italy/473/99
- subtype H7N7, strain A/duck/Potsdam/15/80
- subtype H9N2, strain A/CK/UAE/415/99

There are two reasons why the exact composition of the vaccine cannot be specified in advance:

- as explained earlier, the viruses against which protection is needed are not known when the authorisation is issued

- if it is decided to start vaccinating birds, it will be necessary to be able to tell the difference between birds that have received the inactivated viruses in the vaccine, and birds that have caught the virus that causes disease. The normal way to check for viruses is to take a blood sample and test it for antibodies to the virus. Thus, if a bird has caught the harmful H5N1 virus it will have antibodies to H5 and N1. If the viruses in the vaccine also contain the antigens H5 and N1 but no other antigens, birds that have been vaccinated will also have antibodies to H5 and N1 so there will be no way of distinguishing between them until the bird with the harmful H5N1 virus starts to show signs of illness. In the meantime it could have infected other birds. This problem can be solved if the N antigens in the vaccine are different from the N antigens on any of the harmful viruses that are in circulation when the disease outbreak occurs.

The product also contains the adjuvant* liquid light paraffin, and the excipients polysorbate 80, sorbitan oleate, glycine and water for injections.

Active Ingredients

Production of the active ingredients is by means of well-established methods. Each of the viruses is grown in embryonated chicken eggs. Fluid containing the viruses is collected and the viruses are inactivated using formaldehyde prior to refrigerated storage.

Other Ingredients

Certificates of analysis have been provided for the adjuvant and the excipients, and reference made to the European pharmacopoeia. Adequate assurances have been provided regarding other materials used in production of the product, such as the eggs in which the viruses are grown.

Packaging materials

The glass bottles and the stoppers comply with the relevant European Pharmacopoeia monographs. The polyethylene terephthalate (PET) bottles comply with the general European Pharmacopoeia monograph for plastic containers and with an in-house specification for PET as there is no European Pharmacopoeia monograph specific for this material.

* an adjuvant is a substance that is administered with the objective of enhancing the immune response to the antigens.

Manufacture of the Product

The product is manufactured in accordance with GMP*. The required amounts of each inactivated virus are calculated and these are mixed with set amounts of the ingredients that can be dissolved in water, followed by the ingredients that are not soluble in water. The mixture is then emulsified, prior to filling the bottles and fitting them with stoppers and caps. The product is prepared under sterile conditions. It may be produced in different batch sizes depending on the amount needed at the time.

In-process control tests include tests for amount of virus, inactivation of virus, sterility and absence of undesirable biological matter such as dead bacteria, which could cause adverse reactions in vaccinated birds.

The components of the product were demonstrated to comply with relevant guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicines.

Finished Product Quality Control

Standard tests (amount of vaccine in bottle, check of virus inactivation, visual tests, sterility, extraneous agents, etc) are applied to the finished product. The potency and identity of each viral component is checked indirectly by investigating the antibody response of chicks to the H components of the vaccine. This is a well-established test that is routinely used for influenza viruses and it is considered adequate for this provisional marketing authorisation. Safety tests are done on each batch using 1 day-old chickens and 14 – 28-day old chickens.

Results for three batches of vaccine containing only the H5N2 virus indicated that a consistent product can be produced and the company has made a commitment to provide further data on batches containing different combinations of virus subtypes.

Stability of the product

Stability of bulk antigen

Data have been provided which indicate that the virus-containing fluid collected from eggs may be stored refrigerated for up to 12 months

Stability of finished product

The company has tested the stability of batches of vaccine containing each of the proposed viruses separately, but not together. These batches were contained in the PET bottles and the data showed that a shelf-life of 24 months is appropriate for vaccine stored in these containers. Based on experience of similar products, a shelf-life of 12 months was approved for the vaccine when stored in glass bottles.

Stability of the product once the bottle has been started

It is intended that once started, a bottle of the product will all be used during the same day.

* GMP = Good Manufacturing Practice

CONCLUSIONS ON QUALITY

The company has provided satisfactory descriptions of the production and of the quality control procedures both during and after manufacture of Nobilis Influenza. These should ensure that a product of consistent quality can be manufactured.

