15 February 2023
EMA/85856/2023
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Innovax-ILT-IBD (EMEA/V/C/005905/0000)

Vaccine common name: Avian infectious laryngotracheitis, infectious bursal disease and Marek's disease vaccine (live recombinant)

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

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Introduction

The applicant Intervet International B.V. submitted on 13 December 2021 an application for a marketing authorisation to the European Medicines Agency (the Agency) for Innovax-ILT-IBD, through the centralised procedure under Article 3(1) of Regulation (EC) No 726/2004 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 15 April 2021 as Innovax-ILT-IBD has been developed by recombinant DNA technology.

At the time of submission, the applicant applied for the following indications:

- to reduce mortality, clinical signs and lesions caused by avian Infectious Laryngotracheitis (ILT) virus and Marek's disease (MD) virus.
- to prevent mortality and to reduce clinical signs and lesions caused by Infectious Bursal Disease (IBD) virus.

The active substance of Innovax-ILT-IBD is a cell-associated live recombinant Turkey Herpesvirus (strain HVT/IBD/ILT), expressing the VP2 protein of Infectious Bursal Disease virus and the glycoproteins gD and gI of Infectious Laryngotracheitis virus. The product is intended for subcutaneous or *in ovo* administration.

Innovax-ILT-IBD is presented in glass ampoules of 2 ml containing either 2000 or 4000 doses.

The CVMP considers that the recombinant HVT strain containing an expression cassette with the VP2 gene of Infectious Bursal Disease virus and glycoprotein D (gD) and glycoprotein I (gI) genes of Infectious Laryngotracheitis virus is a new active substance, as claimed by Intervet International B.V.

The rapporteur appointed is Jacqueline Poot and the co-rapporteur is Leona Nepejchalová.

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

On 15 February 2023, the CVMP adopted an opinion and CVMP assessment report.

On 14 April 2023, the European Commission adopted a Commission Decision granting the marketing authorisation for Innovax-ILT-IBD.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system has been provided, which fulfils the requirements of Directive 2001/82/EC. Based on the information provided, it is accepted that the

applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Union or in a third country. In addition, a declaration form provided in the dossier states that the current DDPS version 3.0 has already been assessed in procedure EMEA/V/C/IG0967/G (a grouped variation approved in 2018, impacting several products, including other vaccines of the Innovax range, introducing an updated version of the existing DDPS).

Manufacturing authorisations and inspection status

The active substance and (frozen) vaccine are manufactured, either at the Intervet Inc. site in Millsboro, US or at the Intervet International site in de Bilt, the Netherlands.

Batch release is performed at the Intervet International site in Boxmeer, The Netherlands.

The solvent batch release is performed at the Intervet International site in Boxmeer in The Netherlands.

For the sites listed above, Good Manufacturing Practice (GMP) certificates covering the appropriate activities were presented.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system is considered in line with legal requirements.

The GMP status of the active substance(s) and of the finished product manufacturing sites has generally been satisfactorily established and is in line with the applicable legal requirements.

Part 2 – Quality

Chemical, pharmaceutical and biological/microbiological information (quality)

Qualitative and quantitative particulars of the constituents

Qualitative and quantitative particulars

The vaccine consists of a deep frozen suspension of cell-associated recombinant serotype 3 Herpesvirus of Turkey (HVT) expressing the VP2 gene of Infectious Bursal Disease virus (IBD) and the gD and gI glycoproteins of Infectious Laryngotracheitis virus (ILT), at a titre between $10^{3.2}$ and $10^{4.6}$ plaque forming units (PFU) per dose. Stabilisers (bovine serum, veggie medium) and a cryoprotectant (DMSO) are included in the formulation.

The solvent is a sterile, watery solution which contains a stabilizer (sucrose), buffering agents (potassium dihydrogen phosphate, disodium hydrogen phosphate dihydrate and sodium chloride) and a colouring agent/indicator (phenolsulfonphthalein – Phenol red). The vaccine is mixed with the solvent prior to use.

Container and closure

The vaccine is filled in 2 ml heat-sealed, type I, sterile glass ampoules in accordance with the European Pharmacopoeia (Ph. Eur. 3.2.1 - Glass containers for pharmaceutical use). The ampoules are stored on a cane and attached to the cane is a coloured clip displaying the dose (2,000 doses: salmon-pink coloured clip, and 4,000 doses: yellow coloured clip).

The solvent is filled in 400, 800, 1200 and 1600 ml multilayer plastic (MLP) bags including a port system with injection and insertion point. The bags meet the requirements of European Pharmacopoeia 3.2.2.1 for plastic containers for aqueous solutions for parenteral infusion. The forming, filling, closing/sealing and terminal heat sterilisation of the bags is performed in a continuous process.

The specifications and certificates demonstrating Ph. Eur. compliance for the ampoules and bags are included in the dossier.

Product development

Innovax-ILT-IBD is a frozen, cell associated vaccine that contains the recombinant serotype 3 Turkey Herpes Virus (HVT) expressing genes from the Infectious Bursal Disease virus (IBD) and Infectious Laryngotracheitis Virus (ILT). The vaccine can be used to stimulate active immunity against Marek's disease (MD), Infectious Bursal Disease (IBD) and Infectious Laryngotracheitis (ILT). HVT is an avirulent virus which has been widely used as a vaccine strain for prevention of MD. HVT has several features that make it an attractive vector for the delivery of foreign antigens. The most important is the safety profile of the vector. The virus hardly spreads, is fully apathogenic and is not infectious for any species other than the avian one. The same vector (HVT FC-126) is already used in other recombinant vaccines for which the applicant owns a marketing authorisation (Innovax-ILT, Innovax-ND-IBD, Innovax ND-ILT).

HVT strain FC-126 was genetically modified by inserting the VP2 gene of IBD and the glycoprotein D (gD) and glycoprotein I (gI) genes of ILT virus resulting in the vaccine strain HVT/IBD/ILT. The use of a recombinant vaccine has the advantage that protective immunity against both IBD and ILT can be obtained without the use of their respective live attenuated vaccines.

The production system used and pharmaceutical form of the vaccine is identical to other Marek's disease vaccines manufactured by the applicant.

The solvent used with the vaccine is the same as for the other live Marek vaccines manufactured by the applicant. An indicator (phenol red) is included to enable a check on filling of the automated vaccination equipment in the field. The absence of any virucidal effect of the solvent was investigated using several cell associated vaccines and found to be satisfactory.

Description of the manufacturing method

The manufacturing process of the vaccine consists of five main steps.

Primary chicken embryo fibroblast (CEF) cells are inoculated with HVT/IBD/ILT virus seed.
The infected CEFs are harvested, centrifuged, counted cell concentration is adjusted and stabiliser is added. The cell suspension is then filled in sterile 2 ml glass ampoules by automated filling and flame sealing. After labelling the product is frozen in a program freezer and stored in liquid nitrogen.

The manufacturing of the solvent consists of a simple mixing process. The pH is adjusted and the

solution is filter sterilised. After the aseptic filling into MLP bags, the product is terminally sterilised.

Three consecutive batches of vaccine were manufactured validating the production process. For the solvent, three batches filled as 200ml, 1600 ml or 400ml in MLP bags were manufactured, validating the process.

Production and control of starting materials

Starting materials listed in pharmacopoeias

The following starting materials, listed in a pharmacopoeia, are used in the manufacturing of the vaccine: SPF eggs, bovine serum, DMSO.

For the manufacturing of the solvent the following materials are used: sucrose, potassium dihydrogen phosphate, water for injections, sodium hydroxide, hydrochloric acid, phenolsulfonphthalein, sodium chloride and disodium hydrogen phosphate dihydrate.

Example certificates of analysis have been provided and all conform to specifications in the respective Ph. Eur. monographs.

Recently issued CoAs of the SPF egg suppliers are included in the dossier.

A valid EDQM Certificate of Suitability (CEP) for the bovine serum was provided. Validation reports of the irradiation method are included in the dossier.

Specific materials not listed in a pharmacopoeia

Starting materials of biological origin

Master Seed Virus

A Turkey Herpesvirus vaccine strain (HVT FC-126) was genetically modified by insertion of the IBDV VP2 gene and the ILT gD and gI genes and regulatory sequences, to generate HVT/IBD/ILT. The HVT/IBD/ILT virus was multiplied on CEF cells, plaque purifications were performed, expression of IBD VP2 and ILT gD and gI proteins was verified during passaging. One batch was selected to prepare the pre-master. This pre-master seed was used to establish the master seed. The Master Seed Virus (MSV) was produced in CEF cells, supplemented with bovine serum and DMSO, filled in ampoules and stored in liquid nitrogen.

Identity, sterility, absence of mycoplasma and absence of extraneous agents was tested on the master seed lot. Absence of mycoplasma was tested in accordance with 9CFR 113.28 and by PCR method in accordance with Ph. Eur. 2.6.7. (Mycoplasmas); no mycoplasma was detected. Extraneous agents testing was performed by general tests (in accordance with 9CFR requirements). Specific tests for Avian Leucosis viruses, Salmonella, Chicken Anaemia Virus (CAV), Reticuloendotheliosis virus (REV) were performed and found negative.
A risk assessment in accordance with Ph. Eur. 5.2.5 (Management of extraneous agents in immunological veterinary medicinal products), considering both extraneous agents applicable to the animal species of origin of the material (bovine EAs) and those of the target species for the product (avian EAs), was provided.

Working Seed Virus

The Working seed is prepared in the same way as described for the finished product. In the production facilities in the US, the WSV is tested for sterility, absence of Mycoplasma and extraneous agents in accordance with 9CFR requirements, while in the EU facilities this is done in accordance with relevant Ph. Eur. monographs.

Chicken embryo fibroblasts (CEF cells)

CEF cells can be obtained from an external supplier. Alternatively, CEF cells can be produced in-house from embryonated SPF eggs.

