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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Nobilis IB Primo QX (EMEA/V/C/002802/0000)

International non-proprietary name: avian infectious bronchitis vaccine (live)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

On 6 March 2013 the applicant Intervet International B.V. submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Nobilis IB Primo QX through the centralised procedure under Article 3(2)(a) of in accordance with Regulation (EC) No 726/2004 (new active substance).

The product was considered eligible by the CVMP on 13 September 2012 under Article 3(2)(b) of Regulation (EC) No 726/2004 as the product constitutes a significant technical innovation. The rapporteur appointed was A.-M. Brady and co-rapporteur J.-C. Rouby.

Nobilis IB Primo QX contains live attenuated avian infectious bronchitis (IB) virus strain D388.

The proposed indication is for active immunisation of chickens in order to reduce respiratory signs of avian infectious bronchitis caused by QX-like variants of infectious bronchitis virus. The onset of immunity is 3 weeks and the duration of immunity is at least 8 weeks. The proposed routes of administration are by the oculonasal route (eye drop or spray vaccination). The proposed target species is chickens.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

On 10 July 2014, the CVMP adopted an opinion and CVMP assessment report.

On 4 September 2014, the European Commission adopted a Commission Decision granting a marketing authorisation for this veterinary medicinal product.

Scientific advice

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC. A statement signed by the applicant and the qualified person for pharmacovigilance (QPPV), indicating that the applicant has the services of a QPPV and the necessary means for the notification of any adverse reaction occurring either in the European Union (EU) or in a third country has been provided.

Manufacturing authorisations and inspection status

The sites involved in the manufacture of Nobilis IB Primo QX are Intervet International BV, at Boxmeer in The Netherlands and Merck Sharp & Dohme Animal Health S.L. at Salamanca in Spain. They are authorised by EU regulatory authorities and valid certificates of good manufacturing practice (GMP) compliance are available. The Boxmeer site was last inspected in April 2011 and Salamanca in March 2012.

The manufacturing steps for the production of bulk vaccine (virus + stabiliser) of Nobilis IB Primo QX are similar to other live avian vaccines currently produced at the manufacturing sites up to the

lyophilisation stage. Following the production of bulk vaccine, the applicant proposes innovative dispensing, freeze-drying and packaging processes (bulk vaccine is dispensed as droplets, frozen and freeze-dried as sphere-shaped lyophilisate which can be stored at ≤-20 °C up to 12 months prior to final packaging in sealed aluminium laminate cups). The laminate cups constitute a novel primary packaging material for a lyophilised veterinary vaccine.

The Dutch Inspectorate (Supervisory Authority) has confirmed that the processes described for the manufacture of Nobilis IB Primo QX at Intervet International BV, Boxmeer have been inspected and fall under the GMP certificate that was issued to Intervet in 2011. A further inspection of the site is not requested.

It is the intention to carry out production, quality control and packaging of solvent at two sites. The solvent is already authorised for use with a number of the applicant's freeze-dried live avian vaccines. However, as batches of solvent have not recently been produced at one manufacturing site, production would have to be revalidated in accordance with GMP regulations before batches of solvent could be released.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing site was considered in line with legal requirements.

Part 2 – Quality

Composition

Lyophilisate:

The vaccine contains live attenuated avian infectious bronchitis (IB) virus strain D388 at concentrations of $\geq 10^{4.0}$ and $\leq 10^{5.5}$ EID_{50}[1] per chicken dose. Sorbitol, hydrolysed gelatin, pancreatic digest of casein (NZ amine) and disodium phosphate dihydrate are included as excipients. Gentamicin sulphate is present in the vaccine at concentrations up to 50–100 ng per dose as a remnant of the production of the antigen where the antibiotic is added to harvested allantoic fluids to prevent growth of low levels of contamination that may be present in the allantoic fluids during the liquid phase of the product.

Solvent:

Solvent Oculo/Nasal, which is an optional solvent for administration by oculonasal route and is only supplied with the 1,000 dose presentation of vaccine, contains Patent Blue V (E 131) as colouring agent and potassium dihydrogen phosphate, disodium phosphate dihydrate, disodium edetate dihydrate, sodium chloride, water for injections, sodium hydroxide and/or hydrochloric acid (for pH adjustment) as excipients.

Container

The vaccine is filled into cups made of aluminium foil laminate with a polypropylene contact layer and sealed with a lid of the same composition. This is a novel primary packaging material for a lyophilised

[1] egg infective dose 50%.

live veterinary vaccine. Specifications of material used and certificate of compliance for the aluminium cups and lids (which includes the polypropylene contact layers) which meet European Regulation (EC) No 1935/2004 on standards on materials and articles intended for food contact have been provided. A small cup (42 mm diameter) is used for the 1,000 and 5,000 presentations and a large cup (61 mm diameter) is used for the 10,000 presentation.

The solvent is filled into low density polyethylene (LDPE) vials with a halogenobutyl rubber stopper and aluminium cap. If the solvent is used, the rubber stopper of the vial is removed and a specifically designed adaptor is connected to the solvent vial to facilitate the mixing of lyophilisate and solvent. The dropper provided with the solvent is then connected. Specifications of the adaptor and dropper and validation of the size and consistency of the drops delivered by the dropper have been provided. The vial, halogenobutyl rubber stopper, adaptor and dropper meet pharmacopoeial standards.

Development pharmaceutics

Nobilis IB Primo QX was developed in response to the emergence of the D388/QX-like strain of IB virus in European countries from 2003 which causes high occurrence of false layers and impaired broiler performance, respiratory signs, nephritis and mortality. This is therefore a new strain of IB virus (IBV). The viral strain used to develop the vaccine was isolated in 2004 from chickens with IB in the Netherlands and named IB D388 by the Animal Health Service at Deventer in the Netherlands. The IBV D388 isolate was attenuated by passage in specific pathogen free (SPF) chicken eggs, adapted for growth in SPF chicken embryo kidney cell cultures and cloned by plaque purification in SPF chicken embryo kidney cell cultures, followed by passages in SPF chicken eggs before establishing the master seed virus (MSV).

The target quantity of antigen per dose was determined on the basis of protection against challenge with a virulent strain of IBV in a series of dose-response, onset of immunity, duration of immunity, maternally derived antibodies (MDA) and field studies in accordance with European Pharmacopoeia (Ph. Eur.) monograph 0442. Demonstration of protection was assessed by the degree of ciliary activity of tracheal explants. Failure to resist a virulent challenge was indicated by an excessive loss of ciliary motility (ciliostasis) and disruption of the epithelial layer.

Most of the safety studies were carried out using the oculonasal route in addition to data on safety of vaccination by coarse spray, as spraying is likely to create aerosols that could result in the vaccine penetrating further into the lungs. The CVMP public statement on routes of administration of vaccines to poultry (EMA/CVMP/IWP/640481/2013) clarifies that studies are required to justify safety for all recommended routes of administration of poultry vaccines. Safety of an overdose by spray was not investigated however it was considered supported by overdose data by spray for strain Ma5 given that reports of single dose spray administration of IB-QX showed lower lesion scores than single dose Ma5 scores. Therefore it can be considered that the overdose will be no worse than Ma5. However, bearing in mind that Nobilis IB Primo QX has a new vaccine strain and the recent CVMP clarification paper on routes of administration of vaccines to poultry (i.e. to justify the safety and efficacy for all recommended routes of administration of poultry vaccines, studies are required as laid down in the Annex 1 of Commission Directive 2009/9/EC and the Ph. Eur. monograph 0062 on vaccines for veterinary use), a condition has been set that a small scale overdose (10x) study by spray is to be provided post-authorisation.

The vaccine is produced using an innovative freeze-drying process where bulk vaccine is dispersed in droplets that are quickly frozen and subsequently freeze-dried resulting in sphere-shaped lyophilisates which can be stored for up to one year at ≤-20 °C. The infectivity titre per sphere is determined prior to filling into cups made of aluminium foil laminate. The new method of production aims to reduce the

variability of the virus titre per container compared to the classic method of production of freeze dried cake in glass vials. The freeze-dried spheres are of a robust nature, do not appear to abrade easily and are of a clearly visible size. The new primary containers are expected to be more convenient to users as cups with tear-off seals should reduce the work and time needed to open the required number of containers. The primary packaging material is widely used in the food industry and is robust. Cups contain a range of between 3 and 100 spheres for the 1,000 and 5,000 doses presentations (depending on the titre of vaccine virus in spheres) and between 3 and 400 spheres for the 10,000 dose presentation. Opening the cups and decanting the contents into the solvent (either via the adaptor into Solvent Oculo/Nasal for eye drop administration or directly into water of good quality for spray vaccination) for reconstitution under field conditions should be straightforward.

The vaccine does not contain a preservative. The shelf life after reconstitution according to directions is 2 hours. The vaccine is presented in cups of 1,000, 5,000 or 10,000 doses which is practical for administration in that time by spray vaccination. Solvent Oculo/Nasal is available as solvent for the 1,000 dose presentation only.

Method of manufacture

Vaccine virus manufacture consists of a conventional process of production of attenuated IBV strain D388 in embryonated SPF hens' eggs, blending of harvested allantoic fluid with stabiliser and gentamicin to produce bulk vaccine, followed by an innovative freeze-drying process where bulk vaccine is dispersed in droplets that are quickly frozen (≤-90 °C), stored at ≤-40 °C for up to 7 days and subsequently freeze-dried resulting in sphere-shaped lyophilisate. Sphere-shaped lyophilisates may be stored at ≤-20 °C for up to one year. The infectivity titre per sphere is determined and used to calculate the number of spheres of a particular batch required for a given dose presentation. The required number of spheres is then filled into aluminium foil cups using a validated counter unit and sealed with a lid under a dry atmosphere (≤3% humidity). The manufacturing process is adequately described.

