18 April 2024
EMA/220252/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Innovax-ND-H5 (EMEA/V/C/006362/0000)

Vaccine common name: Newcastle disease, avian influenza 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 21 December 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Innovax-ND-H5, through the centralised procedure under Article 42(2)a of Regulation (EU) 2019/6 (**mandatory scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 7 September 2023 as Innovax-ND-H5 has been developed by means of a biotechnological process, i.e. using controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells (Article 42(2)(a)(ii)).

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

For active immunisation of one-day-old chicks or 18–19 day-old embryonated chicken eggs:

- to reduce mortality and clinical signs caused by avian influenza of the H5 subtype, clade 2.2.1
- to reduce viral transmission, replication and shedding after infection with avian influenza of the H5 subtype, clade 2.2.1.

Cross-protection has been established against avian influenza of the H5 subtype, clades 2.3.2.1c, 2.3.4.4 and 2.3.4.4b.

Onset of immunity: 2 weeks

Duration of immunity: 12 weeks

Considering the data provided, the claim suggested by the applicant has been modified as follows:

For active immunisation of one-day-old chicks or 18–19 day-old embryonated chicken eggs to reduce mortality, clinical signs and virus excretion due to infection with highly pathogenic Avian Influenza (HPAI) virus of the H5 type.

Onset of immunity: 2 weeks

Duration of immunity: 12 weeks (reduction of mortality and clinical signs demonstrated with *in ovo* administration)

Additionally, a comment in section 4.1 has been included as follows:

"Challenge strain of the circulating clade 2.3.4.4.b has been used in the efficacy studies."

The vaccine active substance is a cell-associated, live, recombinant turkey herpesvirus (HVT) expressing the F protein of Newcastle disease virus (NDV) and the haemagglutinin antigen of avian influenza virus (AIV) of the H5 subtype (HVT/ND/H5).

The Innovax-ND-H5 vaccine is a live vaccine designed for the immunisation of avian influenza (H5). The vaccine also induces active immunity against Marek's disease and Newcastle disease.

The products consist of two separate containers: one is a glass ampoule containing the vaccine in a deep-frozen state, with 2000 or 4000 doses, while the other is a multilayer plastic bag containing the solvent, with varying volumes of 400, 800, 1200, or 1600 ml per bag. Prior to vaccination, the content of the glass ampoule must be thawed, withdrawn with a syringe and reconstituted with the solvent by injecting it in the plastic bag. The resulting mixture is then administered via subcutaneous injection at a dosage of 0.2 ml per bird or via *in ovo* injection 0.05 ml per embryonated egg.

The target species are chickens and embryonated chicken eggs.

The rapporteur appointed is Cristina Muñoz Madero and the co-rapporteur is Manuela Leitner.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances. This legal basis was agreed due to the current epidemiological situation of avian influenza in Europe. Because of this legal base, the assessment of Innovax-ND-H5 will be focused on the AI claim only.

For the assessment of this procedure, an accelerated timetable was applied for by the applicant and agreed by the CVMP. In fact, the benefit of the immediate availability on the market of a veterinary medicinal product against HPAI virus strain H5, the one currently circulating in the European Union (EU), was recognised by the CVMP.

The assessment of Innovax-ND-H5 will be carried according to Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council, and applicable guidelines, mainly Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021).

On 18 April 2024, the CVMP adopted an opinion and CVMP assessment report.

On 22 May 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Innovax-ND-H5.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF), has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

The vaccine is manufactured at the Intervet International site in de Bilt, the Netherlands.

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

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

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.

The GMP status of the active substance and of the finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Quality documentation (physico-chemical, biological, and microbiological information)

More detailed information on several aspects of the quality part would normally be required for an application under Art. 8 of Regulation (EU) 2019/6. However, these data gaps were considered acceptable under an Art. 25 marketing authorisation procedure and, considering the exceptional circumstances, the data provided were considered sufficient to conclude on the benefit risk balance of the product. Some specific obligations to supplement the data presented in Part 2 were identified.

Qualitative and quantitative composition

The finished product is presented as concentrate and solvent for suspension for injection containing cell-associated live recombinant turkey herpesvirus (strain HVT-ND-H5), expressing the fusion protein of Newcastle disease (ND) virus and the haemagglutinin antigen of avian influenza virus (AIV), H5 subtypes as active substance at potency/titre $10^{3.3}$ – $10^{4.6}$ plaque forming units (PFU) per dose.

The product contains no adjuvants.

Other ingredients are: bovine serum, veggie medium and dimethyl sulfoxide (DMSO).