Specifications of excipients and other starting materials (e.g. materials of biological and non-biological origin, media) are defined and analytical methods are provided.

Starting materials of non-biological origin

Starting materials not listed in pharmacopoeia include: veggie medium, veggie protease and leupeptin; example certificates of analysis are provided.

In-house preparation of media and solutions consisting of several components

Media and solutions used during production can be purchased or prepared in house by the applicant.

Control tests during the manufacturing process

The proposed control tests during the manufacturing process are considered adequate to support a consistent process. The following tests are performed during manufacturing of the vaccine: check on cytopathic effect on monolayers before harvest, cell count after cell harvest and filling volume during filling.

No tests are proposed to be performed during manufacturing of the solvent. This is acceptable based on the manufacturing process (dissolving of components, filling, sterilising).

Control tests on the finished product

The product is tested for identity, potency, sterility and absence of mycoplasmas. These tests are suitably validated. No tests for appearance are proposed since the finished product is stored in liquid nitrogen. Testing for adjuvants, residual humidity and inactivation are not applicable for this product. Testing for excipients, pH and osmolality is not proposed, this is adequately justified based on the frozen storage of the product and the large dilution performed immediately after thawing. The validation of the titration and identity test is acceptable.

The solvent is tested for appearance, clarity, pH, sucrose content, identity, sterility and filling. The tests performed on the solvent are considered suitable to control the quality.

Batch-to-batch consistency

Three consecutive production batches of Innovax-ILT-IBD were manufactured in support of the batch-to-batch consistency. The results of the in-process control and finished product testing indicate that the production process results in a product of consistent and appropriate quality. Batch

protocols are provided in the dossier. The batches conformed with all specifications.

In addition, the applicant provided a summary of batch consistency data on Innovax-ND-ILT and Innovax-ND-IBD; these results are considered relevant to the manufacturing of Innovax-ILT-IBD since the products share platform (parent virus) and production process. These products batches also complied with all specifications and test results indicate a consistent production process, both within and between the different vaccines.

Three batches of solvent for cell associated poultry vaccines were filled in multilayer plastic bags, at 200, 1600 and 400 ml. The batches conformed to all specifications. Certificates of analysis are provided in the dossier.

Stability

Stability of the finished product

The applicant proposes a shelf life of 36 months for the finished product. A stability study is ongoing. The specifications tests include virus titration only since the product is contained in flame-sealed glass ampoules and stored in liquid nitrogen. Therefore, no test for integrity of the container is considered necessary.
Results of virus titration up to 35 months (one batch), 25 months (two batches), 21 months (one batch) and 12 months (three batches) are available in the dossier. The results show no tendency for a decrease of titre.
To further support the stability of the product, the applicant provided the results of stability studies performed with Innovax-ND-IBD (6 batches) and Innovax-ND-ILT (3 batches) stored for 39 months. These results also show no decrease in titre over the 39 months storage for either of the nine batches.
Based on the stability data provided on Innovax-ILT-IBD batches, but also based on the stability data provided for other authorised vaccines from the applicant based on the same backbone virus and manufactured according to the same method (Innovax-ND-IBD and Innovax-ND-ILT, both stable up to 39 months) it is considered that the proposed shelf life of 36 months is adequately supported. The applicant commits to provide the final stability report as soon as it is available.

Stability of the reconstituted product

In-use stability was investigated for the diluted vaccine suspension.

An in-use shelf life of two hours is proposed for the product diluted in solvent for cell associated poultry vaccines. Mixing Innovax-ILT-IBD with Nobilis Rismavac does not affect the in-use stability of the vaccine.

Stability of the solvent

A shelf life of 36 months at ≤30 °C is proposed for the solvent in MLP bags. In total, 8 batches of solvent were entered into a stability study (200ml, 400ml, 2x 800ml, 1000ml, 3x1600ml). Appearance, clarity, pH, sucrose content and identity were tested after 3, 6, 12 and 18 months for the first five batches and up to 12 months for the three 1600ml batches. The study is ongoing and further time points are 24, 30 and 36 months, with sterility additionally tested at 36 months. The results show that the batches conform to the requirements at all timepoints tested so far.
An additional stability study was performed where the same batches were stored at 40°C for 6 months and were tested for appearance, clarity, pH, sucrose content and identity, potassium, phosphate, phenolsulfonphthalein and sterility after 1, 3 and 6 months. The results of this accelerated stability study show that all batches complied with all the specifications at every

timepoint.
The available results fully support the stability of the solvent for the claimed shelf life of 36 months. The applicant commits to provide the final results of the stability study as soon as they are available.

Overall conclusions on quality

Innovax-IBD-ILT is a live recombinant vaccine for active immunisation of chickens against Marek's Disease, Infectious Bursal disease and Infectious Laryngotracheitis. The vaccine is available in ampoules containing 2000 or 4000 doses and, before use, it is diluted in a solvent supplied in plastic bags containing 400, 800, 1200 or 1600 ml.

One dose of vaccine contains between $10^{3.2}$ and $10^{4.6}$ PFU of virus strain HVT/IBDV/ILT as active ingredient. The virus is grown on chicken embryo fibroblast (CEF) cells produced from embryos obtained from SPF chicken flocks. The cells containing the virus are harvested and combined with bovine serum and a cryoprotectant (DMSO) to allow storage in liquid nitrogen. The manufacturing method can be considered as standard for this type of vaccine.

Procedures have been implemented to ensure the absence of extraneous agents in the starting materials of animal origin. A risk assessment in accordance with Ph. Eur. 5.2.5 requirements was provided, concluding that there is no need for final product testing for extraneous agents. A TSE risk assessment for the starting materials used is provided. The risk that the final product may transmit TSE to the target animal is considered negligible.

Adequate information on starting material is provided. The production method, including appropriate in-process controls and quality control on the finished product together with control of the starting materials, ensure a consistent quality of batches of vaccine. The whole production process was evaluated at production scale and shown to be consistent.

The results of the stability tests for the final product showed no loss in infectivity titre during a 35 month storage period in liquid nitrogen. Based on the stability data provided on Innovax-ILT-IBD batches, but also based on the stability data provided for other authorised vaccines from the applicant based on the same backbone virus and manufactured according to the same method (Innovax-ND-IBD and Innovax-ND-ILT, both stable up to 39 months) it is considered that the proposed shelf life of 36 months is adequately supported. Stability data of reconstituted product show that the vaccine remains stable at room temperature for 3 hours, the proposed 2 hours in-use shelf life is considered sufficiently supported. The data presented to support the stability of the solvent, at the moment cover only up to 18 months. Nevertheless, the claimed shelf life of 36 months is considered acceptable based on extrapolation of data obtained from storage at increased temperatures.

In conclusion, the production process is adequately described and controls in place are appropriate to ensure the quality of the product at release and throughout the shelf life.

In addition, the applicant is recommended to provide the following information post-authorisation (as a recommendation): the applicant should provide the final results of stability studies on the finished product and the solvent as soon as these become available. The applicant has already committed to this and the Committee considered this to be acceptable.

Part 3 – Safety

Introduction and general requirements

The active substance, cell-associated live recombinant turkey herpesvirus (strain HVT/IBD/ILT) expressing the VP2 protein of Infectious Bursal disease virus and the glycoproteins gD and gI of Infectious Laryngotracheitis virus, is a new active substance not authorised for a veterinary medicinal product in the EU before. A full safety file in accordance with Article 12(3)(j) of Directive 2001/82/EC as amended, EMA/CVMP/IWP/206555/2010 "Guideline on requirements for the production and control of immunological veterinary products", Ph. Eur. monograph 0062 (Vaccines for veterinary use) and Ph. Eur. monograph 5.2.6: (Evaluation of safety of veterinary vaccines and immunosera) has been provided.

Safety documentation

Fifteen safety studies were conducted to investigate the safety of the product. This included one laboratory study investigating the safety of the administration of a 10-fold overdose and two clinical trials. The vaccine was administered by the in ovo (i.o.) and subcutaneous (s.c.) routes, as recommended. Laboratory studies were carried out using SPF chickens of the minimum age recommended for vaccination, using pilot batches diluted to contain the maximum titre of vaccine virus. Production batches were used in the field trials.

Studies applicable to live vaccines and genetically modified organism (GMO)-containing products were conducted to investigate the dissemination of the vaccine strain, the spread from vaccinated animals to non-vaccinated in-contact animals and reversion to virulence.

Laboratory tests

Safety of the administration of one dose

In line with Ph. Eur. monograph 0589 (Marek's disease vaccine, live), only overdose safety testing was performed.

Safety of one administration of an overdose

Safety of an overdose was investigated in two laboratory studies.

Study 1: Safety testing of an overdose of HVT-IBD-ILT by the i.o. or the s.c. route, and safety testing of a maximum dose of Nobilis Rismavac administered simultaneously mixed with a maximum dose of HVT-IBD-ILT by the i.o. route.

The study was performed under GLP conditions and fully in accordance with the requirements of Ph. Eur. monograph 0589 (Marek's Disease vaccine, live). A group of embryonated SPF eggs and a group of day-old SPF chicks were vaccinated with a 10-fold overdose of HVT-IBD-ILT MSV on the 18th day of embryonation or the day of hatch via the s.c. route. In a third group, 18-day-old embryonated eggs were vaccinated with a maximum dose of HVT-IBD-ILT mixed with a maximum dose of Nobilis Rismavac. A group of untreated birds was maintained as MD-sensitive (challenge) controls. One group of eggs was inoculated with solvent only and was kept as negative controls. At day 7, the first 4 groups were challenged with the virulent RB1B strain. Birds in the vaccinated

groups were monitored daily for clinical signs and general health up to day 123. Birds in the challenge control group were monitored for 50 days for clinicals signs of MD. At the end of the experiment, all birds were euthanised, necropsied and analysed for macroscopic evidence of MD.