The solvent is manufactured by a conventional procedure in which the required amount of components are weighed and dissolved in water for injections, the pH is adjusted to 6.8–7.2, sterilised by filtration through a 0.2 µm filter into a bulk vessel, filled into vials and stoppered. The process is adequately described.

Control of starting materials

Active substance

The master virus seed used to produce the vaccine virus was tested to demonstrate freedom from extraneous agents and shown to be free from the agents listed in Ph. Eur. monograph 2.6.24. The methods used to test for avian nephritis virus and Marek's disease virus deviated from the types of test recommended in Ph. Eur. monograph 2.6.24 and information was provided to show that they were at least as sensitive as those indicated and of appropriate specificity. The IBV QX Belgian challenge strain used as the challenge strain in the efficacy studies was used to hyper-immunise chickens to prepare antiserum 3024 used in tests for extraneous agents. Sequence analysis of the S1 gene PCR product of the IBV QX Belgian challenge virus strain identifying it as a QX strain has been provided.

The chicken flocks used to produce the SPF embryonated eggs used for the production of vaccine virus SPF embryonated eggs were tested for extraneous agents and certified as chicken flocks free from specified pathogens for the production and quality control of vaccines in accordance with Ph. Eur.

However, some of the test methods used by some of the suppliers deviated from the type of test recommended in Ph. Eur. monograph 5.2.2 for several of the agents tested; where the test method used was not the same as that recommended in the Ph. Eur. information was provided to show that they were at least as sensitive as those indicated and of appropriate specificity.

Excipients

The certificate of analysis for NZ amine (pancreatic digest of casein) demonstrates compliance with specifications of the U.S. Pharmacopeial Convention (USP) monograph referenced for pancreatic digest of casein relevant to its use as part of the freeze drying stabiliser; omission of tests relating to the use of NZ amine as peptone for bacteriological cultures is considered acceptable.

Whilst the certificate of analysis for Patent Blue V, which is used as a colouring agent in the solvent, does not demonstrate complete compliance with the Ph. Fr. monograph for Patent Blue V (E 131) provided, it can be accepted from assessment of information provided that the starting material is fit for purpose. Patent Blue V is a food approved colorant (E131) and the tests performed show suitability for use as a food additive. Colouring material authorised for use in foodstuffs intended for human consumption is also authorised for use in medicinal products (Directive 78/25/EEC).

All other excipients (gelatin, sorbitol, disodium phosphate dihydrate, potassium dihydrogen phosphate, disodium edetate dihydrate, sodium chloride, water for injections, sodium hydroxide and/or hydrochloric acid (for pH correction)) comply with respective Ph. Eur. monographs.

A viral safety risk assessment has been provided. Tryptose solution is sterilised by autoclaving for at least 15 minutes at 121 °C and stabiliser solution which contains gelatine and NZ amine is sterilised by autoclaving for at least or at 115 °C for 30 minutes before use; validation data for this process have been provided using *Bacillus stearothermophilus*. A report on viral inactivation related to steam sterilisation of biological products prepared by Virbac Laboratories for IFAH-Europe has been provided. This provides sufficient evidence that the tryptose and stabiliser solutions can be considered as free from extraneous viruses with a high level of confidence following the sterilisation treatments described.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

A declaration of compliance with the annex to Directive 2001/82/EC for Nobilis IB Primo QX and a risk assessment regarding transmissible spongiform encephalopathy (TSE) in accordance with Directive 1990/104/EC and Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) have been provided.

During the production of Nobilis IB Primo QX, the following starting materials of ruminant origin are used: gelatin, NZ amine (pancreatic digest of casein) and tryptose. Only EDQM certified bovine-derived gelatin is used and the bovine component in NZ amine and tryptose is derived from milk sourced from healthy animals in the same condition as milk collected for human consumption. The original IBV was isolated from a Dutch chicken which is not considered to be TSE relevant.

It is concluded that the risk of transmitting TSE infectivity through the use of this vaccine is negligible.

Control tests during production

Control tests carried out during antigen production include: bioburden test on harvest (to select aliquots acceptable for vaccine production); check on homogeneous dispensed volumes (to ensure homogeneous dispensing volumes of a batch); check on freeze-drying (to check conditions during freeze-drying); and virus titration (to determine the viral titre per sphere).

The results of the analysis of in-process control tests of three consecutive production runs of freeze-dried intermediate bulk vaccine prepared using antigen produced at Salamanca for three batches of vaccine and the results of the analysis of in-process control tests of three consecutive production runs of freeze-dried intermediate bulk vaccine prepared using antigen produced at Boxmeer for three batches of vaccine used in the trials were presented which demonstrate compliance with the required specification. Manufacturer's batch protocols for each of the final batches were provided.

No in-process control tests are carried out during production of the solvent.

Control tests on the finished product

Antigen:

The description of the following methods used for the control of the vaccine finished product and the specifications were provided: Final inspection, identification of active substance, virus titration, bacteriological and mycoplasmas tests (to demonstrate the absence of pathogenic micro-organisms and to demonstrate that the number of saprophytic micro-organisms is below the limit of acceptance), extraneous agents tests and residual humidity.

Some of the control tests on the finished product are carried out on freeze-dried bulk spheres (finished product before filling) and some on finished product (spheres filled into final container). Virus titre, identity and freedom from extraneous agents and mycoplasmas are tested on the freeze-dried bulk spheres before filling while spheres filled into the finished container are tested for virus titre, identity, residual humidity, bioburden and appearance.

A targeted filling objective of 4.5 $\log_{10}$ EID_{50}/dose was proposed (based on the viral titre per sphere determined by in process titre test on bulk sphere); as a minimum titre at release of 4.2 $\log_{10}$ EID_{50}/dose determined by confirmatory finished product titration test was considered sufficient to compensate for titre loss during shelf life and variability of the titration method and ensures that the vaccine has a minimum titre of 4.0 throughout shelf life. The CVMP considered that the proposed release specification of 4.2 $\log_{10}$ EID_{50}/dose will be achieved with an overage of 0.5 $\log_{10}$ / target of 4.5 $\log_{10}$ EID_{50}/dose and thus, the target value can be set at 4.5 $\log_{10}$ EID_{50}/dose.

The CVMP recommends that the correctness of the targeted filling objective is demonstrated post-authorisation by the applicant, as follows: (1) to subject the first 3 marketed batches of Nobilis IB Primo QX to full ongoing stability studies, applying the finished product method with increased precision; this must confirm that the proposed approach ensures the minimum titre throughout shelf life; (2) to provide comparative data between filling objective and finished product titration results after the first 20 vaccine batches have been released for marketing to confirm the proposed approach and robustness of the filling process for Nobilis IB Primo QX.

The results of the analysis of three consecutive production runs of vaccine prepared from antigen produced at Boxmeer and of three consecutive production runs of vaccine prepared from antigen blend produced at Salamanca were presented to demonstrate compliance with the required specification.

Batch-to-batch consistency and conformity with specifications for all tests performed during production and on the finished product have been demonstrated with the consecutive batch protocols provided.

The following quality control tests are carried out on the solvent: average contents, appearance, clarity, pH, identity and sterility. The results of the analysis of three consecutive batches of solvent were presented which demonstrate compliance with the required specifications and batch-to-batch consistency.

Stability

Based on the data currently provided by the applicant for consistency batches a shelf life of 12 months of vaccine (total time of vaccine stored as bulk spheres and/or filled in cups) at ≤–20 °C followed by up to 15 months at 2–8 °C is acceptable, pending further stability data of (Salamanca) final product in cup at ≤–20 °C for 12 months followed by 18 months at 2–8 °C.

Stability of the vaccine at 30 °C for 3 days was also investigated. The vaccine has been shown to be stable at 30 °C for up to 3 days.

Reconstituted Nobilis IB Primo QX is stable in tap water, in reverse osmosis water or in tap water with Vac Safe (which may be added to drinking water to neutralise chlorine) and in Solvent Oculo/Nasal for 2 hours at room temperature as assessed by virus titration tests.

Stability data on Nobilis IB Primo QX mixed with Nobilis IB Ma5 is supported by compatibility data in sections on safety and efficacy.

The data presented on stability of Solvent Oculo/Nasal originates from an original marketing authorisation dossier for the solvent and the raw data is no longer available to generate new batch protocols as these have been disposed of in line with the GMP regulations. However, no change in solvent composition has been introduced since the initial stability study and considering the nature and composition of the product (saline solution authorised for reconstitution of many of the applicant's freeze-dried products) a shelf life of 48 months at ≤ 25 °C can be maintained.

Overall conclusions on quality

Information regarding the qualitative and quantitative composition, the starting materials, production method, quality controls, and stability are provided in this part of the dossier. Six batches of vaccine (three batches produced with antigen manufactured at Salamanca and three batches produced with antigen manufactured at Boxmeer) and three batches of solvent were provided in order to demonstrate batch to batch consistency.