The solvent contains sucrose, sodium chloride, disodium hydrogen phosphate dihydrate, phenolsulfonphthalein (phenol red), potassium dihydrogen phosphate and water for injections.

Prior to vaccination, the content of the vaccine ampoules combined with the solvent and the resulting mixture is administered via subcutaneous injection at a dosage of 0.2 ml per bird or via *in ovo* route at a dosage of 0.05 ml per embryonated egg.

The applicant provided the qualitative and quantitative composition per dose or per ml of the vaccine in the dossier.

Container and closure system

The product is available in a type I glass ampoule of 2 ml containing 2000 or 4000 doses (2000 doses: salmon-pink coloured clip, and 4000 doses: yellow coloured clip) combined with 400-, 800-, 1200- or 1600-ml solvent multilayer plastic bags. After filling, the ampoule is sealed by hot air welding.

The bags are overwrapped and terminally sterilised by autoclaving. The solvent is filled in 400, 800, 1200 and 1600 ml multilayer plastic (MLP) bags. Presentations with a nominal filling volume of 200, 400, 500, 600, 800, 1000, 1200 and 1600 ml are generally available for this solvent. However, this is because the same solvent is used for other Innovax range products. For Innovax-ND-H5, as indicated on the PI, only the 400, 800, 1200 and 1600 mL presentations are used.

The pack sizes are consistent with the vaccination schedule and intended use.

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 its quality.

Product development

An explanation and justification for the composition and presentation of the vaccine has been provided.

Innovax-ND-H5 is based on the naturally apathogenic HVT FC-126 strain (parent) vector.

The backbone carrier of all Innovax vaccines range consists of recombinant HVT FC-126 virus with the insertion of, so far, one or more of the following genes: VP2 gene of infectious bursal disease virus (IBDV), gD and gI genes of infectious laryngotracheitis virus (ILTV), F gene of Newcastle disease virus (NDV). This backbone is now used to express also the H5 protein of avian influenza. The hemagglutinin protein (H5) of avian influenza virus (AIV), subtype H5N2, is a primary target for vaccine development due to its critical role in the life cycle of the virus.

Hemagglutinins are responsible for the binding of the virus to the cell receptors of the host, a pivotal step in the initiation of infection.

Prior to injection, the vaccines are mixed with the solvent.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

Description of the manufacturing method

Chicken embryo fibroblasts (CEFs) are inoculated with the 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.

The process is considered to be a standard manufacturing process.

The major steps of the manufacturing process have been validated by three consecutive pilot batches and one further commercial batch of the finished product in addition to three batches of solvent for cell-associated poultry vaccines (200, 400 and 1600 ml). It has been demonstrated that the manufacturing process is capable of producing a finished product of intended quality in a reproducible and consistent manner.

Based on the provided batch data for Innovax-ND-H5, further clarification on the rather broad manufacturing scale of the batches in the range of 2 to 110 L would generally be required. Considering the data from already authorised Innovax vaccines, this data gap is acceptable under an Art. 25 marketing authorisation.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Certificates of analysis have been provided for the following starting materials used in the manufacturing of the vaccine: chicken flocks free from specified pathogens, specific pathogen free (SPF) eggs, bovine serum, DMSO. Certificates of analysis have been provided for the following starting materials used in the manufacturing of the solvent: sucrose, potassium dihydrogen

phosphate, phenolsulfonphthalein, sodium chloride and disodium hydrogen phosphate dihydrate and all conform to Ph. Eur. specifications.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

Live Turkey Herpes Virus strain HVT-ND-H5

A Turkey Herpesvirus vaccine strain (HVT FC-126) was genetically modified by insertion of the NDV F gene, the AIV H5 gene and regulatory sequences, to generate HVT-ND-H5. The HVT-ND-H5 virus was multiplied on CEF cells, plaque purifications were performed, expression of NDV F and AIV H5 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 frozen in liquid nitrogen. The MSV was controlled for identification, bacterial and fungal contamination, mycoplasma, absence of extraneous agents and titration.

The working seed virus (WSV) is prepared as described for the finished product. The WSV is tested for sterility and absence of mycoplasma in accordance with relevant Ph. Eur. monographs.