The hatchability after i.o. vaccination with Innovax-ILT-IBD was 96.7%, while hatchability was 93.3% and 91.7% respectively in the non-treated and the solvent control groups. There was no significant difference between the groups. Birds were susceptible to MD since all birds in the challenge control group showed clinical signs of MD. At necropsy on day 123, no macroscopic lesions were found in the vaccinated or solvent control groups and it was concluded that no birds died from causes attributable to the vaccine.

It can be concluded that Innovax-ILT-IBD is safe in one day old chickens when administered by the s.c. route and in 18-day-old embryonated eggs when applied i.o. at a 10-fold maximum overdose. In addition, simultaneous -mixed- application of Innovax-ILT-IBD and Nobilis Rismavac to 18-day-old embryonated eggs via the i.o route was shown to be safe.

Study 2: Safety testing of "Bursal Disease-Infectious Laryngotracheitis-Marek's Disease Vaccine, Serotype 3, Live Marek's Disease Vector Master Seed virus" by the i.o. and s.c. routes in SPF chickens.

The study was designed in accordance with requirements set out in Title 9 § 113.330 of the US Code of Federal Regulations (CFR). The study was not performed in compliance with GLP principles and the setup slightly differed from what is required by Ph. Eur. monograph 0589 (Marek's disease vaccine, live). The study was, however, performed to an acceptable standard. The study included four groups, one group of 18-day-old embryonated SPF chicken eggs that were inoculated i.o. with a 3-fold overdose of Innovax-ILT-IBD MSV. A second group of 18-day-old embryonated SPF chicken eggs were inoculated i.o. with solvent only. A group of 50-day-old SPF chickens were vaccinated s.c. with a 3-fold overdose of Innovax-ILT-IBD MSV. A second group of day-old SPF chicks was kept as MD sensitivity controls. The vaccinated and challenge control groups were challenged at day 5 with MDV RB1B. Challenge control birds were followed up for 56 days, vaccinated birds for 122 days. All birds were observed daily for clinical signs of MD and general health and, at the end of the monitoring period, all surviving birds were necropsied and evaluated for macroscopic lesions associated with MD.

Hatchability in the group vaccinated i.o. was 96.3% and 91.3% in the solvent controls. There was no significant difference between these groups. Birds were susceptible to MD, since 84% of control birds showed clinical signs of MD. No clinical signs were observed in the vaccinated and negative control groups. No macroscopic lesions of MD were observed at necropsy at the end of the observation period in any of the groups and no chickens died from causes attributable to the vaccine.

It can be concluded that the data support the safety of Innovax-ILT-IBD in chickens from one day of age by the s.c. route or in 18-day-old embryonated eggs by the i.o. route when applied at a 3-fold maximum overdose.

Safety of the repeated administration of one dose

The vaccine is intended to be administered once in the lifetime of a bird, either i.o. to embryonated eggs or at day-old. Therefore, a study to test the safety of repeated administration was not performed, which is considered acceptable.

Examination of reproductive performance

There is no data suggesting that vaccination with a HVT vaccine affects the reproductive tract of the vaccinated animals. Experience with licensed HVT vaccines in the same range confirms this. In line with this, the applicant has concluded that Innovax-ILT-IBD would not adversely affect the reproductive performance of chickens without providing data. This can be accepted.

Examination of immunological functions

The parent strain HVT is apathogenic and it is not known to be immunosuppressive in chickens. This was further confirmed in a study using Innovax-ILT. Innovax-ILT is based on the HVT FC-126 strain with gD and gI genes of avian Infectious Laryngotracheitis virus (ILTV) inserted. In this study, birds were vaccinated with an overdose of Innovax-ILT on day 0 and with a dose of Nobilis ND Clone 30 on day 15. A second group was vaccinated with Nobilis ND Clone 30 alone and a third group was left unvaccinated. All three groups received a virulent NDV challenge. Full protection was found in both groups of vaccinated birds, whereas all controls showed clinical signs of NDV. It was concluded that Innovax-ILT vaccination did not adversely affect immunological function.

The study was appropriately designed and executed to an acceptable standard. The results of the study support the conclusion that HVT vaccines do not adversely affect the immune system and are considered relevant for the Innovax-ILT-IBD vaccine strain. It is therefore concluded that there is no indication the vaccine would adversely affect the immune system.

Special requirements for live vaccines

Six laboratory studies were performed in order to fulfil the requirements for live vaccines: five studies investigating spread to target and non-target species and one study to determine the dissemination of the vaccine strain in the target animal.

Spread of the vaccine strain

The parent virus, HVT FC-126, is known only to infect avian species. After HVT vaccination, spread from chicken to chicken occurs rarely, although spread to turkeys can occur, mainly through feather dust. Five well-designed studies were performed in order to investigate the spread of the vaccine strain.

Spread in the target species was investigated by keeping unvaccinated chickens comingled with a group of hatch mates vaccinated with a 10-fold overdose of the MSV at day old. At study day 14 and 28, 10 birds from each group, and at day 49, all remaining birds, were euthanised and spleens harvested for virus titration and virus detection by PCR. No clinical signs were observed in any bird. In vaccinated animals, virus was isolated from spleen samples taken at day 14, 28 and 49. In the in-contact birds, all samples were negative by culture and PCR. No macroscopic or microscopic lesions of MD were found. In conclusion, no evidence of spreading to target species was found in the study.

Spread in the non-target species turkey was evaluated by keeping unvaccinated turkeys comingled with a group of hatch mates vaccinated with a 10-fold overdose of the MSV at day old. At study day 16 and 30, 10 birds from each group, and at day 51 all remaining birds were euthanised and blood and spleens were harvested for virus titration and virus detection by PCR. Non-treated hatch mates were found to be HVT negative. No clinical signs indicative of MD were observed in any bird. Virus

was isolated from all spleen and blood samples taken at day 30 and in some samples from both groups at day 51. No macroscopic lesions of MD were found. In conclusion, the vaccine was shown to be safe in turkeys and that it can spread to in-contact birds.

Spread from chickens vaccinated at day of age with a 10-fold dose of the MSV to in-contact turkeys was investigated in a study with a similar setup as the study described above. No clinical signs indicative of MD were observed and, at necropsy, no macroscopic lesions indicative of MD were found. The virus was shown to replicate in chickens, with the most blood samples being positive in week 2. Samples taken from turkeys were negative throughout the study. In conclusion, no evidence of spread from chickens to turkeys was found.

Spread in non-target species was investigated in two weeks old Japanese quail. One group of birds was vaccinated with a 2.5-fold overdose of the MSV and one group was kept as in-contact birds. In addition, one group of birds was vaccinated with the same dose of parent HVT virus and kept comingled with another group of birds. Spleens were sampled after 2, 4 and 6 weeks. Non-treated hatch mates were found to be HVT-negative. No clinical sings were observed in the birds. Virus was detected by culture in both vaccinated groups after 2, 4 and 6 weeks, but not in samples from the in-contact birds. No lesions indicative of MD were found at necropsy. The vaccine and the parent HVT strain were found to be safe for quail and no evidence of spread to in-contact quail was found for either virus.

A study investigating the safety and spread of an overdose of Innovax-ILT in mice was also presented. This study was previously submitted as part of the dossier of the related vaccine Innovax-ILT and is considered relevant, since it concerns a vaccine derived from the same parent HVT strain. No evidence of infection or spread was detected in this study.

Dissemination in the vaccinated animal

One GLP-compliant study was performed to evaluate the dissemination in the target species. Three groups of 18-day-old embryonated eggs were included. One group was vaccinated i.o. with a standard dose of the vaccine, one group was vaccinated with the same dose of the parent HVT virus and one group was inoculated with uninfected CEF cells. After hatching, birds were place in isolators and, at regular intervals, birds were necropsied for virus detection sampling. The HVT-lBD-ILT vaccine and the HVT FC126 virus strains were both isolated from almost all of the samples (peripheral mononuclear blood cells, bursa, spleen, lung, feather follicles and tracheal washing) taken after 1, 2, 3, 4 and 5 weeks. The pattern of virus isolation was similar for both viruses, although the virus plaque counts were overall higher for HVT when compared to the HVT-IBD-ILT vaccine strain. It can be concluded that the virus disseminates in chickens and that there is no indication that the HVT-lBD-ILT recombinant virus has undergone a change in tissue tropism or an increased capacity for replication in comparison to the HVT parent strain.

Reversion to virulence of attenuated vaccines

Studies on reversion to virulence are not required by Ph. Eur. monograph 0589 (Marek's Disease vaccine, live) when naturally non-pathogenic strains are used (i.e. HVT). Nevertheless, a reversion to virulence study has been performed for Innovax-IBD-ILT.

One day-old SPF birds were vaccinated with HVT-IBD-ILT MSV. Necropsy was performed on day 7 and spleen cells were used for infection of the next group of birds. This was repeated for groups 3 and 4. Virus was recovered from each passage. Spleen cells from group 4 were inoculated into 35 birds in group 5. Fifteen of these birds were necropsied on day 7 and 20 birds were observed until

day 50 before being necropsied to check for MD-associated lesions. Gene expression analysis (ILT-gD, ILT-gI and VP2) and genotypic analysis was attempted on spleen cells recovered from group 5, but the virus density was too low. Virus from passage 5 expanded on CEF cells was therefore used instead. The HVT-to-insert ratios for ILT-gD, ILT-gI and IBD-VP2 were the same for passage 5-expanded virus and MSV. The consensus sequence obtained from the virus expanded at passage 5 was 100% homologous to the confirmed MSV insert sequence. The birds inoculated with passage 4 were observed for 7 weeks: no signs of illness were noted, at necropsy no Marek associated lesions were observed.