The live IBV strain D388/QX antigen is produced by a conventional process in the allantoic cavity of embryonated SPF eggs. After mixing with stabiliser it is freeze-dried in spheres which may be stored before filling into aluminium cups which are then sealed. The freeze-drying process where bulk vaccine is dispersed in droplets and freeze-dried as spheres and the primary packing are novel for live veterinary vaccines in the EU. The solvent is a saline solution and is already authorised for use with other freeze-dried live avian vaccines manufactured at the Boxmeer and Salamanca production sites. The production methods as well as the in-process and final product quality control are appropriate to ensure the compliance with the specifications and a reproducible and consistent quality of the vaccine. The production process is described in sufficient detail to give confidence that the manufacture will yield a safe and effective vaccine of consistent quality and adequate stability suitable for the expected use of the vaccine in the EU.

The freeze-dried spheres are of a robust nature, do not appear to abrade easily and are of a clearly visible size. The primary packaging material is widely used in the food industry, its specifications have been adequately described. The primary packaging is considered robust. Cups contain a range of between 3 and 100 spheres for the 1,000 and 5,000 dose presentations (depending on the titre of vaccine virus in spheres) and between 3 and 400 spheres for the 10,000 doses presentation. The range of spheres in a cup is mentioned on the packaging. In the event that the integrity of the cup is compromised spheres shrink, turn brown and stick to the container and a warning to that effect has been placed on the SPC that in such case the product should not be used. Opening the cups and decanting the entire contents into the solvent, either via the adaptor into Solvent Oculo/Nasal for eye drop administration or directly into water of good quality for spray vaccination, for reconstitution under field conditions should be straightforward. The instructions for reconstitution and administration are adequately described in the SPC and package leaflet.

Compliance of starting materials during manufacture and control tests on the finished product are appropriate to ensure the compliance with the quality specifications mentioned. Acceptance limits are properly established.

The stability of the active ingredient and finished product has been supported with batches of antigen produced at both manufacturing sites. Based on the data currently provided by the applicant for consistency batches a shelf life of 12 months of vaccine (total time of vaccine stored as bulk spheres and/or filled in cups) at ≤–20 °C followed by up to 15 months at 2 °C to 8 °C is acceptable, pending further stability data of (Salamanca) final product in cup at ≤-20 °C for 12 months followed by 18 months at 2–8 °C. An estimated average loss of 0.23 titre units was observed over 18 months at 2–8 °C and the applicant's proposal to standardly apply an overage filling of at least 0.5 $\log_{10}$ EID_{50}/dose is reasonable. The data presented on stability of Solvent Oculo/Nasal originates from an original marketing authorisation dossier for the diluent and the raw data is no longer available to generate new batch protocols as these have been disposed of in line with the GMP regulations. However, no change in solvent composition has been introduced since the initial stability study and considering the nature and composition of the product (saline solution authorised for reconstitution of many of the applicant's freeze-dried products) a shelf life of 48 months at ≤ 25 °C can be maintained.

The CVMP considers the presented analytical dossier as adequate and sufficiently detailed to give confidence that the finished product is produced according to a consistent procedure of adequate standards and includes adequate controls.

Based on the review of the data on quality, the manufacture and control of Nobilis IB Primo QX are considered acceptable.

In addition, the applicant is recommended to provide the following information (post-authorisation):

1. to subject the first 3 marketed batches of Nobilis IB Primo QX to full ongoing stability studies, applying the finished product method with increased precision; this must confirm that the proposed approach ensures the minimum titre throughout shelf life;

2. to provide comparative data between filling objective and finished product titration results after the first 20 vaccine batches have been released for marketing; this must confirm the proposed approach and robustness of the filling process for Nobilis IB Primo QX.

Part 3 – Safety

Safety documentation

Study reports were provided in which a single dose ($10^{5.5}$ EID_{50}), a repeated dose over the course of one day (2 x $10^{5.5}$ EID_{50}) and an overdose ($10^{6.5}$ EID_{50}) of vaccine was administered to one-day-old chicks. The applicant has also carried out studies investigating dissemination of a single dose of vaccine ($10^{5.5}$ EID_{50}) in chicks and spread from vaccinated chicks to non-vaccinated contacts, safety for the reproductive tract, reversion to virulence, and two field trials ($10^{4.7–4.8}$ EID_{50}). Two of the studies investigated interactions with Nobilis IB Ma5 which contains live attenuated infectious bronchitis (IB) virus strain Ma5.

In the studies, vaccine was administered by the oculonasal route with the exception of the field trials where administration was by spray vaccination. The applicant noted that the oculonasal route controls the actual dose to the chickens better and that the trachea of the chicken is the port of entry for the vaccine in both routes of recommended administration. The applicant also considered the oculonasal method of administration as the most sensitive of the similar respiratory, oral and ocular (nebulisation) routes used for vaccination. Safety data on vaccination by spray were also provided because administration of the vaccine by spray is likely to create aerosols that might result in the vaccine penetrating further into the lungs which could have different safety implications as compared to oculonasal vaccination. Therefore, the applicant carried out an additional study in which a single dose ($10^{5.5}$ EID_{50}) of vaccine was administered to one-day-old chicks by spray administration; an overdose was not tested as later described, however, this study also investigated potential recombination events when Nobilis IB Primo QX and Nobilis IB Ma5 were administered simultaneously by spray.

No studies were carried out to investigate spreading to other species, which is justified since IBV is only infective for chickens, or to investigate safety when given during lay, as the administration of vaccine is not indicated during lay.

Laboratory tests

In general, the tests were carried out in compliance with Ph. Eur. monographs 0062, 5.2.6 and 0442. Safety for the respiratory tract and kidneys were investigated in single dose, repeated dose, overdose and reversion to virulence studies; safety for the reproductive tract was investigated in single dose and reversion to virulence studies. Safety and relevant performance measures for broilers were investigated in the field trials. Laboratory studies were good laboratory practice (GLP) compliant and carried out in one-day-old SPF chicks seronegative to IBV D388, the minimum age recommended for vaccination, using the master seed lot of vaccine (batch 15D10). Production batches 10544, 10545 and 10547 were used in the field trials which were carried out in one-day-old Ross 308 broiler chicks certified as unvaccinated for IB.

One laboratory safety study, IMD/0171/10, investigated the safety for the respiratory tract and kidneys of a single dose, overdose, repeat dose and absence of reversion to virulence using six groups of one-day-old birds. Discussion of the results for the various groups is included under the relevant headings below.

Production batch 110544 was used in an additional safety study IMB/0100/13 to investigate safety for the respiratory tract and kidneys of a single dose by spray. This study also investigated potential recombination events when Nobilis IB Primo QX and Nobilis IB Ma5 were administered simultaneously by spray. Discussion of the results for the various groups is included under the relevant headings below.

Clinical signs of avian IB or deaths attributable to the vaccine virus were not observed in any of the safety studies.

Safety of the administration of one dose

Safety of a single dose ($10^{5.5}$ EID_{50}) administered to 19 one-day-old chicks by the oculonasal route was tested in study IMD/0171/10.

Inflammatory lesions were not seen during histological examination of the kidney.

The mean ciliostasis scores for vaccinated chickens 5, 7 and 10 days post-vaccination were low and were 0.33, 6.33 and 0 respectively (out of a maximum score of 40 for each). These are in line with authorised vaccines against IB.

A high score for ciliostasis of 37/40 was observed in one vaccinated chicken 7 days post-vaccination; a possible explanation of the significance of the high ciliostasis score in this bird was provided.

This study is a valid demonstration of the safety of administration of a single dose to one-day-old chicks by the oculonasal route.

Safety of an approximate single dose ($10^{5.5}$ EID_{50}) administered to 24 one-day-old chicks by spray vaccination using a nozzle sprayer was tested in study IMB/0100/13. Dose reconciliation determined that birds received 18.5% less than the expected dosage therefore receiving $10^{5.4}$ EID_{50}.

Inflammatory lesions were not seen during histological examination of the kidney.

The mean ciliostasis scores for vaccinated chickens 5, 7 and 10 days post-vaccination were low and were 6, 9, and 11 respectively (out of a maximum score of 40 for each). These are in line with authorised vaccines against IB. However, the mean ciliostasis scores of chicks administered a 1x dose of Nobilis IB Primo QX by coarse spray (study IMD/0100/13) were greater at all time-points post-vaccination than the mean ciliostasis scores of chicks administered either a 1x or 10x dose of Nobilis IB Primo QX by the oculonasal route (studies IMD/0171/10 and IMD/0123/10) with the exception of 5 days post-vaccination with a 10x dose in study IMD/0123/10.

Nasal exudate was observed in one bird at 7 days and one bird at 10 days post-vaccination with Nobilis IB Primo QX.

This study is a valid demonstration of the safety of administration of a single dose to one-day-old chicks by the spray.

Safety of one administration of an overdose

Safety of a ten times overdose ($10^{6.5}$ EID_{50}) administered to one-day-old chicks by the oculonasal route was tested in two studies; 19 chicks were vaccinated in IMD/0171/10 (Group 1) and 24 chicks in IMD/0123/10.

Inflammatory lesions were not seen during histological examination of the kidney in IMD/0171/10. In IMD/0123/10 mild inflammatory lesions were observed in the kidneys of one bird 5 days post-vaccination and in one bird 10 days post-vaccination.

The mean ciliostasis scores for vaccinated chickens 5, 7 and 10 days post-vaccination were low in both studies: 3.67, 7.17 and 7.43 respectively (out of a maximum score of 40 for each) in IMD/0171/10 and 11.13, 5.75 and 10.71 respectively in IMD/0123/10. These are in keeping with those of authorised IB vaccines.