CEF cells

Primary CEF cells are used for the production of the vaccine. The CEFs can either be obtained from external suppliers or are prepared in-house from embryonated chicken eggs. Two examples of certificates of analysis from two different suppliers are attached for CEF cells as well as for the embryonated chicken eggs. Nevertheless, the following information is missing:

- The applicant should indicate whether the full set of extraneous agents testing is performed for all CEF cells. The list of extraneous agents tested by one of the supplier does not mention testing for Altadenovirus (Avian Adenovirus Serogroup 3), which is required according to Ph. Eur. 5.2.2. However, in the document "Extraneous agents risk assessment in the final product," the applicant states that the SPF eggs are tested for Altadenovirus. In the CoA from another supplier, no details regarding extraneous agents testing are mentioned. Therefore, the applicant is requested to clearly indicate whether the same extraneous agents testing procedures are performed irrespective of the source of embryonated SPF eggs or CEF cells.
- The applicant should confirm that all bovine sera and trypsin used for cell cultivation in all sites are appropriately tested for extraneous agents.
- It should be confirmed explained whether the extraneous agents testing programs for all eggs/CEF cells from all possible suppliers are in line with the requirements of Ph. Eur. 5.2.2.
- The applicant is asked to further elaborate how absence of Chlamydia spp. In the CEF preparations is guaranteed.

With the data provided, it is possible to conclude on the benefit/risk of the vaccine to be used under exceptional circumstances. However, this information is considered necessary to confirm the conclusion and should be provided as a specific obligation, which the applicant will need to fulfil by July 2024.

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.

The following media are purchased or prepared in-house: veggie medium, growth medium and veggie protease/EDTA working solution.

Certificate of analysis of the veggie medium and the veggie protease/EDTA working solution are provided.

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.

Control tests on the finished product

The finished product is tested for identity, potency, sterility and absence of mycoplasmas.

The sterility and absence of mycoplasmas tests are in line with Ph. Eur. 2.6.1, 0062 and 2.6.7. These tests are considered generally suitable and specifications are provided. No tests for appearance are proposed since the finished product is stored in liquid nitrogen.

Testing for excipients, adjuvants, residual humidity, inactivation and filling volume are not applicable for this product.

The titration and identity tests are performed according to Ph. Eur. 0589. The tests are not currently validated and this is acceptable in an exceptional circumstances context. With the data provided, it is possible to conclude on the fitness for purpose of the test. However, additional details concerning the monoclonal antibodies used for identity and potency testing, as well as for the internal standard, should be provided to confirm this conclusion.

Specifically, the following information should be provided:

- Monoclonal mouse-antibodies for AIV-H5 and NDV-F respectively are used for the immunofluorescence staining. A precise description and protocol for the preparation of the monoclonal antibodies is lacking (AIV-H5 MoAb and NDV-F MoAb).
- Potency: An internal reference standard is used as positive control in the potency test. More detailed information should be provided from which batch the internal standard originates and how it was qualified. It should be also detailed how the titre specifications were established.

This is considered as a specific obligation that the applicant will need to fulfil by July 2024.

Batch-to-batch consistency

The applicant presented data from three consecutive pilot or R&D batches and one further

commercial batch of the finished product. During the manufacture of the finished product, the CPE before harvest, cell count, and filling volume test are carried out. Test descriptions and the limits of acceptance for in-process controls were presented. The in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing. The results of the in-process tests fulfil the established requirements.

The finished product was tested for identity, virus titre, sterility and mycoplasmas. The proposed tests and limits of acceptance are generally considered adequate to ensure the quality of the finished product upon release. The relevant tests for finished product are satisfactorily validated, except for the titration and identity tests. The results of the finished product tests fulfil the established requirements, however, additional details related to the tests of H5 protein identity and batch titre/potency need to be provided as a specific obligation.

Three batches of solvent for cell-associated poultry vaccines were filled in multilayer plastic bags at 200, 400 and 1600ml and tested for appearance, clarity, pH, sucrose contain and identity, potassium, phosphate, phenolsulfonphtalein, sterility and content on average. The tests performed on the solvent are considered suitable to control the quality. Appropriate limits have been set for each of these tests.

Stability

Stability of the finished product

A shelf life of 36 months under liquid nitrogen storage conditions is proposed for Innovax-ND-H5. The applicant has presented real time stability data up to 9 months for three pilot batches of an on-going study, and data up to 66 months for one further R&D batch. The batches of Innovax-ND-H5 are identical to those proposed for marketing and were packed in the primary packaging proposed in the dossier. The vaccine titre (PFU/vial) was used as an indicator of product stability of the vaccine. Additionally, supporting data up to 39-40 months of the authorised Innovax-ILT, Innovax-ND-IBD, Innovax-ND-ILT and Innovax-ILT-IBD vaccines are presented.

Innovax-ND-H5 is considered to be stable for 36 months when stored at ≤ -140°C in liquid nitrogen. As confirmation, final data from the 39-months on-going stability study should be provided.