The confirmation of phenotypic and genotypic stability of MSV+5 as well as the known genetic stability and safety of the parent strain together with the data provided are considered to adequately support the absence of reversion to virulence during five *in vivo* passages. Although the requirements of the monograph with respect to study design were not fully met (i.e. the number of animals, follow up period), the totality of data is considered acceptable.

Biological properties of the vaccine strain

Based on the studies described in section B.2 to B.6, the biological properties of the HVT/IBD/ILT vaccine strain are the same as for the parent strain HVT FC-126, apart from expressing the inserted IBDV VP2 and ILTV glycoprotein genes.

Recombination or genomic reassortment of the strains

A risk assessment addressing the risk of recombination or genomic reassortment for Innovax-ILT was provided in the dossier. This risk assessment is considered to be relevant for the HVT/IBD/ILT strain. For the HVT parent strain, no observations on recombination between vaccine or field strains of MDV have ever been made. It is concluded by the applicant's expert that, for recombination with other Marek strains, "the risk of using Innovax-ILT, or any similar HVT recombinant vaccine, in the field for recombination with other vaccines or with field challenge strains is no greater than the risk of using HVT itself (FC126) and is essentially zero". The risk of recombination with viruses other than MDV in the field was also addressed and it was concluded that "Innovax-ILT, or any similar recombinant HVT vaccine, poses no additional risk for this sort of recombination beyond that inherent in HVT itself".

In the risk assessment, recombination with ILTV, which itself is a herpesvirus, is specifically addressed, since two ILTV genes have been inserted into the strain contained in Innovax-ILT. In Innovax-ILT-IBD, the same ILTV genes have been inserted. It is concluded, based on literature data, that interspecific recombination among alpha herpesviruses requires a very high degree of genetic relatedness. Therefore, with regard to interspecific recombination between avian herpesviruses, recombination would be highly unlikely given the divergence of the genomes.

Furthermore, many other HVT recombinant vaccines are used worldwide. They all are safe vaccines, which have been extensively used in the field, thereby confirming the safe nature of HVT based vaccines.

Therefore, it can be concluded that the risk of recombination with other MDs, Infectious laryngotracheitis virus or Infectious bursal disease virus strains can be considered effectively zero.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with the CVMP "Guideline on user safety for immunological veterinary medicinal products"

(EMEA/CVMP/IWP/54533/2006) and the CVMP "Guideline on user safety for pharmaceutical veterinary medicinal products" (EMEA/CVMP/543/03-Rev.1).

The user may be exposed to the vaccine by accidental (self-)injection or when a glass ampoule explodes during the thawing process. The active substance is not infectious to mammals and the excipients are commonly used in veterinary medicinal products. Both do not pose a risk for the user. The consequences of exposure by accidental self-injection, dermal exposure and inhalation are therefore considered to be negligible. The consequences of an ampoule bursting are estimated to be of medium severity (skin cuts). The overall risk for the user is therefore considered to be of medium to low magnitude. A warning concerning the handling of ampoules has been included in the SPC.

Based on the above user risk assessment, the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Excipients

The safety of the excipients included in the product has been previously assessed and no specific risks have been identified.

MRLs

The active substance being a principle of biological origin intended to produce active immunity is not within the scope of Regulation (EC) No 470/2009.

The excipients listed in the SPC are either allowed substances for which Table 1 of the Annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product. The excipients which are not covered by Regulation 37/2010, i.e. phenolsulfonphthalein, bovine serum and "Veggie medium" (incl. EGF), are considered being devoid of pharmacological activity at the dose used in the animal and are therefore considered not falling within the scope of the above-mentioned Regulation.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

Innovax-ILT-IBD can be given mixed with Nobilis Rismavac, to be administered either via the s.c. or i.o. route. The vaccine can also be applied on the same day but via different administration routes with the live Newcastle disease vaccines Nobilis Clone 30 or Nobilis ND C2 or the infectious bronchitis vaccines Nobilis IB Ma5 mixed with Nobilis IB 4-91. Studies were performed to investigate the safety of the associated use of these vaccines.

The safety of simultaneous mixed use of Innovax-ILT-IBD and Nobilis Rismavac was investigated. In a GLP-compliant safety study, the mixed use in 18-day embryonated eggs (i.o.) was found to be safe with no effects on hatchability and no clinical signs or macroscopic lesions.

A study was performed in which day-old SPF chicks were vaccinated with Innovax-ND-IBD subcutaneously and at the same time received a dose of Nobilis ND C2 or Nobilis ND Clone 30 via the ocular route. Control groups received only the ND vaccines or were not vaccinated. No clinical signs were observed in any of the groups. It can therefore be concluded that associated use is safe.

A study in which day-old SPF chicks were vaccinated with Innovax-ND-IBD subcutaneously at the same time with a mixed dose of Nobilis IBMa5 and IB 4-91 via the oculo-nasal route was performed. Controls were vaccinated with Innovax-ND-IBD alone, the mixed IB vaccines alone or with Nobilis Marexine (s.c. route), alone or concurrently with the mixed IB vaccines. No clinical signs were observed. All groups passed the safety requirements of Ph. Eur. monograph 0442 (Avian infectious bronchitis vaccine (live)). There was no difference in average ciliostasis scores between the groups vaccinated with Nobilis IB Ma5 and IB 4-91 alone or concurrently with Innovax-ND-IBD or Marexine CA126.

The data provided on the safety of simultaneous non-mixed use of Innovax-ND-IBD and ND and IB vaccines is considered relevant to Innovax-ILT-IBD. Both Innovax-ND-IBD and Innovax-ILT-IBD were derived from the same parent HVT Fc-126 strain and generated using the same genetic techniques for inserting foreign genes. For both vaccine strains, it was shown by *in vivo* studies that their biological properties, in particular virulence, pathogenicity, shedding and dissemination, were not changed when compared directly to the parent HVT Fc-126 strain. The studies presented on associated uses of Innovax-ND-IBD and of mixed use of Innovax-ILT-IBD with Nobilis Rismavac showed no safety issues. Based on the available data, associated use as proposed for Innovax-ILT-IBD is not expected to cause any safety issues.

Field studies

Two combined safety and efficacy field studies were performed in the Netherlands.

In both studies, small groups of eggs or birds were taken from the field and used for laboratory challenge studies. These results are not discussed here since the results are not relevant for the safety of the vaccine.

The data from both field studies support the safety of i.o. or subcutaneous vaccination with Innovax-ILT-IBD mixed with Nobilis Rismavac.

Study 1 A controlled field trial in the Netherlands to assess the safety and efficacy of in ovo vaccination of Innovax-ILT-IBD in 18 day embryonated eggs	
Objectives	To evaluate safety and efficacy under field conditions.
Study sites	Broiler farm in the Netherlands.
Study design	Controlled study with matched controls.
Compliance with regulatory guidelines	GCP.
Animals	18-day old embryonated broiler eggs.
Eligibility criteria	Candled (no infertile eggs included).
Test product	Innovax-ILT-IBD mixed with Nobilis Rismavac in solvent CA. Innovax-ND-IBD in solvent CA.
Control product/ Placebo	
Vaccination scheme	Vaccination at day 0.

Safety end points	General health and feed intake up to day 14 after hatch, hatching results, key performance parameters, medication use and mortality.
Statistical method	As the sub-flock (house) was the statistical unit (n = 2), no statistical analysis was performed but only descriptive statistics were used.
Results	
Outcomes/safety observations	Hatchability was similar and acceptable in both groups. Both groups were scored as normal until day 10 (general health and feed intake). A slightly lower mortality was observed in the control house (2.52%) compared to the test house (2.92%). The mortality % in both houses during the study was comparable to what was seen in previous production cycles at the farm. The performance results were comparable between the groups, with the test house performing slightly better.
Adverse events	None reported.
Discussion	
Discussion/conclusions further to assessment	The study was performed to an appropriate standard and no clinical signs were observed after vaccination. Differences in mortality and performance between the treatment groups were relatively small and fall within the variability observed for the farm. The data generally support the safety of mixed use of Innovax-ILT-IBD and Nobilis Rismavac *in ovo* in commercial chicks.

Study 2 A controlled field trial in the Netherlands to assess the safety and efficacy of subcutaneous vaccination of Innovax-ILT-IBD in day-old broiler chickens	
Objectives	To evaluate safety and efficacy under field conditions.
Study sites	Broiler farm in the Netherlands.
Study design	Controlled study with matched controls.
Compliance with regulatory guidelines	GCP.
Animals	Day old broiler chicks (Ross 308).
Eligibility criteria	Healthy day-old chicks from one parental flock.
Test product	Innovax-ILT-IBD mixed with Nobilis Rismavac in solvent CA. Innovax-ND-IBD in solvent CA.
Control product/placebo	
Vaccination scheme	Vaccination at day 0.
Safety end points	Immediate reactions, general health and feed intake up to day 14, mortality, key performance parameters, medication use.

Statistical method	As the sub-flock (house) was the statistical unit (n = 2), no statistical analysis was performed but only descriptive statistics were used.
Results	
Outcomes/safety observations	No immediate reactions were observed. Both groups were scored as normal until day 14 (general health and feed intake). A slightly higher mortality was observed in the control house (2.6%) compared to the test house (2.2%). The mortality % in both houses during the study was comparable to what was seen in previous production cycles at the farm. The performance results were comparable between the groups, with the control house performing slightly better.
Adverse events	None reported.
Discussion	
Discussion/conclusions further to assessment	The study was performed to an appropriate standard and no immediate reactions or clinical signs were observed after vaccination. Differences in mortality and performance between the treatment groups were relatively small and fall within the variability observed for the farm. The data support the safety of mixed use of Innovax-ILT-IBD and Nobilis Rismavac in commercial (MDA+) chicks.