Ciliostasis was observed in some individual birds at each day post-vaccination including high scores for one bird (39/40) 7 days post-vaccination and one bird (38/40) 10 days post-vaccination in IMD/0171/10, and medium-high scores for two birds (34/90 and 39/40) 5 days post-vaccination, one bird (25/50) 7 days post-vaccination, and two birds (21/40 and 37/40) 10 days post-vaccination in IMD/0123/10. On the basis of the justification provided, the CVMP considered this acceptable.

These studies meet the safety requirements of Ph. Eur. monograph 0442.

Safety of a ten times overdose ($10^{6.5}$ EID_{50}) administered to one-day-old chicks by spray was not tested.

Safety data after vaccination by spray (overdose) were not provided. This vaccination method is likely to create aerosols that result in the vaccine penetrating further into the lungs which may have different safety implications as compared to oculonasal vaccination and it is a requirement of Directive 2001/82/EC that an overdose of the product shall be administered by each recommended route of administration to animals of the most sensitive categories of the target species, unless the selection of the most sensitive of several similar routes is justified.

Assessment of the data provided on safety of single dose of vaccine (maximal titre) administered by spray shows that:

- Safety for the respiratory tract has been demonstrated following administration of a single dose of IB Primo QX by spray. Safety of an overdose of Nobilis IB Primo QX by spray vaccination is not known.
- Equivalence between the oculonasal and coarse spray routes has not been demonstrated in the studies provided as it appears that ciliostasis is greater following administration of a single dose of Nobilis IB Primo QX by spray than either a single dose or an overdose of Nobilis IB Primo QX administered by oculonasal route.
- However, the ciliostasis scores in chickens administered a single dose of Nobilis IB Primo QX by spray were less than those of chickens administered a single dose of Nobilis IB Ma5 by spray and therefore one conclusion would be that safety of Nobilis IB Primo QX is no worse than Nobilis IB Ma5 which is authorised and there is no reason to expect that safety of an overdose of Nobilis IB Primo QX administered by spray would be any worse than that of Nobilis IB Ma5.
- The applicant has met the safety requirements of Ph. Eur. monograph 0442 which requires demonstration of safety by the oculonasal route only of a quantity of vaccine virus equivalent to not less than 10x the maximum virus titre likely to be contained in one dose of the vaccine.

Based on an assessment of the data there is no reason to believe Nobilis IB Primo QX would be unsafe to administer by spray. However, bearing in mind that Nobilis IB Primo QX has a new vaccine strain and the recent CVMP clarification paper on routes of administration of vaccines to poultry (to justify the safety and efficacy for all recommended routes of administration of poultry vaccines, studies are required as laid down in Annex I of Directive 2009/9/EC and Ph. Eur. monograph 0062 on vaccines for veterinary use), the CVMP requested that a small scale overdose (10x) study by spray is completed post-authorisation and this has been set as a condition to the marketing authorisation.

Safety of the repeated administration of one dose

Safety of two single doses ($10^{5.5}$ EID_{50}) administered over the course of the same day to 19 one-day-old chicks by the oculonasal route was tested in IMD/0171/10 (Group 5).

No inflammatory lesions were seen during histological examination of the kidney.

The mean ciliostasis scores were 1.33, 0.83 and 1.71 on days 5, 7 and 10 days post-vaccination respectively. These were considered to be low and are in keeping with those of authorised vaccines against IB.

It is a requirement of Ph. Eur. monograph 5.2.6 that an interval of at least 14 days should be allowed between repeat administrations of one dose, for the development of any hypersensitivity reaction. The applicant has justified deviating from the normal Ph. Eur. requirement in this case because the vaccine is intended to be administered only once in the lifetime of the birds and the study was carried out to cover the possibility that birds might be accidentally vaccinated twice inside the hatchery.

Examination of reproductive performance

Safety for the reproductive tract of a single dose ($10^{5.5}$ EID_{50}) administered to one-day-old chicks by the oculonasal route was tested in two studies: 140 chicks were vaccinated in IMD/0090/10 and 48 in IMD/0166/10.

No abnormalities were observed post-mortem in the left oviducts of female chickens which survived to the end of the studies 74–76 days post-vaccination (60 animals in IMD/0090/10 and 48 animals in IMD0166/10). Only the left oviducts were examined for abnormalities and cysts for safety for the reproductive tract. This is acceptable since in chickens only the left ovary and oviduct are functional.

The studies met the requirements of Ph. Eur. monograph 0442 for safety for the reproductive tract.

The administration of Nobilis IB Primo QX is not indicated during the period of lay and the safety of the vaccine during lay was not tested.

Examination of immunological functions

No evidence of adverse effects of Nobilis IB Primo QX on immunological functions was observed in any of the safety or efficacy studies. Effects of IBV on immunological functions have never been reported. Additionally, in compatibility studies to support the associated use of Nobilis IB Primo QX and Nobilis IB Ma5 there was no evidence that concurrent use of Nobilis IB Primo QX and Nobilis IB Ma5 would result in adverse effects on immunological functions and results demonstrate that concomitant specific immunity build-up of each IBV strain is not affected. It is therefore unlikely that this vaccine will have an adverse effect on immunological function.

Special requirements for live vaccines

Spread of the vaccine strain

Spread of the vaccine strain from vaccinated to unvaccinated chickens was investigated in two studies in which one-day-old chicks were vaccinated with a single dose ($10^{5.5}$ EID_{50}) of vaccine by the oculonasal route and left in contact with unvaccinated sentinels for up to 20 days. In IMD/0167/10, 24 chicks were vaccinated and put in contact with 24 sentinels. Birds from both groups were sampled at days 2, 6, 13 and 20 days post-vaccination and tested for presence/titre of the vaccine strain in tissues from the trachea, lungs, caecal tonsils, kidneys, cloacal swabs, proventriculus, and gonads. In IMD/0124/10, 12 vaccinated chicks were placed in contact with 7 sentinels for 20 days and sera from both groups were tested for antibodies to IBV D388 at day 20.

In IMD/0167/10, the vaccine strain was isolated from the trachea and proventriculus of 9/10 and 10/10 sentinels respectively after 13 days contact and from the trachea and proventriculus of 8/10 and

4/10 sentinels respectively after 20 days contact. The vaccine strain was not found in any of the other sentinel tissues sampled.

In IMD/0124/10, eight out of 12 vaccinates had virus neutralising (VN) antibodies to IBV D388 at 20 days post-vaccination with a mean of 5.1 $\log_2$. Three out of 7 in-contacts had detectable VN antibodies against IBV D388 with a mean of 3.4 $\log_2$ after being in-contact with vaccinates for 20 days.

It is concluded that the vaccine virus can spread to in-contact unvaccinated chickens. Studies were not carried out to investigate spreading to other species, justified as IBV is only infective for chickens.

Dissemination in the vaccinated animal

Dissemination of the vaccine strain in vaccinated chicks was also investigated in studies IMD/0167/10 and IMD/0124/10.

In IMD/0167/10 vaccine strain was isolated from the trachea and proventriculus of most vaccinated chicks for at least 20 days post-vaccination, from the lungs and kidneys of most vaccinated birds up to 6 days post-vaccination, and from the caecal tonsils and cloacal swabs of most vaccinated birds at day 8 post-vaccination.

In IMD/0124/10, eight out of 12 vaccinates had VN antibodies to IBV D388 at 20 days post-vaccination with a mean of 5.1 $\log_2$.

In conclusion live attenuated IBV strain D388 disseminates following oculonasal vaccination with $10^{5.5}$ EID_{50} in one-day-old chicks and can be shed from vaccinated chickens to contact birds 13–20 days post-vaccination.

Reversion to virulence of attenuated vaccines

Increase in virulence of the vaccine strain was investigated in four studies in accordance with Ph. Eur. monographs 5.2.6 and 0442.

Sequential passage of vaccine strain through five groups of SPF chicks seronegative to D388 was investigated in studies IMD/0057/10 and IMD/0127/10; a single dose ($10^{5.5}$ EID_{50}) of test vaccine was administered to chicks in the first group by the oculonasal route and at passages 2, 3, 4 and 5, 0.05 ml of tracheal mucosa suspensions prepared from birds of the preceding passage was administered to each bird by the same route. Chicks were 13–14 days of age at the start of the study and the time between passages was 4 days. Each passage group consisted of 5 birds.

In IMD/0057/10 the vaccine strain was recovered at passage 1 but could not be recovered at passages 2, 3, 4 or 5 although smaller embryos in eggs used to isolate virus from tracheal mucosa were noted between the second and fourth passage. The study was repeated in IMD/0127/10 and vaccine strain was recovered at all 5 passages. There were no clinical signs of disease observed at any of the passage levels.

Passage 4 was inoculated into 25 chickens to prepare a larger volume of the virus (titre $10^{3.89}$ EID_{50}/ml) which was evaluated for safety for the respiratory tract and kidneys (IMD/0171/10, Group 2) and safety for the reproductive tract (IMD/0166/10, Group 2). In these studies groups of one-day-old chicks were inoculated with $10^{2.59}$ EID_{50} of IB D388 master seed virus (MSV) tracheal mucosa passage 5 and compared to groups of chicks inoculated by the same route with $10^{2.59}$ EID_{50} of test vaccine used to inoculate the first passage.

In IMD/0166/10 no abnormalities were found in left oviducts in the birds vaccinated either with material used for the first passage (at inoculum titres of $10^{2.29}$ EID_{50} per bird) or virus recovered at the final passage level (at inoculum titres of $10^{2.59}$ EID_{50} per bird). In this study groups of birds were also vaccinated with doses of $10^{5.5}$ EID_{50} per bird (see studies on single dose application) and $10^{6.5}$ EID_{50} per bird (see studies on overdose) and abnormalities were not seen in the left oviducts of any of these birds.