This is considered a specific obligation that the applicant will need to fulfil by June 2026.

In-use shelf life

An in-use shelf life of two hours is proposed for the product diluted in solvent for cell associated poultry vaccines. Mixing Innovax-ND-H5 with Nobilis Rismavac does not affect the in-use stability of the vaccine.

Stability of the solvent

The applicant proposes a shelf life of 36 months at ≤ 30°C for the solvent in 400-, 800-, 1200- and 1600-ml multilayer plastic bags. In an ongoing 36-month study, the sucrose content, sucrose identity, pH, clarity, appearance and sterility parameters are studied for 8 batches stored at 30°C. Data at 3, 6, 12 and 18 months are presented for the batches of 200 ml, 400 ml, 800 ml (2x) and 1000 ml, and only up to 12 months for the three batches of 1600 ml. At the timepoints tested, the parameters remain within the limits.

In a 40°C study, the same parameters and additional ones (potassium, phosphate, phenolsulfonphtalein and sterility) were tested for the same batches at 1, 3 and 6 months. The results show that the parameters remain within the limits over time.

The study is still ongoing for bigger presentations; nevertheless, the solvent stability of 3 years is considered acceptable considering the existing experience with the same solvent, which is used for many other vaccines from the Innovax range.

Absence of virucidal effect solvent for cell-associated poultry vaccines

Data from other Innovax and Nobilis vaccines are presented to demonstrate the absence of the virucidal effect of the solvent for cell-associated poultry vaccines. Results from different batches demonstrated that the solvent has no virucidal effect after 2-hour storage at 15-25ºC.

New active substance (NAS) status

The applicant requests for consideration of the active substance cell-associated live recombinant turkey herpesvirus (strain HVT-ND-H5), expressing the fusion protein of Newcastle disease virus and the haemagglutinin antigen of avian influenza virus (AIV) of the H5 subtypes, contained in the medicinal product Innovax-ND-H5 as a new active substance, mainly due to the new H5 of AIV insert.

In comparison to the known active substances from previously authorised vaccines in the European Union against AI, Nobilis Influenza H5N2 and Newflend ND H9, the vaccine Innovax-ND-H5 differs significantly in the composition of the active substance:

- In Nobilis Influenza H5N2: Inactivated whole avian influenza virus antigen of H5N2 subtype (strain A/duck/Potsdam/1402/86).
- In Newflend ND H9, the active substance is a recombinant turkey herpes virus, strain rHVT/ND/H9 expressing the fusion protein of Newcastle disease virus and H9 protein of avian influenza).

Innovax-ND-H5 also differs significantly in properties with regard to safety and efficacy from the above-mentioned substance already authorised in the EU.

Overall conclusions on quality

More detailed information on several aspects of the quality part would normally be required for an application under Art. 8 of Regulation (EU) 2019/6. However, these data gap were considered acceptable under an Art. 25 marketing authorisation procedure and, considering the exceptional circumstances, the data provided were considered sufficient to conclude on the benefit risk balance of the product. Some specific obligations to supplement the data presented in Part 2 were identified.

Innovax-ND-H5 is a live recombinant vaccine for active immunisation in chickens against avian influenza (H5). The vaccine is available in ampoules containing 2000 or 4000 doses and, before use, it is diluted in a solvent supplied containing 400, 800, 1200 or 1600 ml per container.

One dose of vaccine contains between $10^{3.3}$ and $10^{4.6}$ PFU of virus strain HVT-ND-H5 as active ingredient. The virus is grown on chicken embryo fibroblasts (CEF) derived from SPF chicken flocks. The cells containing the virus are harvested and combined with bovine serum and cryoprotectant (DMSO) to allow storage in liquid nitrogen. The manufacturing method can be considered as standard for this type of vaccine. Some gaps have been identified; however, these are considered data gaps acceptable under an Art. 25 authorisation.