Environmental risk assessment

An assessment of environmental risk according to the CVMP "Note for guidance: Environmental risk assessment for immunological veterinary medicinal products" (EMEA/CVMP/074/95) has been provided.

Considerations for the environmental risk assessment

The HVT virus host range is limited to avian species. The HVT virus is non-pathogenic for the target species and other avian non-target species. The HVT FC-126 parent virus has been safely used in the poultry industry for over 40 years. Based on the results of five transmission studies, the insertion of the IBDV VP2 and ILT gD and gI protein genes has not altered the host range, pathogenicity or spreading capacity of the HVT FC-126 strain. Spread of the HVT/IBD/ILT vaccine strain from the target species was not observed, but is, based on literature data, nevertheless considered to be possible during the lifetime of the bird. The vaccine virus may survive for months in feather dust from vaccinated animals. The vaccine preparation does not contain any toxic or pharmacologically active components.

In case in-contact chickens or turkeys or other avian species are infected with the vaccine virus, the consequences for the environment are negligible, as the vaccine virus is apathogenic to avian species.

Based on the data provided, the ERA can stop at phase I. Innovax-ILT-IBD is not expected to pose a risk for the environment when used according to the SPC.

Environmental risk assessment for products containing or consisting of genetically modified organisms

Innovax-ILT-IBD falls within the scope of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms. Detailed information on the possible risks for humans and for the environment has been provided.

The parent strain is a naturally apathogenic strain that has been used in vaccines for decades. The vaccine strain was generated by homologous recombination. The expression cassette contains the IBD VP2 gene under the control of the immediate-early promotor from the murine cytomegalovirus and the ILT gD and gI genes under the control of their own promotors. Reversion to virulence studies (*in vivo* and *in vitro*) did not show any tendency for genetic instability or reversion. Loss of the inserted expression cassette is unlikely and will not result in alteration of the virulence. Recombination with other viruses has never been described for HVT even though mixed infections and the use of polyvalent vaccines containing more than one MDV serotype are very common in chickens. Recombination events are therefore considered to be highly unlikely for HVT/IBD/ILT. The HVT/IBD/ILT virus does not contain any antibiotic resistance genes or other markers that may present a risk.

Taken together, any risk emerging from the use of the vaccine viruses is expected to be negligible for humans and low for the environment.

Overall conclusions on the safety documentation

Safety of the application of a tenfold overdose of Innovax-ILT-IBD administered subcutaneously to day-old chicks and to 18-day-old embryonated chicken eggs was investigated in accordance with regulatory requirements. The vaccine was found to be safe as it induced no clinical signs or macroscopic lesions. Repeated administration was not investigated since the vaccine is to be applied by single injection either i.o. or on the first day of life. This is considered acceptable.

Reproductive performance was not studied and a warning to such effect is included in the SPC. This is considered acceptable based on the safety profile of the parent strain. Specific studies regarding the influence of Innovax-ILT-IBD on the immune system were not performed. This was adequately justified.

Although no evidence of spread to either chickens or turkeys was obtained from the studies in chickens, the vaccine strain is considered to be able to spread from vaccinated chickens via feather dust. Spread to in-contact chickens and turkeys can therefore not be excluded. An appropriate warning mitigating this risk is included in the SPC. The application of a tenfold dose of the vaccine to turkey and quail was shown to be safe. Dissemination of Innovax-ILT-IBD in chickens was compared to the parent strain. Although the parent strain replicated slightly better, it could be concluded the biological properties of Innovax-ILT-IBD are comparable to its parental HVT strain (FC-126) in terms of tissue tropism.

No specific study was provided to evaluate the properties of the vaccine strain when administered to mammals. This was appropriately justified. The risk of Innovax-ILT-IBD posing a threat to mammals is considered to be negligible.

A reversion to virulence study was performed. The study was appropriately designed albeit not fully in accordance with Ph. Eur. requirements. It can be concluded the virus did not acquire virulence during passaging. The results of safety testing of the fifth *in vivo* passage were supported by testing of phenotypic and genotypic stability. Taken together, the data are considered to sufficiently support the absence of reversion to virulence.

The applicant has sufficiently addressed the biological properties of the vaccine strain and the risk of recombination or genomic reassortment occurring. The risk is considered to be negligible.

The user safety has been adequately addressed and appropriate warnings are included in the SPC.

Residue studies are not required. The withdrawal period is set at zero days.

Safety of associated mixed use of Innovax-ILT-IBD with Nobilis Rismavac was investigated using embryonated eggs, the study set up is considered justified and safety was confirmed. The safety of the associated use (at the same moment by different routes) of Innovax-ILT-IBD with Nobilis ND C2 or Nobilis Clone 30 and of Innovax-ILT-IBD with Nobilis IB Ma5 mixed with Nobilis IB 4/91 was adequately justified.

Based on the data provided, the ERA can stop at phase I. Innovax-ND-ILT is not expected to pose a risk to the environment when used in accordance with the SPC.

Information concerning the deliberate release of genetically modified organisms has been provided in a separate part of the dossier. Sufficient information regarding the origins, method of recombination, stability, biological properties and genomic sequence of the vaccine strain is provided. Any risk emerging from the use of the Innovax-ILT-IBD vaccine virus is negligible for humans and can be considered to be low for the environment.

Two field safety studies were performed in broiler farms in the Netherlands. The results of these studies generally support the safety of the vaccine, when used mixed with Nobilis Rismavac, in both day-old chicks and 18-day-old embryonated eggs.

In conclusion, when used as specified in the SPC, the vaccine is considered to be generally safe for the target animal, the environment, the user and the consumer.

Part 4 – Efficacy

Introduction and general requirements

Innovax-ILT-IBD is intended for subcutaneous administration (0.2 ml) to day-old chicks or *in ovo* administration (0.05 ml) to 18-19-day-old embryonated chicken eggs. The minimum recommended dose is $10^{3.2}$ PFU/bird.

The proposed indications are:
- to reduce mortality, clinical signs and lesions caused by avian infectious laryngotracheitis (ILT) virus and Marek's disease (MD) virus
- to prevent mortality and to reduce clinical signs and lesions caused by infectious bursal disease (IBD) virus.

The claimed onset of immunity is:
- IBD: 3 weeks of age
- ILT: 4 weeks of age
- MD: 5 days of age.

The claimed duration of immunity is:
- IBD: 100 weeks
- ILT: 100 weeks

- MD: entire risk period.

In addition, it is claimed that Innovax-ILT-IBD can be mixed with Nobilis Rismavac to be administered by *in ovo* or subcutaneous routes.

Innovax-ILT-IBD can be used on the same day (at different administration site and different route) with Nobilis ND Clone 30 or Nobilis ND C2 or Nobilis IB 4-91 or Nobilis IB Ma5.

Efficacy was demonstrated in compliance with the European Directive 2001/82/EC (as amended by 2004/28/EC and Directive 2009/9/EC), and the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7 (Evaluation of efficacy of veterinary vaccines and immunosera). The immunogenicity sections of Ph. Eur. monographs 0589 (Marek's disease vaccine (live)), 0587 (Infectious bursal disease vaccine (live)) and 1068 (Avian infectious laryngotracheitis vaccine (live)) were used as the basis for the efficacy evaluation in SPF chickens.

Challenge model:

To confer early protection against very virulent strains of MDV, HVT vaccines are used in association with vaccines based on the Rispens CVI988 strain. Since the applicant would like to continue to support this commonly accepted vaccination regime against MD, studies were performed to support the mixed use of Innovax-ILT-IBD and Nobilis Rismavac. To support protection against MD, the efficacy of Innovax-ILT-IBD alone was evaluated by challenge with vMDV (GA5), and the efficacy of Innovax-ILT-IBD mixed with Nobilis Rismavac was evaluated by challenge with vvMDV (RB1B).

The challenge strain RB1B was isolated in the 1980's from a flock of chickens experiencing heavy losses due to MD, the strain was obtained in 1989 and no detailed information on the long-term passage history is available. The OIE indicates that RB1B is representative of vvMDV and it is a relevant strain for the current situation in Europe.

The MDV challenge strain GA5 was obtained from ATCC and passed three times in chickens to produce GA5 challenge material. GA5 is classified as vMDV and it is abundantly present in Europe. The OIE indicates that GA5 is representative of vMDV and it is a relevant challenge strain for the current situation in Europe.

The very virulent IBDV challenge strain CS89 was isolated from a flock of broilers in East Anglia. Using the nucleotide sequences of the VP2 gene, it was demonstrated that CS89 is clustered together with other vvIBDV strains. In Europe, very virulent strains and classical strains of IBDV are present; therefore, it is justified to use this strain to demonstrate the efficacy of the vaccine.

The ILT-96-3 strain is the standard USDA ILTV challenge virus, derived from a serial of vent brush type laryngotracheitis virus from the early 60's. The 96-3 is described as the 6th embryo passage. The virus is relevant to the European situation since for ILTV no different serotypes are described. Recently, genotypic differences were described for some ILTV field strains. Different genotypes of ILTV are however found to be antigenically closely related.

The challenge models are considered adequately validated, in line with the relevant Ph. Eur. monographs.

Efficacy parameters and tests:

The efficacy parameters, as described in the relevant Ph. Eur. monographs, were investigated in the efficacy studies.

Efficacy documentation

Seventeen studies were conducted to investigate the efficacy of the product and included 15 laboratory studies and 2 field trials. The laboratory studies were well documented and carried out in SPF chickens or embryonated eggs of the minimum age recommended for vaccination, using pilot or production batches. Production batches were used in the field trials.

One of the batches was manufactured at the US manufacturing site and, during the formulation, gentamycin was added to it. The presence of gentamycin is not considered to significantly affect efficacy (or safety) in the target animal, the US batch is therefore considered representative.