PART III. SAFETY ASPECTS

Introduction

Because there is an urgent need to have available a vaccine against the types of highly pathogenic avian influenza that are now in circulation, the company has not so far had the time to do all the tests required for a full marketing authorisation. It was therefore necessary to glean as much information as possible from the study reports that were available at the time the provisional marketing authorisation was issued. This information includes the reports of studies on:

- the safety, for chickens, of another inactivated poultry vaccine which is manufactured in a similar way
- the safety, for chickens, of one of the components of Nobilis Influenza (the H5N2 component)
- the safety, for ducks, of another inactivated vaccine which contains the same adjuvant (light liquid paraffin) as Nobilis Influenza.

No studies have been performed to investigate safety of the product for other birds.

Laboratory Tests

Two studies which complied with GLP* have been carried out in 4 week-old chickens. In one study the birds were injected with a double dose of an inactivated poultry vaccine that had been prepared in a similar way to Nobilis Influenza (i.e. viruses are grown in eggs and inactivated using formaldehyde, and the finished product is a water-in-oil emulsion). The injection was given in the breast muscle, the thigh muscle or subcutaneously in the neck. In the other study, birds were given a single dose of the vaccine but the dose was repeated after 42 days. These birds were injected either in the breast muscle or subcutaneously in the neck. No signs of illness occurred in any of the birds but some of the birds that had been injected in the thigh had swelling of the thigh muscle. This disappeared within 3 weeks. Some of the vaccine remained visible at the injection site for 42 days and, in some cases, tiny abscesses developed after subcutaneous injection. The changes observed were typical of those that occur after injection of a water-in-oil emulsion.

In another group of studies, 2 – 4 weeks old chickens were injected into the leg muscle with a form of the Nobilis Influenza vaccine that contains only one of the approved viruses, H5N2. All birds were given a double dose of vaccine followed by a single dose 21 days later. None of the birds showed any signs of ill health or of injection site reactions.

* GLP = Good Laboratory Practice

Information from the batch testing of the product in 1-day old chickens indicates that the product is suitable for vaccinating birds of this age.

With regard to ducks, a large study investigated the effects of another duck vaccine produced in a similar way to Nobilis Influenza. Some of the ducks were given a single subcutaneous dose of the product, some were given a double dose, and the rest were given a single dose which was repeated after 2 or 6 weeks.

No adverse reactions to the injection were observed on clinical examination of the ducks which were given a single or double dose in one injection. However, at *post mortem*, reactions at the injection site were observed one week after the injection, and remnants of the vaccine were visible in ducks given a single dose. In the ducks given a double dose of vaccine, similar reactions occurred but they were slightly larger and were still visible two weeks after the injection. Two out of ten of the ducks given a single dose repeated after 2 weeks developed a small hardening at the injection site after the second injection but this disappeared after a week and one of ten ducks given a single dose repeated after 6 weeks was observed to limp after the second injection. As in the case of chickens, the reactions observed were typical of those that occur following vaccination with this type of product.

No information is available on use of the vaccine in laying birds, and the SPC and information provided with the product make this clear.

Field Studies

The data available on the safety of Nobilis Influenza when used in the field, is restricted to trials of viral components of the product in Hong Kong, Italy and The Netherlands. Although these trials were primarily aimed at establishing efficacy, no safety issues arose, and these studies therefore provided some reassurance regarding safety in field use.

CONCLUSIONS ON SAFETY

Conclusions on Target Species Safety

The full range of safety studies has not yet been conducted. Preliminary studies, together with data on other, similar products, indicate that Nobilis Influenza will not cause any unexpected adverse effects in the target species when used in the field. The reactions seen in chickens and ducks are typical of the reactions that commonly occur after injection of vaccines of this type. The quality control of the product includes appropriate tests to ensure that each of the viruses that may be included in the product is effectively inactivated. Limited information from the use of the vaccination against H5N1 in other countries provided further reassurance as to the safety of the product. The information available meets the requirement that, for a provisional marketing authorisation, the major safety questions have been answered. The company has made a commitment to provide additional data if it becomes necessary to renew the provisional marketing authorisation or if a full marketing authorisation is needed.

Conclusions on User Safety

A user risk assessment indicates that the main risk for people administering the product to birds is the possibility of accidentally injecting themselves. The possible outcome of injecting a product containing mineral oil is well-documented and a detailed warning on the appropriate action to take is included in the summary of product characteristics and on the information provided with the product.

Conclusions on Consumer Safety
None of the ingredients of Nobilis Influenza are such as would cause unacceptable residues in meat from treated birds. There is no need for a withdrawal period and no consumer safety concerns.

Conclusions on Environmental Safety
An environmental risk assessment for this product indicates that the formulation and use of the vaccine is similar to other authorised avian vaccines produced by the company. Since it has been agreed that such vaccines pose a negligible risk to the environment, the same conclusion applies to Nobilis Influenza.