Some measures, which are considered sufficient under an Art. 25, have been implemented to ensure the absence of extraneous agents in starting materials of animal origin. Nevertheless, additional information has been requested to confirm the control strategy of extraneous agents for CEF cells. Although a conclusion can be reached on the suitability of the testing, the following

information should be provided as a specific obligation that the applicant will need to fulfil by July 2024:

- The applicant should indicate whether the full set of extraneous agents testing is performed for all CEF cells. The list of extraneous agents tested by the supplier does not mention testing for Atadenovirus (Avian Adenovirus Serogroup 3), which is required according to Ph. Eur. 5.2.2. However, in the document "Extraneous agents risk assessment in the final product," the applicant states that the SPF eggs are tested for Atadenovirus. In the CoA from the supplier, no details regarding extraneous agents testing are mentioned. Therefore, the applicant is requested to clearly indicate whether the same extraneous agents testing procedures are performed irrespective of the source of embryonated SPF eggs or CEF cells.
- The applicant should confirm that all bovine sera and trypsin used for cell cultivation in all sites are appropriately tested for extraneous agents.
- It should be confirmed explained whether the extraneous agents testing programs for all eggs/CEF cells from all possible suppliers are in line with the requirements of Ph. Eur. 5.2.2.
- The applicant is asked to further elaborate how absence of Chlamydia spp. In the CEF preparations is guaranteed.

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.

Control tests performed during the manufacturing process are CPE before harvest, cell count and filling volume. The in-process tests are deemed to be adequate to control all the critical steps in the manufacturing.

Finished product control tests have generally been adequately described.

The combined identity/titration test is acceptable and considered "fit for purpose" as indicated in the guideline for the authorisation of IVMP under exceptional circumstances. However, details on the antibodies used for identification are missing, together with the corresponding specification. Detailed information about the internal reference standard (how it is originated or qualified) is missing. Overall, the data provided are sufficient to reach a conclusion on the fitness for purpose of the test. Despite of that, the missing information should be provided as a specific obligation that the applicant will need to fulfil by July 2024.

The control tests performed on the solvent are deemed adequate to control the quality.

The consistency of the manufacturing process is based on three R&D batches and one industrial batch. Established specifications were fulfilled, showing the consistency of the manufacturing for these batches. The consistency of the manufacturing for the solvent is demonstrated.

Data on stability for Innovax-ND-H5 and other authorised Innovax vaccines have been provided. Based on the available data, and according to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021), the stability is accepted as 3 years. As only partial stability data have been submitted in the dossier, the applicant should provide, as a specific obligation, confirmation results of real time stability studies for the vaccine, up to 39 months. This specific obligation will need to be fulfilled by June 2026.

The proposed 2-hour in-use shelf life is considered supported.

The use of Innovax-ND-H5 when mixed with Nobilis Rismavac is accepted.

The proposed 36-month shelf life of the solvent is considered acceptable.

Part 3 – Safety documentation (safety and residues tests)

General requirements

The active substance of Innovax-ND-H5 is the cell-associated live recombinant turkey herpesvirus (strain FC-126), expressing the fusion protein of Newcastle disease virus (ND) and the haemagglutinin antigen of avian influenza virus (AIV), H5 subtype. The applicant has applied for classification as a new active substance not authorised for a veterinary medicinal product in the EU before.

There are no novel excipients used in the manufacturing of the vaccine and the construction of the recombinant turkey herpesvirus, strain FC-126 has been described in detail. The active substance is to be considered as a GMO and the special requirements for live vaccines and GMO vaccines have been addressed by the applicant using data from other Innovax vaccines.

The assessment is performed according to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021) with specific reduced data requirements for avian influenza vaccines. Guideline on live recombinant vector vaccines for veterinary use, (EMA/CVMP/IWP/390313/2023), is also taken into account.

In principle, the use of the safety studies performed with other Innovax vaccines manufactured as Innovax-ND-H5 can be considered acceptable for some aspects of the safety assessment. This approach is acceptable under an Article 25 marketing authorisation procedure.

Safety documentation

Belonging to the same applicant, several vaccines using the same backbone carrier are already authorised. According to the Guideline on data requirements for authorisation in exceptional circumstances (EMA/CVMP/IWP/251947/2021), data from similar/comparable IVMPs, which are already authorised, may be acceptable in some cases. Moreover, for IVMPs containing a GMO, it is acceptable for an applicant to submit data which have been generated for similar GMP construct already authorised to fulfil part of the requirements for safety.

According to the specific reduced data requirements for vaccines against avian influenza (Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances – Table 2), for live recombinant vaccines, the safety of the administration of an overdose to birds of the minimum age recommended for vaccination should be demonstrated. This study has been carried out and is assessed below.

According to the same Guideline, the studies for the examination of reproductive performance may be omitted and data from similar vaccines can be used as supportive data. The absence of impact on the reproductive performance of the parent strain has been justified by the applicant based on the scientific literature and the experience with other licensed vaccines containing the same HVT parent strain.

The spread of the vaccine strain is demonstrated with several studies carried out with the parent strain HVT FC-126 (but different inserts) and turkeys (as natural host of HVT) were also

investigated. For the study of dissemination in the vaccinated animal, the applicant provides results of different studies with vaccines manufactured as Innovax-ND-H5.