Laboratory trials

Dose determination

The minimum dose proposed for Innovax-ILT-IBD ($10^{3.2}$ PFU) is similar to other related HVT FC-126-based authorised vaccines from the applicant (Innovax-ND-IBD, Innovax-ILT, Nobilis Marexine CA126). Dose determination studies were therefore not provided.

Onset of immunity

Marek's disease

Two studies were performed in support of the onset of immunity (OOI) against Marek's disease. One study was performed to investigate protection against virulent MDV (vMDV) after *in ovo* vaccination of 18-day-old embryonated eggs and one study to investigate OOI after subcutaneous vaccination of day-old SPF chicks. The studies were designed fully in accordance with Ph. Eur. 0589 (Marek's disease vaccine (live)). A vMDV challenge strain (GA5) was used. The vaccine was used at a dose below the minimum one. The requirements for validity were met. The results of both studies support an onset of immunity at 5 days of age. The claims for reduction of mortality, clinical signs and lesions of MDV are supported by the results.

An additional study was performed to investigate the OOI against MD after associated mixed use with Nobilis Rismavac after *in ovo* vaccination of 18-day-old embryonated eggs and subcutaneous vaccination of day-old SPF chicks. The study was designed fully in accordance with Ph. Eur. 0589 (Marek's disease vaccine (live)). A vvMDV challenge strain (RB1B) was used. Both vaccines were applied at a dose ($10^{3.0}$ PFU) below the minimum one. The requirements for validity were met. Based on the results obtained, it can be concluded that the protection afforded by Nobilis Rismavac against vvMDV was not negatively affected by simultaneous mixed use with Innovax-ILT-IBD. The requirements for immunogenicity were met and the claimed reduction of mortality, clinical signs and lesions is supported by the data with an onset of immunity of 4 days of age.

Infectious bursal disease

Two studies were performed to support the claimed onset of immunity of 3 weeks for IBDV. Both studies were designed fully in accordance with the Ph. Eur. monograph 0587 (Avian infectious bursal disease vaccine (live)) immunogenicity tests. In the first study, the requirements of the monograph were met for a dose ($10^{3.0}$ PFU) below the minimum of Innovax-ILT-IBD applied via subcutaneous or *in ovo* routes. When Innovax-ILT-IBD was mixed with Nobilis Rismavac, both vaccines at a below-minimum dose ($10^{3.0}$ PFU), the immunogenicity requirements (≥90% protection) were met for the *in ovo* (90%) but not for the subcutaneous route (85%). The applicant performed an additional study,

repeating the mixed vaccination with minimum doses of both vaccines applied via the subcutaneous route. In this study, 100% protection against a highly virulent challenge was achieved after mixed use. It can therefore be concluded that interference is not a significant problem for the mixed use of Innovax-ILT-IBD and Nobilis Rismavac with respect to protection against IBD.

The onset of immunity against IBD at three weeks of age is supported by the data. Prevention of mortality in all groups vaccinated with the single vaccine and a reduction in clinical signs and lesions were shown in all the groups vaccinated with Innovax-ILT-IBD alone.

Infectious laryngotracheitis

One study was performed to investigate the onset of immunity against infectious laryngotracheitis. The study included groups vaccinated *in ovo* or subcutaneously with a dose ($10^{3.1}$ PFU) below the recommended minimum dose of the vaccine. In addition, the mixed use with Nobilis Rismavac was tested for both administration routes, with both vaccines at a dose below the minimum. The design of the immunogenicity test described in Ph. Eur. monograph 1068 (Avian infectious laryngotracheitis virus, (live)) was followed with the exception of the number of birds in the group vaccinated with Innovax-ILT-IBD. Due to a low hatching percentage, the number of birds in this group was 15 instead of 20. However, the results of the group vaccinated with the mixed vaccines can be considered as a worst-case scenario. The challenge was adequate in accordance with the monograph (clinical signs and/or lesions in 90% of control birds). The results support an onset of immunity at 4 weeks of age, after vaccination via the *in ovo* or subcutaneous routes. Reduction of mortality, clinical signs and lesions is supported. No interference was observed after mixed use with Nobilis Rismavac.

Duration of immunity

Marek's disease

No studies were performed to determine the duration of immunity of Innovax- ILT-IBD against Marek's Disease. HVT causes a persistent infection in chickens. The virus remains present lifelong and therefore protection against Marek's Disease by HVT is generally accepted to be lifelong.

Infectious bursal disease

To confirm the long-term duration of immunity for IBD, a duration of immunity study in birds vaccinated subcutaneously with Innovax-ILT-IBD mixed with Nobilis Rismavac was performed. Both vaccines were used at a minimum dose. During this study, the serological response against IBDV was evaluated at different timepoints and a challenge with IBDV strain CS89 was performed at 11 weeks. The challenge was performed in accordance with Ph. Eur. 0587 (Avian infectious bursal disease vaccine (live)). The level of protection was 75%, which is lower than the Ph. Eur. requirement for onset of immunity. Nevertheless, mortality was prevented and clinical signs and lesions were reduced. The difference between the vaccinated and control group was found to be statistically significant. This is considered acceptable to support a duration of immunity of 11 weeks.

Serological data up to timepoint 100 weeks was generated. The non-vaccinated birds remained negative.

Sustained antibody response as well as a high percentage sero-positive birds for IBD was observed for 100 weeks following vaccination. The applicant concludes that the VP2 gene of IBDV is stably expressed and lifelong protection is confirmed. An overview of IBD-antibody levels and protection

percentages was provided: while almost 80% of vaccinated but seronegative birds were protected, 96% of the vaccinated seropositive birds were found protected. Thus, seropositive birds can be expected to be adequately protected from IBDV. Since average antibody titres were high up to 100 weeks, and 87% of birds were seropositive at this timepoint, the claimed DOI of 100 weeks for IBD is considered adequately supported.

Infectious laryngotracheitis

A duration of immunity study was performed in birds vaccinated subcutaneously with Innovax-ILT-IBD mixed with Nobilis Rismavac. During this study, the serological responses against ILTV were evaluated at different timepoints and challenges with ILT strain 96-3 were performed. The challenges were performed following Ph. Eur. 1068 (Avian infectious laryngotracheitis vaccine (live)). The vaccines used for this study were at the minimum dose and mixed use is considered the worst-case scenario. After the challenges performed at 12, 40, 81 and 100 weeks of age, a significant reduction of mortality, clinical signs and lesions due to ILTV was achieved in the vaccinated birds. The level of protection obtained was 84%, 72%, 83.3% and 67% respectively. The lower protection at 40 weeks (72%) likely being an effect of biological variability. The serological data shows no decrease in titre or percentage positive birds over the first 80 weeks and a slight decrease at 100 weeks, which is an indication of a sustained immune response. Since after challenge at 100 weeks a clinically relevant and statistically significant protection was observed, the data are considered to support the proposed 100 weeks duration of immunity against ILT.

Maternally derived antibodies (MDA)

Marek's disease

In the field study S20205-00, embryonated commercial eggs were vaccinated *in ovo,* at the farm, with standard doses of Innovax-ILT-IBD or Innovax-ILT-IBD mixed with Nobilis Rismavac. Eggs from both groups, as well as non-inoculated eggs from the same hatch, were transported to the laboratory. A challenge study was performed in line with Ph. Eur. 0589 (Marek's disease Vaccine (live)) requirements for immunogenicity testing and can be considered valid. Birds were challenged at 7 days while the claimed onset of immunity is at 5 days of age. This is considered acceptable for a study in MDA+ birds. The relative protection percentage achieved was 53% for Innovax-ILT-IBD and 66% for Innovax-ILT-IBD mixed with Nobilis Rismavac. This is lower than the 80% RPP (relative protection percentage) limit set by Ph. Eur. 0589 (Marek's disease vaccine (Live)) and lower than the protection achieved at OOI in SPF eggs and birds vaccinated with Innovax-ILT-IBD alone or mixed with Nobilis Rismavac. It is noted that a vvMDV challenge strain was used for both the associated use and the single vaccine whereas normally a combination of serotype 3 and serotype 1 or 2 vaccines would be used against vvMDV. In addition, the applicant provided public data evidencing high variability in outcomes of (identical) MDV vaccination-challenge studies. Considering the protection achieved against vvMDV in MDA+ birds using other authorised vaccines based on the same HVT backbone (Innovax range) as well as the indicated high variability observed in vaccination-challenge studies for MDV, it can be accepted that protection against (vv)MDV in MDA+ birds is adequately supported by the data.

Infectious bursal disease

Vaccinated eggs were taken from the field study S20205-00 in order to test the protection against infectious bursal disease in birds with MDA: two challenge studies were performed with birds derived from these eggs. In addition, one challenge study was performed using birds vaccinated at day of age, taken from the field study S20206-00. The challenge studies were appropriately designed following the Ph. Eur. 0587 (Avian infectious bursal disease vaccine (live)) immunogenicity

test. The control birds did not show clinical signs and the severity of bursal lesions was not in accordance with the monograph requirement, however this can be considered acceptable since the studies were performed in MDA+ birds. IBD prevalence in the controls was 50%, 100% and 100% respectively in the three studies, while protection was 100%, 75% and 55%. The low prevalence in the controls corresponded with high protection in the vaccinates, suggestive of a lower virulence of the challenge in the first study (challenge at week 5, *in ovo* vaccinated birds). The protection observed in the three studies was statistically significant. Since only 55% protection was found against IBD after s.c. vaccination and challenge at 5 weeks, it cannot be excluded that there is some impact of MDA on the onset of immunity against IBD. The applicant therefore proposed a warning sentence that onset of immunity against IBD may be delayed in MDA+ birds.