PART IV. EFFICACY ASPECTS

Introduction
As in the case of the safety aspects, preliminary information only is available on the efficacy of Nobilis Influenza. The information is predominantly in the form of laboratory trials, and mostly investigated the efficacy of the individual viral components of the vaccine, although some information is available on a vaccine containing two viral components, and three publications provide information on use of vaccination under field conditions against H5N1 in Hong Kong, and against the H7 subtype in Italy and The Netherlands. There is also some information on the duration of immunity.

Laboratory Trials

Efficacy Against H5 Subtypes of the Avian Influenza Virus
The efficacy of the H5N2 component of Nobilis Influenza has been studied in chickens and ducks which had no antibodies to H5 at the start of the trials. When exposed to highly pathogenic H5N1, the vaccinated birds showed few, if any, signs of illness and there was a substantial reduction in mortality. In the case of chickens, there was a strong antibody response to vaccination and a reduction in the number of birds excreting the virus. At the time of writing, the equivalent results for ducks were still awaited but the clinical signs indicate that antibody levels would be expected to have increased following vaccination.

In a further trial, chickens were vaccinated with either the H5N2 component of Nobilis Influenza or the H5N6 component. The development of antibodies against H5 was noted 2 weeks after vaccination and increased at 3 weeks and again at 4 weeks. Following exposure to a highly pathogenic H5N2 virus strain, all the vaccinated birds remained clinically well, even if they were exposed two weeks after vaccination, when antibody levels had not reached their peak.

The information from these trials were supported by three other reports of the efficacy of similar vaccines.

Efficacy Against H7 Subtypes of the Avian Influenza Virus
The ability of the H7 component of Nobilis Influenza to protect against pathogenic types of the H7 virus has been investigated in chickens, pheasants and ducks.

In the case of chickens, vaccinated birds developed protective levels of antibodies to H7 and showed no signs of disease when exposed to a pathogenic H7 virus seven days after vaccination, although virus was detected in swabs collected from these birds. When vaccinated

chickens were exposed to pathogenic H7 virus fourteen days after vaccination, there were no signs of disease, virus was only found in one swab collected from one of these birds and transmission of the virus to vaccinated chickens in contact with the exposed birds was blocked. When unvaccinated chickens were placed in contact with vaccinated infected birds, very few of the unvaccinated birds became ill, indicating that spread of virus was reduced by the vaccine. Unvaccinated chickens exposed directly to the pathogenic H7 virus, became ill and many died.

In ducks, vaccinated birds were also protected from signs of disease following exposure to pathogenic H7 virus fourteen days after vaccination, although virus was found in swabs collected from some of them. Vaccinated ducks placed in contact with the vaccinated infected birds also remained free of disease and did not excrete any virus, i.e. transmission to vaccinated contact ducks was blocked.

In pheasants, there was evidence of some spread of pathogenic virus from vaccinated infected birds to vaccinated contact ones, but this was much less than that from unvaccinated infected birds to unvaccinated contact birds. Vaccinated pheasants showed no signs of disease whereas unvaccinated ones had a high mortality rate when exposed to pathogenic H7.

Efficacy Against H9 Subtypes of the Avian Influenza Virus
The efficacy of the H9N2 component of Nobilis Influenza has been studied in chickens and turkeys which had no antibodies to H9 at the start of the trials.

Most chickens vaccinated with the H9 component of Nobilis Influenza developed antibodies to H9 and remained well when exposed to a pathogenic type of H9, although 2.5% failed to develop antibodies and subsequently developed respiratory disease and died. This was a significant reduction compared with 84% of unvaccinated birds which died when exposed to the pathogenic H9.

A protective effect was observed in turkeys. In this case, none of the birds exposed to pathogenic H9 shows any signs of illness, even if they had not been vaccinated. However, at *post mortem* it was noted that vaccinated birds were protected against H9-induced damage to the pancreas.

Duration of Immunity
Limited information is available on the duration of immunity to H5 and H9. In the case of H5, the data relate to a different strain of an H5 virus but, since the response to different strains has been shown to be similar, the data do provide a reasonable indication as to the duration of immunity that can be expected to the H5 component of Nobilis Influenza. In this study, elevated levels of antibodies were found 45 weeks after vaccination. With regard to H9, a detailed study in female chickens vaccinated by the intramuscular or subcutaneous routes showed antibodies two weeks after first vaccination which increased further until the second vaccination six weeks later. Antibody levels remained high for more than a year. This experiment also found significant levels of maternal antibodies in chicks from vaccinated birds although there is no information on the effect these maternal antibodies might have on subsequent vaccination of the chicks. The SPC therefore includes a warning to this effect.