The specific Ph. Eur. monograph 0589 (Marek's disease vaccine, live) is applicable to this product since the live vector of the vaccine is the HVT (Turkey's herpesvirus). The Ph. Eur. General Chapter 5.2.6 has been also taken into account.

The overdose safety study is described below.

The vaccine was administered by the subcutaneous and *in ovo* route, as recommended. The preclinical study was reported not to be GLP compliant but this is acceptable according to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021). The safety of a maximum dose of Innovax-ND-H5 administered simultaneously with a maximum dose of a vaccine against Marek's disease was also studied. The study was carried out in one-day old chickens and in 18-days old embryonated SPF eggs, using a GMP batch.

The applicant also provided 10 combined safety and efficacy clinical trials with four vaccines based on the same backbone carrier. In line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021), clinical trials are not required. However, the results of these trials can be considered as supportive.

Pre-clinical studies

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.

Moreover, the specific reduced data requirements for vaccines against avian influence, according to Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances, require the study of the safety of one administration of an overdose. Such study is presented in the following section and is considered to cover the safety of the administration of one dose.

Safety of one administration of an overdose

One pivotal overdose pre-clinical study was provided. The study was not compliant with GLP standards. However, this is acceptable based on the above mentioned Guideline. An overdose which exceeds 10 times the recommended dose, was administered by the routes recommended, in the recommended species and categories. Animals were of the minimum age as required and divided in four groups. The batch used was produced and tested under GMP/GLP.

Group 1 consisted of 40 one-day-old chickens vaccinated by subcutaneous route and **group 2** consisted of 62 18-day old embryonated SPF eggs.

- Observations and examinations for signs of systemic and local reactions were performed in chickens and eggs for 122 days after administering the 10x recommended dose by subcutaneous and *in ovo* route, respectively. In particular: post-mortem macroscopic and microscopic examinations were performed on day 122;
- hatchability was also monitored with control and vaccinated eggs.

The results showed that the hatchability of the *in ovo* vaccinated group was not significantly

different from that of the non-inoculated control group and hatchability in all groups was more than 80%. Results also showed that all chickens remained in good health for the entire duration of the study. Only two birds from the *in ovo* and subcutaneous vaccinated animals respectively died. The post-mortem examination revealed macroscopial lesions not related with the vaccine.

A third group (**Group 3**) was vaccinated with Innovax-ND-H5 mixed with Nobilis Rismavac (live Marek's disease vaccine). Results showed that the mixed use is safe when *in ovo* vaccination is performed with both vaccines in the same syringe. Two birds were found dead during the observation period (till D122) but the necropsies didn't reveal histological lesions related to the vaccines. In the necropsies carried out at the end of the observation period in all survival chickens, one nodule were found in the hearth of one chicken and the histological results are pending. However, is considered that there are enough data to support that, the mixed use of Innovax-ND-H5 and Nobilis Rismavac is safe. The appropriate sentence has been included in the SPC, section 3.8.

A fourth group (**Group 4**) was included in the study. Forty SPF chickens were inoculated with 0.2 ml of Marek challenge virus strain RB1B at a final dose of 26 CID_{50}/dose of 0.2 ml by intramuscular administration. Chickens were observed daily for 70 days after challenge with particular attention to clinical signs associated with Marek's disease (neurological, lymphoproliferative, lymphodegenerative signs and skin leucosis). Post-mortem examination was performed on all intercurrent deaths during the monitoring period. When necessary (no specific macroscopical lesions of Marek's disease or the chickens showed clinical signs of Marek's disease without macroscopical lesions), histological analysis were performed. Results:

- One chicken died before the challenge. Necropsy revealed signs compatible with yolk sac inflammation.
- Three chickens did not show any Marek's disease during the entire observation period and were scored as negative for MDV infection.
- 36 chickens showed severe clinical signs of disease within 19 days after inoculation. After the necropsy, all of them were positive for Marek's disease (most of them showed atrophy of the thymus, enlarged organs or tumours). 92.3% (36/39) of the birds were positive for Marek's disease.

The test was valid: less than 10% of chickens died within the first 7 days and more than 70% of the chickens showed macroscopical lesions of Marek's disease.

To confirm that the vaccine complies, these chickens should be compared to chickens belonging to group 1 (40 vaccinated chickens) where any of the chickens showed notable clinical signs or macroscopic lesions of Marek's disease or died from causes attributable to the vaccine virus. In addition, at 120 days post-vaccination, the number of surviving chickens of group 1 was not fewer than 80 per cent of the effective number (100%).