Infectious laryngotracheitis

A challenge study to investigate the protection against ILT in MDA+ birds was performed with birds taken from the field study S20206-00. Day-old commercial chickens were vaccinated by the subcutaneous route with Innovax-ILT-IBD vaccine mixed with Nobilis Rismavac. Vaccinated and control chickens from the same hatch were transported to the laboratory. The challenge was performed at 5 weeks after vaccination which is one week after the claimed OOI, this is considered acceptable. The relative protection observed against ILT was 80% which is considered clinically relevant. Moreover, the difference between control and vaccinated groups was statistically significant. The result supports the reduction of mortality, clinical signs and lesions of ILT in MDA+ birds.

Interactions

Efficacy after associated non-mixed use of Innovax-ILT-IBD with Nobilis ND C2, Nobilis ND Clone 30, Nobilis IB Ma5 and Nobilis IB 4-91 was investigated in a number of studies, addressing the different pathogens involved.

Marek's disease

The onset of immunity against MD is based on the replication of the vaccine strain in the vaccinated bird. For HVT based vaccines, viraemia can be used as an indicator for virus replication and, subsequently, protection. This approach was previously accepted in support of absence of interactions for other vaccines of the Innovax range. Spleens were harvested at 6 days post vaccination to evaluate viraemia after associated non-mixed use of Innovax-ILT-IBD with ND and IB vaccines which is considered relevant for the OOI of 5 days of age. Groups were vaccinated with a standard dose of Innovax-ILT-IBD s.c., either alone or concurrently with Nobilis ND C2 (oculo/nasal route - oc.), Nobilis ND Clone 30 (oc.), Nobilis IB Ma5 (oc.) or Nobilis IB 4-91 (oc.) respectively. The average virus titre in the groups was highly similar. It can be concluded that there is no indication of interference.

Infectious bursal disease

One controlled, randomised, challenge study was performed to investigate the protection against IBD after associated use of Innovax-ILT-IBD with Nobilis ND and IB vaccines. Day-old SPF chicks were vaccinated with a standard dose concurrently with Nobilis ND C2 (oc.), Nobilis ND Clone 30 (oc.), Nobilis IB Ma5 (oc.) or Nobilis IB 4-91 (oc.) respectively. All birds were challenged at 3 weeks post vaccination with vvIBDV CS89. The requirements of Ph. Eur. 0587 (Avian infectious bursal disease vaccine (live)) were met, 9 out of 10 control birds died after challenge, protection was 100% in all vaccinated groups. It can be concluded that no interference on protection against IBDV occurred.

Infectious laryngotracheitis

As there was no change in the onset of immunity for the IBD (3 weeks) and MD components (5 days) following the associated use with the IB and ND vaccines, it is unlikely that the associated use of the ND and IB vaccines will have any effect on the 4 weeks onset of immunity for the ILT component. In addition, it was demonstrated that the associated use of ND and IB vaccines has no interference on efficacy of the previously licenced vaccines from the Innovax vaccine range including Innovax ILT, Innovax-ND-IBD, Innovax-ND-ILT. Therefore, in line with the 3Rs principle, no additional efficacy study was performed for the ILT component with the associated use with the ND and IBD vaccines. This approach is accepted, in particular since the vaccine was shown to replicate at a similar rate after associated use with ND and IB vaccines.

Infectious bronchitis

One controlled, randomised, challenge study was performed, in accordance with Ph. Eur. 0442 (Avian infectious bronchitis vaccine (live)), to investigate the protection against IB after associated use of Innovax-ILT-IBD with Nobilis IB vaccines. Day-old SPF chicks were vaccinated with a standard dose of Innovax-ILT-IBD (s.c.) concurrently with a standard dose of Nobilis IB Ma5 (oc.) or Nobilis IB 4-91 (oc.). Birds were challenged at 3 weeks post vaccination with IBV M41 or IBV 4-91. The test was valid since for both challenges 100% of control birds showed cessation or extreme loss of vigour of ciliary activity. Protection achieved was 85% and 100% which meets the criterion (≥80%) of Ph. Eur. 0442 for immunogenicity. It can therefore be concluded that no significant interference occurred.

Newcastle disease

One controlled, randomised, challenge study was performed, in accordance with Ph. Eur. 0450 (Newcastle disease vaccine (live)), to investigate the protection against ND after associated use of Innovax-ILT-IBD with Nobilis ND vaccines. Day-old SPF chicks were vaccinated with a standard dose of Innovax-ILT-IBD (s.c.) concurrently with a standard dose of Nobilis ND C2 (oc.) or Nobilis ND Clone 30 (oc.). Birds were challenged at 3 weeks post vaccination with NDV Herts 33/56. All control chickens died or were euthanised due to severe clinical signs. The level of protection in both vaccinated groups met the requirement of at least 90% protection. It can be concluded that there is no interference on NDV efficacy when either Nobilis Clone 30 or Nobilis C2 is administered on the same day as Innovax ILT-IBD.

The challenge at 3 weeks does not cover the registered 2 weeks OOI for Nobilis ND C2. The applicant therefore included a warning sentence stating that after associated use, OOI for ND and IB was demonstrated at 3 weeks.

Field trials

Two combined safety and efficacy clinical trials, in which birds were vaccinated either via the *in ovo* or the subcutaneous route, were performed in the Netherlands. Safety and performance parameters were assessed, as well as efficacy against MDV, IBDV and ILTV by way of laboratory challenges.

The study design and results (safety- and performance parameters) of both studies is described in the safety section of this report.

Efficacy data were obtained from laboratory challenge studies using birds derived from both field studies. The results of those studies are summarised in this report in the section on the influence of maternally derived antibodies on the efficacy of the vaccine. Briefly, the following results were reported:

MDV challenge one week after *in ovo* vaccination: Innovax-ILT-IBD 53% RPP, Innovax-ILT-IBD + Nobilis Rismavac 66% RPP.

IBDV challenge 5 weeks of age after *in ovo* vaccination: Innovax-ILT-IBD + Nobilis Rismavac 100% protection (prevalence 50% in controls). Challenge 7 weeks of age after *in ovo* vaccination: Innovax-ILT-IBD + Nobilis Rismavac 75% protection (prevalence 100% in controls).
IBDV challenge 5 weeks of age after s.c. vaccination: Innovax-ILT-IBD + Nobilis Rismavac 55% protection (prevalence 100% in controls).

ILTV challenge 5 weeks of age after s.c. vaccination: Innovax-ILT-IBD + Nobilis Rismavac 80% protection (prevalence 67% in controls).

The results of the field studies do not contradict results of the laboratory studies. The relatively low protection percentage for MDV is likely a consequence of the use of a very virulent challenge strain and the known high variability in outcome of MDV challenge studies. Based on the totality of data, including those from other vaccines based on the same HVT backbone (Innovax range), adequate protection in MDA+ birds is considered sufficiently supported. Since it cannot be excluded that some delay in the onset of immunity to IBD occurs in MDA+ birds, a warning sentence to this extent is included in the SPC.

Overall conclusion on efficacy

In total, 15 laboratory studies and two field studies were performed to evaluate efficacy. The laboratory efficacy studies were performed in accordance with the immunogenicity tests described in the following monographs: Ph. Eur. 0589 (Marek's disease vaccine (live)), Ph. Eur. 0587 (Avian infectious bursal disease vaccine (live)), Ph. Eur. 1068 (Infectious laryngotracheitis vaccine (live)), Ph. Eur. 0450 (Newcastle disease vaccine (live)) and Ph. Eur. 0442 (Avian infectious bronchitis vaccine (live)). Onset and duration of immunity studies in SPF chickens were done using vaccine batches at or below the minimum dose stated on the label. The influence of MDA was investigated using birds derived from the field studies and therefore vaccinated with standard doses.

Onset of immunity

Reduction of mortality, clinical signs and lesions caused by Marek's disease virus was demonstrated in accordance with Ph. Eur. requirements after *in ovo* vaccination of 18-day-old embryonated SPF eggs as well as after subcutaneous vaccination of day-old SPF chicks with an onset of immunity of 5 days of age.

Onset of immunity against infectious bursal disease was established in accordance with Ph. Eur. requirements, at 3 weeks of age, after vaccination of 18-day embryonated SPF eggs or day-old SPF chicks.

The study for onset of protection against infectious laryngotracheitis was performed in accordance with Ph. Eur. requirements. The vaccination of embryonated eggs or day-old birds resulted in protection after challenge at 4 weeks of age. A prevention of mortality and lesions and a reduction in clinical signs were achieved.

Duration of immunity

Protection against MD is considered to last for the entire risk period.

Duration of immunity against IBDV was demonstrated by challenge at 11 weeks post vaccination (Innovax-ILT-IBD mixed with Nobilis Rismavac). Serological data have been provided for up to 100 weeks post vaccination, indicating a high percentage of seropositivity up to this time. The applicant has provided justification for a relation between seropositivity and protection against IBDV. Together the data are considered appropriate to support the claimed DOI of 100 weeks.

Duration of immunity against ILTV was demonstrated by challenge at 100 weeks post vaccination (Innovax-ILT-IBD mixed with Nobilis Rismavac). The claimed 100 weeks duration of immunity is considered sufficiently supported by data.

Influence of MDA

The influence of maternal antibodies on the efficacy of the vaccine was studied using commercial broiler chicks with confirmed levels of MDA against MDV, IBD and ILT. These animals were taken from the field studies.

The protection against vvMDV was 53% in the birds vaccinated with Innovax-ILT-IBD and 66% in the birds vaccinated with Innovax-ILT-IBD mixed with Nobilis Rismavac. Taking into consideration the vvMDV challenge, the results obtained in MDA+ birds vaccinated with other vaccines based on the same HVT backbone (Innovax range) and the known high variability of MDV challenge study outcomes, the totality of data is considered to sufficiently support efficacy in MDA+ birds.