In IMD/0171/10 inflammatory lesions in the kidneys were not seen in either the group inoculated with material used for the 1st passage or in the group inoculated with virus recovered from the final passage. Mean ciliostasis scores for the group inoculated with material used for the 1st passage were low on days 5 (1.00 out of a maximum of 40), 7 (0.33) and 10 (0.14) post-vaccination. In comparison higher ciliostasis scores were observed in the group inoculated with virus recovered from the final passage: mean scores being 26.83 on day 5, 14.17 on day 7 and 3.57 on day 10. Ciliostasis scores dropped from day 5 to day 10. Most individual chickens had high scores for ciliostasis at day 5 post-vaccination and 2 chickens had high scores for ciliostasis at day 7 post-vaccination.

It is concluded that a slight reversion to virulence (increase of the ciliostasis score) was observed following five passages in vivo. A warning was included in section 4.5 of the SPC that 'All chickens on the site should be vaccinated at the same time.'

Biological properties of the vaccine strain

No specific studies have been conducted to determine the intrinsic biological properties of the vaccine strain. In the studies conducted the vaccine strain did not cause clinical signs of avian IB in any of the chicks vaccinated or damage to the development of the reproductive tract; ciliostasis was induced in some vaccinates for at least 10 days post-vaccination (although the mean ciliostasis scores induced in groups of vaccinated chickens were low, some individual vaccinates had high ciliostasis scores) and minor inflammatory lesions were seen in the kidneys of two bids in one of the ten times overdose studies, although inflammatory lesions were not seen in the kidneys of most birds.

Recombination or genomic reassortment of the strains

A claim for compatibility is made in section 4.8 of the SPC: "Safety and efficacy data are available which demonstrate that this vaccine can be mixed and administered with Nobilis IB Ma5". Nobilis IB Primo QX and Nobilis IB Ma5 contain two different live attenuated strains of IBV and the possibility of recombination between IBV strains is widely recognised. An assessment of the possibility of an adverse event due to recombination involving vaccine virus was provided. This estimated the risk very low because attenuation is the consequence of many dispersed changes in the non-structural genome segments. Safety following potential recombination events when Nobilis IB Ma5 and Nobilis IB Primo QX were administered simultaneously by spray was investigated in Study IMD/0100/13. In this study single doses of Nobilis IB Ma5 ($10^{5.6}$ EID_{50}) and Nobilis IB Primo QX ($10^{5.5}$ EID_{50}) were administered simultaneously by spray to a group of 24 one-day-old SPF chicks which were mixed approximately 2 hours following vaccination with a sentinel group of 24 non-vaccinated chicks and left in contact for up to 10 days. Single doses of Nobilis IB Ma5 or Nobilis IB Primo QX alone were also administered by spray to other groups of 24 birds. There was no evidence of increase in mortality, clinical signs of avian IB infection, ciliostasis or kidney lesions either in the group simultaneously vaccinated with Nobilis IB Primo QX and Nobilis IB Ma5 or in the unvaccinated in-contact sentinel group. The mean ciliostasis scores of chickens in the group administered Nobilis IB Primo QX alone were lower than those of chickens in the group administered Nobilis IB Ma5 alone. The group simultaneously vaccinated with Nobilis IB Primo QX and Nobilis IB Ma5 had lower mean ciliostasis scores than birds vaccinated

with Nobilis IB Ma5 alone. The mean ciliostasis scores of the sentinels were indistinguishable from the simultaneous Nobilis IB Primo QX and Nobilis IB Ma5 group.

There was no evidence of increase in virulence (as evidenced by increase in mortality, clinical signs of avian IB infection, ciliostasis or kidney lesions) either in the group simultaneously vaccinated with Nobilis IB Primo QX and Nobilis IB Ma5 or in the unvaccinated in-contact sentinel group within the small study. However, a study of this scale (24 vaccinated chicks and 24 sentinels) cannot be taken as evidence that a recombination event between the two vaccine virus strains resulting in a new and virulent recombinant cannot occur when the enormous potential host population of domestic chickens that are vaccinated every year in the EU against IB is considered. Recombination in IBV is known to occur and while the likelihood of a recombination event between the two vaccine virus strains resulting in a new and virulent recombinant might be considered low, it cannot be ruled out by this study.

Additionally a risk assessment of the possibility of recombination occurring between IBV strains was provided by a suitably qualified expert in avian viruses. The risk assessment notes that recombination is known to randomly occur with IBV. In addition, because IBV is highly infectious and because of the enormous host population the conditions for recombination are highly favourable. The risk assessment concludes that whilst recombination between a live attenuated IBV strain and either another attenuated strain or a virulent field strain is possible, the likelihood of it both occurring and resulting in a new and virulent IBV is considered to be very low. The risk assessment provided agrees with separate independent scientific advice provided to the Veterinary Medicines Directorate (United Kingdom), which concludes that whilst it is correct that IB can undergo homologous recombination there is no evidence to believe that a multivalent IB vaccine is/would be potentially problematic from the point of view of recombination and that the chance of recombination between the Nobilis IB Primo QX vaccine strain and the Nobilis IB Ma5 vaccine strain producing a pathogenic recombinant is very low.

Although the risk of recombination occurring in the event of two different attenuated strains being administered at the same time cannot be discounted, this needs to be considered in the light of the potential benefit of giving the two vaccines together. Chickens are increasingly being exposed to a variety of different strains of IBV and therefore need to be protected against these various strains and the only practical way to achieve this is by simultaneous administration of relevant vaccines. Furthermore the legal requirement for vaccination against IBV Massachusetts like strains in some EU member states would effectively preclude protection against QX strains unless co-administration of two vaccines is permitted.

Furthermore, it needs to be taken into account that if such a recombination event were to occur this would be within an environment where all birds would be fully vaccinated against both parent strains and it would be extremely unlikely that such a recombinant strain would be able to survive and propagate.

It is therefore concluded that the potential benefits of co-administration of Nobilis IB Primo QX with Nobilis IB Ma5 outweigh the potential risk of a new virulent strain arising by recombination between the two vaccine strains and that a claim for compatibility can be included in the SPC providing that appropriate warnings/statements are included in the relevant sections of the SPC that present the recombination risk, “Simultaneous use of both vaccines increases the risk of recombination of viruses and potential emergence of new variants”; that “all chickens on the site should be vaccinated at the same time”; and reinforce the need of disinfection measures after simultaneous use of the vaccines, “The premises must be cleaned and disinfected after each production round”.

Study of residues

Residues of this product present in vaccinated animals are not considered to represent a consumer safety concern. A withdrawal period of zero days is therefore appropriate.

Interactions

A claim for compatibility is made in section 4.8 of the SPC: “Safety and efficacy data are available which demonstrate that this vaccine can be mixed and administered with Nobilis IB Ma5”. The applicant has provided further supporting evidence that the possibility of recombination between these two vaccine strains to produce a recombinant virulent strain is very low. Although the risk of recombination occurring in the event of two different attenuated strains being administered at the same time cannot be discounted, this needs to be considered in the light of the potential benefit of giving the two vaccines together. It is therefore concluded that the potential benefits of co-administration of Nobilis IB Primo QX with Nobilis IB Ma5 outweigh the potential risk of a new virulent strain arising by recombination between the two vaccine strains and that a claim for compatibility can be included in the SPC providing that appropriate warnings/statements are included in the relevant sections of the SPC that present the recombination risk, “Simultaneous use of both vaccines increases the risk of recombination of viruses and potential emergence of new variants”; that “all chickens on the site should be vaccinated at the same time”; and reinforce the need of disinfection measures after simultaneous use of the vaccines, “The premises must be cleaned and disinfected after each production round”.

Field studies

Safety of the vaccine was tested in two field studies in accordance with Ph. Eur. monograph 5.2.6 in which one-day-old chicks in broiler flocks were vaccinated by coarse spray with Nobilis IB Primo QX and/or Nobilis IB Ma5; one carried out in the Netherlands and Germany (12R/0120) and the other in the UK (XAH2121A). Routine batches of test vaccine of intermediate titre were used.

In study XAH211A safety of a single dose target dose of $10^{4.7–4.8}$ EID_{50} of Nobilis IB Primo QX administered to 400 one-day-old Ross 308 broiler chicks by spray vaccination was tested and compared to safety and performance data from 400 one-day-old Ross 308 broiler chicks administered a single dose ($10^{3.9–4.0}$ EID_{50}) of Nobilis IB Ma5 by the same route. Clinical observations were carried out daily for 14 days post-vaccination and performance measures at prescribed intervals to 35 days post-vaccination. None of the vaccinated showed any clinical signs and symptoms associated with IBV infection. Performance measures (mortality, feed intake, feed conversion ratios, weight throughout the study) were similar between the groups vaccinated with Nobilis IB Primo QX and the group vaccinated with Nobilis IB Ma5.

In study 12R/0120 safety of a single target dose of $10^{4.7–4.8}$ EID_{50} of Nobilis IB Primo QX administered to 323,840 one-day-old Ross 308 broiler chicks by spray vaccination simultaneously with a single dose ($10^{3.9–4.0}$ EID_{50}) of Nobilis IB Ma5 by the same route was compared to safety and performance data from 308,750 one-day-old Ross 308 broiler chicks administered a single dose ($10^{3.9–4.0}$ EID_{50}) of Nobilis IB Ma5 by the same route. The study was carried out on three broiler farms in The Netherlands and one in Germany. Clinical observations were carried out daily for 14 days post-vaccination and performance measures at prescribed intervals to 6 weeks post-vaccination. None of the birds vaccinated simultaneously with Nobilis IB Primo QX and Nobilis IB Ma5 showed any clinical signs and symptoms associated with IBV infection. Performance measures (mean slaughter age, mean weight at slaughter, rejects at the slaughter plant, mortality overall, average daily weight gain, feed conversion,

European Production Index) were similar between the groups vaccinated with Nobilis IB Primo QX and Nobilis IB Ma5 and the group vaccinated with Nobilis IB Ma5.