In conclusion, when the vaccine is administered in chickens by subcutaneous use, the test for Residual pathogenicity of the strain complies with the requirements of Ph. Eur. monograph 0589 (Marek's disease vaccine – live).

Safety of the repeated administration of one dose

This study is only required when the vaccine is intended to be administered more than once and this is not applicable for Innovax-ND-H5.

Examination of reproductive performance

No reproductive studies were provided as the product is not indicated to be used during lay. The SPC has therefore been updated accordingly with the standard statement of section 3.7 of SPC (i.e. The safety and efficacy of the veterinary medicinal product has not been established during lay).

The absence of impact on the reproductive performance of the backbone carrier has been also justified by the applicant based on the scientific literature and the experience with other licensed vaccines containing the same HVT parent strain. This is considered acceptable according to the Guideline on requirements for exceptional circumstances.

Examination of immunological functions

No further studies were conducted to investigate the effects of the product on immunological functions but no adverse effects were observed in the specific safety study carried out with Innovax-ILT (vaccine that contains the same parent strain). The study consisted of several vaccinations with a conventional ND vaccine after one vaccination with Innovax-ILT. Subsequently, birds were challenged against ND. All vaccinated animals were protected whereas control birds developed clinical signs of ND.

As the parent strain of Innovax-ND-H5 is the same as Innovax-ILT, it can be considered that the immunological functions of vaccinated animals will not be affected. There are no reasons to expect that the insertion of the H5 gene could modify this immune response in the animals. Therefore, it is considered that Innovax-ND-H5 might not adversely affect the immune response of the vaccinated animal or of its progeny, and no specific studies are required according to Ph. Eur. 5.2.6 and Annex II of Regulation (EU) 2019/6. In addition, the studies for the examination of immunological functions may be omitted according to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances.

Special requirements for live vaccines

Spread of the vaccine strain

The spread of the vaccine strain from vaccinated to unvaccinated animals was investigated in several studies carried out with other Innovax vaccines, none of them being Innovax-ND-H5. The studies were designed to investigate the spread of the parent strain (HVT FC-126) specifically to the host species (turkeys). In addition, other non-target species were vaccinated and left in contact with target and not target species.

Chickens vaccinated with these Innovax vaccines were left in contact with chickens and turkeys. No spread was detected from chickens to in-contact chickens and spread from chickens to in-contact turkeys was showed in animals vaccinated with vaccines containing antigens against ILT, ND and IBD.

Non-target animals were also vaccinated and were left in contact with non-target species. Mice were also vaccinated. Only spread from chickens to turkey was observed.

Although no specific studies were carried out with Innovax-ND-H5, the studies carried out with other vaccines were designed to detect HVT FC-126 in in-contact animals.

All of the vaccines included in the studies contain the same live HVT FC-126 virus strain and there is no reason to expect that the insertion of the gene encoding for Avian influenza (H5) can change the spreading properties of the virus. However, no specific study has been carried out with Innovax-ND-

H5. The CVMP considers that, because this is a vaccine for use in exceptional circumstances of emergency, in such a situation, the approach of using data from similar vaccines of the same company already authorised based in the same vector and also including ND insert (or others) can be accepted. Appropriate warnings have been included in section 3.5 of the SPC.

Dissemination in the vaccinated animal

The dissemination of the vaccine strain in vaccinated animals was investigated in four studies carried out with other Innovax vaccines, none of them being Innovax-ND-H5. One-day-old chickens and 18-day-old embryonated SPF eggs were vaccinated subcutaneously and *in ovo* respectively with Innovax vaccines containing the HVT FC-126 vector and NDV, ILT and IBD inserts.

At 1, 2, 3, 4 and 5 weeks post vaccination, the white blood cells, spleen, feather tips, trachea, lungs and bursa of Fabricius were examined for the presence of virus and/or virus specific DNA. The virus replicated in all the tissues analysed except for tracheal samples. The virus load decreased along the weeks and, at 5 weeks' post-vaccination, the virus was still recovered. The presence of virus in feather follicles was very low from the beginning of the studies. Hence, the shedding of the virus is expected to be limited.

In general, the virus levels were lower for the vaccine strains compared to the parent strain HVT FC-126. This indicates that the parent strain replicates better than the recombinant vaccine.

All of the vaccines included in the studies contain the same live HVT FC-126 virus strain and there is no reason to expect that the insertion of the gene encoding for avian influenza can change the dissemination properties of the virus in the different tissues. However, no specific study has been carried out with Innovax-ND-H5. The CVMP considers that, because this is a vaccine for use in exceptional circumstances of emergency, in such a situation, the approach of using data from similar vaccines of the same company already authorised based in the same vector and also including ND insert (or others) could be accepted.