The protection against IBDV of birds vaccinated with Innovax-ILT-IBD mixed with Nobilis Rismavac at day of age was 55% after challenge at 5 weeks of age with vvIBDV while 100% of controls were affected. After *in ovo* vaccination challenges were performed at 5 and 7 weeks of age with vvIBDV. At 5 weeks a protection of 100% was found while prevalence in controls was 50%, at 7 weeks a protection of 75% was found with 100% prevalence in the controls. Based on the results of these challenge studies as well as the serological data, a delay in the onset of immunity to IBD in MDA+ birds cannot be excluded. A warning sentence to this extent is included in the SPC.

The protection against ILTV was studied in MDA+ birds vaccinated s.c. with a standard dose of Innovax-ILT-IBD mixed with Nobilis Rismavac. After challenge at 5 weeks of age, 80% protection was found which is considered adequate.

Studies on Interactions

The possible interactions between Innovax-ILT-IBD with Nobilis Rismavac were investigated in four studies:

- The onset of immunity against MDV was investigated after associated mixed use of Innovax-ILT-IBD and Nobilis Rismavac in day-old birds and 18-day embryonated eggs. The onset of immunity was confirmed at 4 days by challenge with vvMDV.
- The onset of immunity against IBDV was investigated after mixed application of both vaccines in day-old birds and embryonated eggs. The challenge was performed at 3 weeks of age using IBDV CS89 strain. The onset of immunity was confirmed at 3 weeks of age.
- The protection against ILTV after mixed use was studied in chicks vaccinated *in ovo* or at day-old. The onset of immunity at 4 weeks of age was confirmed in both groups.

In all of these studies, a dose below the minimum one of both vaccines was applied. It can be concluded that no significant interference occurs with respect to immunity against MD, IBD or ILT when Innovax-ILT-IBD is used mixed with Nobilis Rismavac.

The possible interactions with ND or IB vaccines manufactured by the applicant when applied on the same day but via different administration routes was investigated in four studies.

The concurrent use with Nobilis ND C2, Nobilis Clone 30, Nobilis IB Ma5 or Nobilis IB 4-91 showed not to affect the viraemia of the Innovax-ILT-IBD vaccine. The viraemia, determined at 6 days post vaccination, is considered an adequate correlate of protection against MDV and thus it can be concluded that there is no significant interference on protection against MDV after these associated non-mixed uses.

The onset of immunity against IBDV was confirmed at 3 weeks of age after vaccination of day-old SPF birds with Innovax-ILT-IBD and Nobilis ND C2 or Nobilis Clone 30 or Nobilis IB Ma5 or Nobilis IB 4-91.

The possible interference of concurrent use of IB or ND vaccines on efficacy against ILT was not investigated. The applicant justification is that if no interference can be observed for MDV or IBDV, no interference for protection against ILTV is expected. This conclusion is supported.

The onset of immunity (3 weeks) against NDV after associated use of Innovax-ILT-IBD with the ND vaccines was confirmed.

The onset of immunity against IB was supported by the data presented on associated use of Innovax-ILT-IBD with Nobilis IB Ma5 and Nobilis IB 4-91.

Since the challenge at 3 weeks does not cover the authorised 2 weeks OOI of Nobilis ND C2, the applicant has included a statement in the SPC that onset of immunity to ND and IB after associated use was confirmed at 3 weeks.

The omission of studies on the DOI after concurrent use are considered justified since there was no indication of interference on development of immunity against MD, IBD, ND or IB.

Clinical trials

Two combined safety and efficacy field studies were performed. The results concerning general health and production parameters are discussed in Part 3. Vaccinated and control birds were taken from the field study and challenged in the laboratory with MDV, IBDV and ILTV. These birds were shown to be MDA+ for MD, IBD and ILT. The results of the challenge studies are reported in the section addressing the influence of MDA on efficacy of the vaccine.

Part 5 – Benefit-risk assessment

Introduction

Innovax-ILT-IBD is a vaccine containing cell-associated live recombinant turkey herpesvirus (strain HVT/IBD/ILT), expressing the VP2 protein of infectious bursal disease virus and the glycoproteins gD and gI of infectious laryngotracheitis virus.

The product is intended for active immunisation of chickens against Marek's disease, infectious bursal disease and infectious laryngotracheitis. The product is to be applied once via subcutaneous route to day-old chicks or *in ovo* to 18-19-day-old embryonated chicken eggs. The proposed effective dose of $\geq 10^{3.2}$ and $\leq 10^{4.6}$ PFU has been confirmed.

The dossier was submitted in line with requirements of Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

The proposed benefit of Innovax-ILT-IBD is its efficacy in active immunisation of day-old chicks or 18-19-day-old embryonated chicken eggs:

- to reduce mortality, clinical signs and lesions caused by Marek's disease (MD) virus.

- to reduce mortality, clinical signs and lesions caused by avian infectious laryngotracheitis (ILT) virus
- to prevent mortality and to reduce clinical signs and lesions caused by infectious bursal disease (IBD) virus.

This benefit was shown in a number of appropriately designed and well executed laboratory studies. The clinical studies were performed but no field challenge occurred. However, birds taken from the field studies were challenged in the laboratory and the results generally confirm the results obtained in the purely laboratory studies.

The onset of immunity against MD was established at 5 days of age, for IBD at 3 weeks of age and for ILT at 4 weeks of age. No data are provided for the duration of immunity against MDV infection. This is considered acceptable since the HVT virus produces a persistent infection providing a lifelong immunity. The claimed 100 weeks duration of immunity against IBD and ILT is adequately supported by data.

The influence of maternally derived antibodies on the efficacy of the vaccine was investigated in well-designed laboratory studies, using birds derived from the field studies with confirmed MDA against MDV, IBDV and ILTV. Efficacy against MD and ILT was confirmed, the onset of immunity to IBD may be delayed in MDA+ birds and a warning is included in the SPC.

Innovax-ILT-IBD was shown to be efficacious against MD (with an onset of immunity at 4 days of age), IBD and ILT when used mixed with Nobilis Rismavac. The level of protection against IBD at OOI and DOI needs to be further justified for the mixed use with Nobilis Rismavac.

Innovax-ILT-IBD was shown to be efficacious in SPF chickens when administered with Nobilis ND C2 or Nobilis ND Clone 30 or Nobilis IB Ma5 or Nobilis IB 4-91 on the same day but by different routes. The onset of immunity against NDV and IB was confirmed at 3 weeks after associated use, this is specifically indicated in the SPC since it does not cover the authorised 2 weeks OOI for Nobilis ND C2. The omission of studies on DOI after concurrent use are considered justified since there was no indication of interference on development of immunity against MD, IBD, ND or IB.

Additional benefits

Innovax-ILT-IBD provides protection against three important poultry diseases. This limits the number of times the animals are required to be handled.

Innovax-ILT-IBD reduces the need for live attenuated IBD and ILT vaccinations. With this vaccine, long lasting immunity against IBD and ILT can be obtained by vaccination in the hatchery. Contrary to the use of live attenuated ILTV vaccines, there is no risk of establishment of latent ILTV carriers or reversion to virulence.

The vaccine strain was shown to be fully apathogenic to other avian species, limiting the risk to the environment.

Risk assessment

The main potential risks are identified as follows:

Quality:

The formulation and manufacture of Innovax-ILT-IBD is well described and specifications set will ensure that product of consistent quality will be produced provided that conditions are fulfilled.

Safety:

Risks for the target animal:

The product is generally well tolerated in the target animal. No adverse reactions were observed after a tenfold overdose of Innovax-ILT-IBD by the subcutaneous or *in ovo* route. The vaccine strain was obtained by insertion of genes into a naturally apathogenic vaccine strain, which is known to be safe for chickens. The biological properties (safety, dissemination, spread) of the original strain were not changed by the genetic modification, reversion to virulence could not be demonstrated. The chance of recombination with other strains or other viruses occurring is considered to be effectively zero.

Risk for the user:

The user safety for this product is acceptable when used as recommended. Appropriate risk mitigation measures are described in the SPC.

The vaccine is filled in glass ampoules and stored in liquid nitrogen. In exceptional cases ampoules may explode upon heating. Appropriate precautions and warnings for safe handling of the ampoules are included in the SPC.

Risk for the environment:

The vaccine virus is shed with feather dust and can remain infectious in the environment for prolonged periods. Spread to chickens or turkeys was not observed but cannot be excluded. HVT in general can infect avian species only, the related vaccine strain Innovax-ILT was shown to be unable to infect mice. Appropriate measures mitigating the risk of spread of the vaccine strain to turkeys are included in the SPC.

Risk for the consumer:

A residue study is not required. 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 and environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious to reduce mortality, clinical signs and lesions caused by avian infectious laryngotracheitis virus and Marek's disease virus and to prevent mortality and to reduce clinical signs and lesions caused by infectious bursal disease virus. The onset and duration of immunity for MD, IBD and ILT are adequately supported by data.

The influence of maternal antibodies on the efficacy of the vaccine against MDV was studied using commercial broiler chicks with confirmed levels of MDA against MDV, IBDV and ILTV. The level of protection observed against MDV and ILTV is considered adequate while an appropriate warning for a possible delay in OOI for IBDV in the presence of MDA is included in the SPC.

The vaccine can be used mixed with Nobilis Rismavac. OOI against MD was confirmed at 4 days of age, protection against ILT was adequately confirmed at 5 weeks of age while the level of protection against IBD at 5 and 7 weeks of age appears to be inconsistent and needs further justification. The

vaccine can be used on the same day but via different routes with Nobilis ND C2, Nobilis ND Clone 30, Nobilis IB Ma5 or Nobilis IB 4-91. No significant interference was observed with respect to immunity against MD, IBD, ND or IB, while absence of interference for ILT is considered justified.

The formulation and manufacture of Innovax-ILT-IBD is well described and specifications set will ensure that product of consistent quality will be produced.

The product 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. A withdrawal period is not required.

Based on the data presented, the overall benefit-risk is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for Innovax-ILT-IBD is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.