User safety

None of the ingredients in the vaccine is known to cause hazard to the user. No syringes or needles are needed to resuspend the lyophilised vaccine and proposed administration is by spray vaccination or oculonasal administration. There is therefore no risk of accidental self-injection. Advice is provided in the SPC to wash and disinfect hands after use and in the case of spray administration; personal protective equipment consisting of masks with eye protection should be worn when handling the veterinary medicinal product.

Environmental risk assessment

Some increase in induction of ciliostasis occurred in the reversion to virulence study and as a result a recommendation that all birds on the site should be vaccinated is included in the SPC as a mitigation measure.

The chance of recombination occurring between two live IBV vaccine strains when applied at the same time or within a short time interval, or between vaccine strains and wild type IBV, is low, but cannot be excluded. It is unlikely that recombination with a virulent field strain would result in a recombinant that is more virulent than the field strain so the impact of such an event is likely to be minimal. In this respect the risk is similar to other live IB vaccines that have been used for many years without problems.

It is concluded from the phase I assessment that the risk to the environment from the use of this vaccine is low and therefore a second phase investigation is not necessary.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. However, to reduce any potential risks associated with transmission of the virus to other chickens, a recommendation is included in the SPC to vaccinate all the birds on a site at the same time.

Based on the data provided, the environmental risk assessment can stop at Phase I. Nobilis IB Primo QX is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The safety of Nobilis IB Primo QX at single dose and ten times overdose administered to one-day-old chicks by the oculonasal route in laboratory studies or at single dose administered to one-day-old chicks by spray in a laboratory study or by spray in field studies was investigated in accordance with: Ph. Eur. monographs 0062 (Vaccines for veterinary use), 5.2.6. (Evaluation of safety of veterinary vaccines and immunosera), 0442 (Avian infectious bronchitis vaccine (live)) and Directive 2001/82/EC.

The vaccine did not cause clinical signs of avian IB in any of the chicks vaccinated or damage to the development of the reproductive tract; ciliostasis was induced in some vaccinates for at least 10 days post-vaccination (although the mean ciliostasis scores induced over groups of vaccinated chickens were low, some individual vaccinates had high ciliostasis scores). The ciliostasis scores were in keeping with those of already authorised vaccines. An appropriate warning is included in section 4.6 of the SPC to reflect the high ciliostasis observed in some individual birds. Section 4.6 also contains a warning that nasal exudate may occur for at least 10 days following vaccination to reflect adverse reactions

observed in the spray study. Minor inflammatory lesions were seen in the kidneys of two birds in the ten times overdose study, although inflammatory lesions were not seen in the kidneys of most birds. The frequency and severity of the renal lesions are mentioned in section 4.10 of the SPC.

The safety of Nobilis IB Primo QX at ten times overdose administered to one-day-old chicks by spray was not tested. However, based on an assessment of the data there is no reason to believe Nobilis IB Primo QX would be unsafe to administer by spray. Bearing in mind that Nobilis IB Primo QX is a new vaccine strain and the recent CVMP clarification paper on routes of administration of vaccines to poultry (to justify the safety and efficacy for all recommended routes of administration of poultry vaccines, studies are required as laid down in Directive 2009/9/EC, Annex 1 and Ph. Eur. monograph 0062 on vaccines for veterinary use) the CVMP has requested a condition that a small scale overdose (10x) study by spray has to be provided post-authorisation.

Dissemination following oculonasal vaccination with $10^{5.5}$ EID_{50} in one-day-old chicks was observed for at least 20 days post-vaccination. The vaccine virus replicates in the trachea, lung, kidney, caecal tonsil and proventriculus, and was found in the cloacae. Trachea and proventriculus are prime locations of virus replication. The vaccine can be shed from vaccinated chickens and spread to in-contact chickens from which virus could be isolated from the trachea and proventriculus for at least 20 days post-vaccination.

Appropriate care should be taken to separate vaccinated from non-vaccinated chickens. An appropriate warning is included in section 4.4 of the SPC. Other warnings include that precautionary measures should also be taken to prevent spreading to wildlife; cleaning and disinfection of the premises after vaccination should take place and as it is important to avoid introduction of the IB D388/QX vaccine virus into premises in which the wild type strain is not present; the vaccine should only be used after it has been established that the QX-like IBV variant strain is epidemiologically relevant to the site. The IB D388/QX vaccine should only be applied in hatcheries if adequate controls are in place to avoid the spread of the vaccine virus to birds that will be transported to non-IB QX exposed flocks.

Vaccine which has undergone sequential passage through 5 groups of chicks did not cause clinical signs and symptoms associated with IBV infection or kidney lesions. However, passaged vaccine produced greater ciliostasis 5, 7 and 10 days post-vaccination of one-day-old chicks than unpassaged vaccine demonstrating a slight increase in virulence of passaged material. Ciliostasis scores dropped from day 5 to day 10 post-vaccination and by day 10 mean ciliostasis scores were low. Further passage through birds may have the potential to further increase virulence. Therefore, to reduce the risk of the virus spreading between birds a warning is included in section 4.5 of the SPC that all chickens on the site should be vaccinated at the same time.

The safety of Nobilis IB Primo QX and/or simultaneous administration of Nobilis IB Ma5 was tested in laboratory and field studies. In the field, performance measures, scores for respiratory signs and general health were similar between day old chicks vaccinated with Nobilis IB Primo QX and/or Nobilis IB Ma5. Adverse reactions associated with vaccination were not observed. Although the risk of recombination occurring in the event of two different attenuated strains being administered at the same time cannot be discounted, this needs to be considered in the light of the potential benefit of giving the two vaccines together. It is therefore concluded that the potential benefits of co-administration of Nobilis IB Primo QX with Nobilis IB Ma5 outweigh the potential risk of a new virulent strain arising by recombination between the two vaccine strains and that a claim for compatibility can be included in the SPC providing that appropriate warnings/statements are included in the relevant sections of the SPC that present the recombination risk (“Simultaneous use of bot vaccines increases the risk of recombination of viruses and potential emergence of new variants”), reinforce the need of disinfection measures after simultaneous use of the vaccines (“The premises must be cleaned and disinfected after each production run”), and that all chickens on the site must be vaccinated in the

same way. The vaccine is safe for the user and non-target species and the environment, when used as recommended and all birds are vaccinated at the same time.

The safety of the vaccine has not been established during lay because the vaccine is not indicated for use during the period of lay; a warning that safety has not been established during lay has been included in section 4.7 of the draft SPC and a contraindication also added to section 4.3.

Part 4 – Efficacy

Introduction and general requirements

The applicant has carried out a series of trials designed to demonstrate the efficacy of Nobilis IB Primo QX. All were basically carried out in line with the immunogenicity requirement of Ph. Eur. monograph 0442, using ciliary activity as a marker for respiratory disease, but varying method of administration (oculonasal or coarse spray), type of chickens (SPF or commercial broilers), time of challenge after vaccination (3 weeks or 8 weeks) or mixed with Nobilis IB Ma5 vaccine. In each case, the validity requirements of Ph. Eur. monograph 0442 (at least 80% of the control chickens show cessation or extreme loss of vigour of ciliary activity and during the period between the vaccination and challenge no more than 10% of vaccinated or control chickens show abnormal clinical signs or die from causes not attributable to the vaccine) were applied. The vaccine was considered to comply with the efficacy requirement if at least 80% of the vaccinated birds were protected from the respective challenge. The challenge strain was an IB QX strain isolated from chickens in Belgium and shown to be QX by sequence analysis. Analysis of sequencing of the S1 gene PCR product of IB QX Belgian challenge virus strain identifying it as a QX strain has been provided.

Laboratory trials

Dose response and onset of protection

Two studies were carried out in one-day-old SPF chickens in compliance with Ph. Eur. requirements to investigate the dose response and onset of protection, one by each administration route:

In study IMD/0043/11 three groups of 24 and two groups of 10 one-day-old SPF White Leghorn chicks were used. Vaccine doses of 3.5, 2.8 and 2.1 $\log_{10}$ EID_{50} per dose were administered to groups 1, 2 and 3 respectively by the oculonasal route. Groups 4 and 5 were unvaccinated. All of the vaccinated groups and one of the unvaccinated groups were challenged with virulent IBV QX strain Belgium EP5+OC3+EP2 three weeks after vaccination. All of the vaccinated chicks had antibodies to IB QX on the day before challenge. Four days after challenge 100% of the vaccinated birds in groups 1 and 2 and 95% of the birds in group 3 had normal ciliary activity and were considered to be protected against the challenge while none of the challenged controls in group 4 were considered to be protected. All of the non-vaccinated, non-challenged birds in group 5 showed normal ciliary activity.