Efficacy of Bivalent Vaccines
The efficacy of a vaccine containing more than one virus subtype was investigated in two studies in chickens. In the first study, antibody levels following administration of a vaccine containing the H5N2 and H7N1 components of Nobilis influenza were compared with those following administration of a vaccine containing either H5N2 or H7N1. Significantly raised

antibody levels were detected in all vaccinated birds. Rather higher levels were found in birds given the single component vaccines but levels were considered to be high enough to be protective in all birds.

In the second study, antibody levels following administration of a vaccine containing the H7N1 and H9N2 components of Nobilis influenza were compared with those following administration of a vaccine containing either H7N1 or H9N2. As in the earlier study, antibody levels were slightly lower in birds given the two component vaccine but they were nevertheless considered to be high enough to be protective.

Field Trials

Since it would clearly be irresponsible to vaccinate birds and then deliberately expose them to highly pathogenic viruses outside the controlled conditions of the laboratory, information on the use of Nobilis Influenza in the field comprises three published papers describing use in countries where outbreaks of avian influenza have occurred in recent years: Hong Kong, Italy and The Netherlands. The first of these publications refers to an outbreak of highly pathogenic avian influenza subtype H5N1 disease and indicated that H5 vaccine, when used as part of a control strategy, could reduce mortality and interrupt virus transmission in a field setting. The second publication refers to an outbreak of the H7 subtype and it also indicates the value of vaccination as part of a control strategy. The third publication describes the development of a strong antibody response in valuable zoo birds following use of the vaccine in these birds during an outbreak of the H7 subtype in poultry in The Netherlands in 2003.

CONCLUSIONS ON EFFICACY ASPECTS

The company has presented a series of experiments designed to demonstrate the efficacy of the various virus subtypes that might be incorporated into the finished product, depending on the disease situation at the time of production. The information gained from these experiments has been supplemented with information on similar virus subtypes and by published papers.

The product has been shown to be capable of inducing antibodies and of protecting birds from specified virus strains. Most experiments have been done in chickens but there is also some information in ducks, pheasants and turkeys. In chickens, the vaccine is capable of preventing signs of disease and mortality, and of reducing the excretion of pathogenic avian influenza viruses of the relevant sub-types. This reduction in excretion is likely to result in reduced spread of disease. In other species, the degree of protection may not be as great. For example, in ducks, excretion and transmission is reduced, whereas in pheasants, mortality is reduced but the reduction in excretion and spread is much less.

In studies of vaccines containing two viruses, the level of antibodies found was rather less than when there was a single virus component, although the results indicated that a vaccine containing two viruses would still be effective. Immunity appears to be fully effective from two weeks after vaccination and is expected to last for 12 months. There is no information on the possible impact of maternal antibodies on the efficacy of the vaccine.

In conclusion, the company has provided some evidence that the product will work in the field, as is required for a provisional marketing authorisation. Further work on the product continues and will be submitted for assessment if it is necessary to renew the provisional authorisation or to issue a full one.

PART V. OVERALL CONCLUSION ON THE PRODUCT

Vaccination may become a necessary part of the control strategy if an outbreak of avian influenza caused by H5N1 occurs in the UK. For the reasons explained earlier, it is not possible to have suitable vaccines approved well in advance, and this means that a provisional marketing authorisation is appropriate. The data submitted by the company were appropriate for such a situation and demonstrate that a product containing appropriate viruses can be produced if required and that the product can be manufactured to a consistent quality. The major aspects of safety have been addressed in that there are no concerns for consumers of food products from birds vaccinated with this product and there are no environmental safety concerns. The risk to people using the product to vaccinate birds is similar to the risk from other vaccines with a similar adjuvant system, and is adequately explained in the summary of product characteristics and in the information provided with the product. The available information indicates that the product is safe for use in chickens, ducks and turkeys, and there is thus a reasonable expectation that it would be safe and efficacious in other birds too. More conclusive evidence of safety and efficacy would be required to justify a recommendation to treat other birds in a full marketing authorisation but, because of the severity of the disease and the possibility that other birds might help to spread it, it is considered appropriate to provisionally approve use of the product in other birds too.

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)