In study IMD/0038/11 three groups of 24 and two groups of 10 one-day-old SPF White Leghorn chicks were used. Vaccine doses of 3.5, 2.8 and 2.1 $\log_{10}$ EID_{50} per dose were administered to groups 1, 2 and 3 respectively by coarse spray. Groups 4 and 5 were unvaccinated. All of the vaccinated groups and one of the unvaccinated groups (group 4) were challenged with virulent IBV QX strain Belgium EP5+OC3+EP2 three weeks after vaccination. Most of the vaccinated chicks in groups 1 and 2 had antibodies to IB QX on the day before challenge. Four days after challenge 96% of the vaccinated birds in group 1, 13% of the birds in group 2 and none of the birds in group 3 had normal ciliary activity and

were considered to be protected against the challenge. None of the challenged controls in group 4 were considered to be protected. All of the non-vaccinated, non-challenged birds in group 5 showed normal ciliary activity.

It was concluded that vaccination by either route with doses less than the minimum recommended in the SPC were efficacious and met the Ph. Eur. efficacy standard, although oculonasal administration appeared more efficacious than coarse spray.

The influence of maternal antibody (MDA) on the efficacy of the vaccine

Two studies were carried out in MDA-positive one-day-old commercial chickens to investigate the dose response and onset of protection, one by each administration route:

In study IMD/0064/11 three groups of 34 and two groups of 10 one-day-old Ross 308 MDA-positive chicks were used. Vaccine doses of 3.5, 2.8 and 2.1 $\log_{10}$ EID_{50} per dose were administered to 3 groups respectively by the oculonasal route. Groups 4 and 5 were unvaccinated. All of the vaccinated groups and one of the unvaccinated groups (group 4) were challenged with virulent IBV QX strain Belgium EP5+OC3+EP2 three weeks after vaccination. Four days after challenge 80% of the vaccinated birds in group 1, 95% of the birds in group 2 and 90% of the birds in group 3 had normal ciliary activity and were considered to be protected against the challenge. 14% of the challenged controls in group 4 were considered to be protected. All of the non-vaccinated, non-challenged birds in group 5 showed normal ciliary activity.

In study IMD/0067/11 one group of 27, two groups of 34, one group of 17 and one group of 10 one-day-old Ross 308 MDA-positive chicks were used. Vaccine doses of 4.2, 3.5 and 2.8 $\log_{10}$ EID_{50} per dose were administered to groups 1, 2 and 3 respectively by coarse spray. Groups 4 and 5 were unvaccinated. All of the vaccinated groups and one of the unvaccinated groups (group 4) were challenged with virulent IB QX strain Belgium EP5+OC3+EP2 three weeks after vaccination. Five days after challenge 95% of the vaccinated birds in groups 1 and 2 and none of the birds in group 3 had normal ciliary activity and were considered to be protected against the challenge. None of the challenged controls in group 4 were considered to be protected. All of the non-vaccinated, non-challenged birds in group 5 showed normal ciliary activity.

It was concluded that vaccination by either route with doses less than the minimum recommended in the SPC were efficacious and met the Ph. Eur. efficacy standard, although, as for SPF birds, oculonasal administration appeared more efficacious than coarse spray. However, it appears that the anti-QX antibodies detected in studies IMD/0064/11 and IMD/0067/11 were probably cross-reactive antibodies developed in response to vaccination with a different IBV strain. The applicant was asked to address the likelihood that antibodies raised in response to vaccination or infection with a QX strain would probably be more specific and could therefore have a greater impact on vaccine efficacy. While a vaccination-challenge study with chickens born to hens vaccinated with an IB QX vaccine strain would be required to definitively address this concern, based on an assessment of the information provided it can be concluded that it is unlikely that the presence of MDA would interfere with this type of vaccination.

Duration of immunity

Two studies were carried out in one-day-old SPF chickens to investigate the duration of immunity, one by each administration route:

In study IMD/0106/11 three groups of 20, one group of 10 and two groups of 14 one-day-old SPF White Leghorn chicks were used. Vaccine doses of 3.5 and 3.2 $\log_{10}$ EID_{50} per dose were administered to groups 1 and 2 respectively by coarse spray. Groups 3 and 4 were unvaccinated. Groups 5 and 6

were sentinel birds introduced to groups 1 and 2 respectively 2 hours after vaccination. Birds in groups 1, 2, 3, 5, and 6 were challenged with virulent IB QX strain Belgium EP5+OC3+EP2 eight weeks after vaccination. Six days after challenge 89% of the vaccinated birds in group 1 and 55% of the birds in group 2 had normal ciliary activity and were considered to be protected against the challenge. None of the challenged controls in group 3 were considered to be protected while all of the non-vaccinated, non-challenged birds in group 4 showed normal ciliary activity. All of the sentinel birds in group 5 and 43% of the sentinel birds in group 6 were protected against the challenge.

In study IMD/0107/11 one group of 20, one group of 14 and two groups of 10 one-day-old SPF White Leghorn chicks were used. A vaccine dose of 2.8 $\log_{10}$ EID_{50} per dose was administered to group 1 by the oculonasal route. Group 2 was sentinel birds introduced to group 1 two hours after vaccination. Groups 3 and 4 were unvaccinated. Birds in groups 1, 2 and 3 were challenged with virulent IBV QX strain Belgium EP5+OC3+EP2 eight weeks after vaccination. Seven days after challenge 94% of the vaccinated birds in group 1 and 100% of the sentinel birds in group 2 had normal ciliary activity and were considered to be protected against the challenge. None of the challenged controls in group 3 were considered to be protected while all of the non-vaccinated, non-challenged birds in group 4 showed normal ciliary activity.

It was concluded that doses of vaccine less than recommended in the SPC administered to SPF chicks by the oculonasal or coarse spray route achieved a level of efficacy equivalent to the Ph. Eur. standard eight weeks post-vaccination.

Duration of immunity was not investigated in MDA-positive commercial birds because it had been demonstrated that the efficacy of the product is not affected by MDA and that a higher minimum dose (4.0 $\log_{10}$ EID_{50}) is recommended in the SPC. From an animal welfare perspective this was accepted.

Additional studies

Three studies were carried out to investigate the compatibility of Nobilis IB Primo QX with Nobilis IB Ma5 vaccine.

In study IMD/0082/11 twelve groups of one-day-old SPF White Leghorn chicks were used. Groups 1, 2 and 3 were vaccinated with 4.0 $\log_{10}$ EID_{50}/dose Nobilis IB Primo QX, groups 4, 5, and 6 were vaccinated with 3.0 $\log_{10}$ EID_{50}/dose Nobilis IB Ma5 vaccine and groups 7, 8 and 9 were vaccinated with both vaccines (one in each eye). All vaccines were administered by the oculonasal route. Groups 10, 11 and 12 were unvaccinated. Three weeks after vaccination the chicks in groups 1, 4, 7 and 10 were each challenged with 4.0 $\log_{10}$ EID_{50} IBV QX Belgium EP5+OC3+EP2 and the chicks in groups 2, 5, 8 and 11 were each challenged with 4.0 $\log_{10}$ EID_{50} IBV M41 (M41/OC10/EP2). Six days after challenge all of the vaccinated birds were protected against the challenge with the corresponding virulent strains when vaccinated either singly or in combination, while only 67% of QX-vaccinated birds were protected against the M41 challenge and only 60% of the Ma5-vaccinated birds were protected against the QX challenge. None of the unvaccinated controls challenged with either virulent strain were considered to be protected. All of the non-vaccinated, non-challenged birds showed normal ciliary activity.

In study IMD/0021/12 thirteen groups of one-day-old SPF White Leghorn chicks were used. Groups 1 and 2 were vaccinated with 4.0 $\log_{10}$ EID_{50}/dose Nobilis IB Primo QX, groups 3 and 4 were vaccinated with 3.0 $\log_{10}$ EID_{50}/dose Nobilis IB Ma5 vaccine, groups 5, 6 and 7 were vaccinated with both vaccines concurrently (one in each eye), groups 8, 9 and 10 were vaccinated with both vaccines simultaneously (mixed). All vaccines were administered by the oculonasal route. Groups 11, 12 and 13 were unvaccinated. Eight weeks after vaccination the chicks in groups 1, 5, 8 and 11 were each challenged with 4.0 $\log_{10}$ EID_{50} IBV QX Belgium EP5+OC3+EP2 and the chicks in groups 3, 6, 9 and 12 were each

challenged with 4.0 $\log_{10}$ EID_{50} IBV M41 (M41/OC10/EP2). Six days after challenge 85% of the birds vaccinated only with QX vaccine were protected against QX challenge and 96% of birds vaccinated only with Nobilis IB Ma5 vaccine were protected against M41 challenge. 80% and 90% of the concurrently vaccinated birds were protected against QX and M41 challenge respectively, while 90% and 95% of the simultaneously vaccinated birds were protected against the respective challenges. None of the unvaccinated controls challenged with either virulent strain were considered to be protected. All of the non-challenged birds showed normal ciliary activity.

In study IMD/0015/12 eight groups of one-day-old MDA-positive commercial chicks were used. Group 1 was vaccinated with 4.6 $\log_{10}$ EID_{50}/dose Nobilis IB Primo QX, group 2 was vaccinated with 3.9 $\log_{10}$ EID_{50}/dose Nobilis IB Ma5 vaccine, groups 3 and 4 were vaccinated with both vaccines simultaneously (mixed) and groups 5 and 6 were vaccinated with both vaccines concurrently (one in each eye). All vaccines were administered by the oculonasal route. Groups 7 and 8 were unvaccinated. Three weeks after vaccination, the chicks in groups 1, 2, 3, 5 and 7 were each challenged with 4.0 $\log_{10}$ EID_{50} IBV QX Belgium EP5+OC3+EP2. Five days after challenge 90% of the birds vaccinated only with the QX vaccine were protected while all of the birds vaccinated with both vaccines, either concurrently or simultaneously, were protected. None of the unvaccinated challenged controls were considered to be protected. All of the non-challenged birds showed normal ciliary activity.

It was concluded that administration of Nobilis IB Primo QX and Nobilis IB Ma5 in combination – either concurrently or simultaneously – met the immunogenicity requirements of Ph. Eur. monograph 0442 and did not adversely affect the efficacy of either vaccine.

Field trials

Two field trials were carried out to investigate the safety and efficacy of the vaccine. For the efficacy part of the trials a sample of the birds that had been vaccinated in the field with Nobilis IB Primo QX and Nobilis IB Ma5 by coarse spray were transferred to the laboratory and challenged with virulent IBV M41 and/or QX.

The challenge part of study 12R/0120 is described in report IMD/0024/12. Seventy one-day-old Ross 308 broiler chickens that had been vaccinated at one day of age at one of the farms in the Netherlands were used. These were divided between three groups; two of 28 birds (Groups 1 and 2) and one of 14 birds (Group 3). Three groups of 14 unvaccinated chicks that had been hatched separately from the same flock of commercial broilers were used as controls (Groups 4, 5 and 6). Three weeks after vaccination groups 1 and 4 were challenged with a virulent IB QX strain and groups 2 and 5 were challenged with M41. Groups 3 and 6 were not challenged. 100% of the birds in group 1, 90% of the birds in group 2 were protected from the respective challenges. None of the unvaccinated challenged controls were considered to be protected while 100% and 80% of the non-challenged birds in groups 3 and 6 respectively showed normal ciliary activity.

The challenge part of study XAH2121A is described in report IMD/0053/12. Forty two one-day-old Ross 308 broiler chickens that had been vaccinated at one day of age at a farm in the UK were used. These were divided between two groups, one of 28 birds (Group 1) and one of 14 birds (Group 2). Two groups of 14 unvaccinated chicks from the same flock of commercial broilers procured prior to vaccination were used as controls (Groups 3 and 4). Three weeks after vaccination groups 1, 2 and 3 were challenged with a virulent IB QX strain. Group 4 was not challenged. 93% of the birds in groups 1 and 2 were protected from the challenge. None of the unvaccinated challenged controls were considered to be protected while 80% of the non-challenged birds in group 4 showed normal ciliary activity.

It was concluded that Nobilis IB Primo QX is efficacious when administered in the field by coarse spray, either alone or mixed with Nobilis IB Ma5.

Overall conclusion on efficacy

The minimum efficacious dose when administered by the oculonasal route was less than when administered by coarse spray but, in both cases, this was less than the minimum specified for the vaccine ($\geq 10^{4.0}$ EID_{50}). An onset of immunity of 3 weeks in SPF and MDA-positive commercial broiler chickens and a duration of immunity of 8 weeks in SPF chickens was shown. The applicant has justified not doing a duration of immunity study in commercial broiler chickens on the basis of the similar efficacy demonstrated in SPF chickens when challenged 3 weeks after vaccination. The indications claimed in section 4.2 of the draft SPC ("For active immunisation of chickens in order to reduce respiratory signs of infectious bronchitis caused by QX-like variants of infectious bronchitis virus") are therefore acceptable.

Additional studies indicated that simultaneous or concurrent administration of Nobilis IB Primo QX with Nobilis IB Ma5 did not adversely affect the efficacy of either vaccine.

Part 5 – Benefit-risk assessment

Introduction

Nobilis IB Primo QX is a live attenuated vaccine that is presented in a novel form as sphere shaped lyophilisates. These are filled into sealed aluminium laminate cups. The 1,000-dose presentation may be supplied with a solvent for oculonasal administration.

Nobilis IB Primo QX is a vaccine against the D388/QX like strains of infectious bronchitis virus.

Benefit assessment

Direct therapeutic benefit

Infectious bronchitis (IB) virus has the ability to mutate or change its genetic makeup readily. As a result, numerous serotypes have been identified and have complicated efforts at control through vaccination. In Europe, various "Holland variants," usually designated using numbers (D-274, D-212) are recognised. In 2004, severe egg production problems were reported in the Netherlands and respiratory signs have also been reported in broilers older than 4 weeks of age. In birds in production the problems are characterised by a low production rate. These initial cases were associated to earlier outbreaks of nephropathogenic infectious bronchitis that had occurred in 2003 in broilers and pullets from which an unidentified variant IBV was isolated. This original isolate was similar to a Chinese isolate known as QX. The Dutch isolate was later named D388 by the Animal Health Service at Deventer in the Netherlands. This virus continues to cause major economic problems in several European countries and also in other parts of the world, suggesting that in many areas, it is probably currently the IB variant of most concern for breeder/layer flocks.

The product has been shown in two laboratory studies to reduce ciliostasis, which may be indicative of respiratory disease, in chicks vaccinated by the oculonasal or coarse spray routes at one day of age with an onset of immunity of 3 weeks and a duration of immunity of 8 weeks. The minimum specified dose is efficacious in SPF chicks and in commercial broiler chicks that had been vaccinated against

different strains of infectious bronchitis virus. The product was shown in two field trials to be efficacious when administered in the field by coarse spray, either alone or mixed with Nobilis IB Ma5.

Additional benefits

Nobilis IB Primo QX is supplied in a novel presentation as freeze-dried spheres sealed in aluminium cups.

Risk assessment

Main potential risks have been identified as follows:

For the target species:

The product is well tolerated in the target species when used as recommended.

The vaccine could produce clinical disease in vaccinated birds if the vaccine virus is insufficiently attenuated. However, safety studies have demonstrated the ciliostasis scores for vaccinated birds are generally low although occasionally higher scores can occur. The average ciliostasis scores seen were comparable to other authorised IB vaccines and are therefore considered acceptable.

The vaccine virus could revert to virulence. The virus was shown to induce higher ciliostasis scores after five passages through chickens and there is a risk that further passages could result in greater virulence. A recommendation to vaccinate all the birds on a site at the same time should reduce the chance of significant bird-to-bird transmission occurring.

Use of the live vaccine could introduce the QX strain of IB to sites where it was not previously present. QX-like strains of IBV are now widely present within Europe but in some countries (e.g. the UK) it is still restricted to certain sites. The use of the vaccine should therefore be restricted to sites where the QX strain has been detected and those that are epidemiologically related.

There is a risk that the vaccine strain could recombine with a field strain of IBV or another vaccine strain if both infected a bird at the same time. It is generally recognised that there is a risk that such recombinations could occur between strains of IBV. It is unlikely that recombination with a virulent field strain would result in a recombinant that is more virulent than the field strain so the impact of such an event is likely to be minimal. Additionally, a recommendation to vaccinate all birds on the site at the same time should minimise the risk of this occurring. The risk that recombination between two different vaccine strains might result in a new virulent strain is also considered to be low.

For the user:

The CVMP concluded that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

The person administering the vaccine will almost inevitably be exposed to the live vaccine virus while administering it oculonasally or by coarse spray. Mammals are not known to be susceptible to IBV so the likely impact of this is negligible.

For the environment:

The product is not expected to pose any risk to the environment when used as recommended.

The vaccine virus could spread to other birds or wildlife and cause disease in them. Spread from vaccinated to unvaccinated in-contact birds has been shown to occur but chickens are the only species that is known to be naturally infected with IBV and it is not considered to be pathogenic for

mammals. Since the vaccine has been shown to be safe for chickens any other chickens that became exposed to the virus would effectively become vaccinated. However, to reduce any potential risks associated with transmission of the virus to other chickens, a recommendation is necessary in the SPC to vaccinate all the birds on a site at the same time.

For the consumer:

Residues of this product present in vaccinated animals are not considered to represent a consumer safety concern. The withdrawal period is set at zero days.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks.

The following measures that are included in the SPC to minimise the above mentioned risks include:

- All the birds on a site should be vaccinated to reduce the risk of bird to bird transmission.
- Restriction of use of the vaccine to sites where the QX strain has already been identified and sites that are epidemiologically related.
- The use of personal protective equipment consisting of masks with eye protection when administering by coarse spray.
- Premises must be cleaned and disinfected after each production round. This is particularly crucial when the two vaccines Nobilis IB Primo QX and Nobilis IB Ma5 have been administered simultaneously.
- Recombination risk is presented where the two vaccines Nobilis IB Primo QX and Nobilis IB Ma5 are administered simultaneously: simultaneous use of both vaccines increases the risk of recombination of viruses and potential emergence of new variants.

The CVMP considered that information on overdose (10x) by spray administration is needed to complete the safety profile of the product and that therefore an additional small scale study is necessary, however that the data can be provided post-authorisation. The submission of such study is included as a condition of the marketing authorisation.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the indication for the active immunisation of chickens, from one-day-old onwards, to reduce respiratory signs of infectious bronchitis caused by QX-like variants of IBV.

The formulation and manufacture of the product is well described and specifications set will ensure that a product of consistent quality will be produced.

It is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings has been included in the SPC. The withdrawal period is set at zero days.

The risk of recombination following administration at the same time as Nobilis IB Ma5 vaccine is considered to be low.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete product information.

Conclusion

Based on the original and complementary data presented the CVMP concluded that the quality, safety and efficacy of Nobilis IB Primo QX were considered to be in accordance with the requirements of Directive 2001/82/EC.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommended the granting of the marketing authorisation for Nobilis IB Primo QX.

In addition, the CVMP has recommended a condition for the marketing authorisation.