Increase in virulence of attenuated vaccines

The HVT FC-126 strain is naturally apathogenic and it has not been obtained by attenuation. Ph. Eur. monograph 0589 (Marek's disease vaccine, live), states in section 2-3-2: "The test for increase in virulence is required for Marek's disease virus vaccines but not for turkey herpesvirus vaccine strains, which are naturally apathogenic".

However, the results of reversion to virulence studies performed with other Innovax vaccines are provided. In all of them, five animal-to-animal passages were performed in chickens. Animals of the first passage were inoculated with a suspension of WBC of the previous passage. Summarising the results, the vaccine virus was successfully passaged five times in chickens. The genetic and phenotypic profile of the virus recovered from chickens inoculated with passage 5 was unchanged compared to the inoculum of the first passage.

In conclusion, Ph. Eur. monograph 0589 (Marek's disease vaccine) does not require a reversion to virulence test in vaccines containing the turkey herpesvirus. As in the case of other Innovax vaccines, the HVT has been modified by the insertion of different genes. For these other vaccines, the test has been performed and no reversion to virulence has been shown when other genes have been inserted in the same vector. Therefore, in order to meet the requirements of the reversion to virulence test, the data submitted under this procedure in accordance with Article 25 are considered acceptable.

Biological properties of the vaccine strain

No specific studies have been conducted with Innovax-ND-H5 to determine the intrinsic biological properties of the vaccine strain. In the studies conducted with other Innovax vaccines, the vaccine strains have not acquired biological properties not already present in the parent strain.

The biological properties of the parent strain with the insertion of gene encoding for H5 protein has not been specifically studied. It has been demonstrated that the parent strain, when encoding for other antigens, is able to disseminate into the animals. However, the level of replication is always lower with the vaccine encoding for different virus proteins than the parent HVT FC-126 strain. This characteristic should be due to a change in the biological properties of the strain.

Based on the observations from other Innovax vaccines, it can be concluded that the vaccine strain of Innovax-ND-H5, apart from expressing the specific inserted genes, has not acquired biological properties not already present in the parent strain.

Recombination or genomic reassortment of the strains

The applicant provided a scientific justification supporting the absence of evidence of recombination of the vaccine strain contained in Innovax-ND-H5.

There is no gene deletion in the genetic modification of the parent strain HVT FC-126, just the insertion of genes encoding for proteins of NDV and AIV. If a loss of these genes should occur, this would result in the HVT strain with a similar behaviour than other HVT vaccines.

HVT vaccines have been used worldwide for years and no reports on recombination with HVT wild strains have been reported.

The risk of recombination or genomic reassortment of the vaccine virus has been properly addressed and is considered appropriated.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/IWP/54533/2006.

The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection and dermal and/or oral exposure. The active substance is a non-pathogenic virus for humans being the host only avian species. Therefore, it does not pose a risk for the user.

The excipients are commonly used in other vaccines and do not pose a risk for the user.

As a result of the user safety assessment, the following advice to users/warnings for the user are considered appropriate:

"*The handling of liquid nitrogen should take place in a well-ventilated area.*

Innovax-ND-H5 is a virus suspension packed in glass ampoules and stored in liquid nitrogen. Before withdrawing ampoules from the liquid nitrogen canister, personal protective equipment consisting of gloves, long sleeves and a facemask or goggles should be worn when handling the veterinary medicinal product. In order to prevent serious wounds, by either the liquid nitrogen or the ampoules when removing an ampoule from the canister, hold the palm of the (gloved) hand holding the ampoule away from the body and face. Care should be exercised to prevent contaminating the hands, eyes and clothing with the ampoule content.

CAUTION: The ampoules have been known to explode on exposure to sudden temperature changes. Do not thaw in hot water or ice-cold water. Thaw the ampoules in clean water at 25 °C–27 °C."

The information provided to the user in the SPC is similar to that provided for other Innovax vaccines, and indicates that the present candidate product should be stored and handled under the same conditions. This is considered acceptable.

Study of residues

MRLs

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

The excipients listed in section 2 of 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, with the exception of bovine serum, Veggie medium (with recombinant human epidermal growth factor (EGF)) and phenolsulfonphtalein (phenol red).

The acceptability of bovine serum, Veggie medium (incl. EGF) and phenolsulfonphtalein (phenol red), was considered by the CVMP during the initial evaluations of Innovax-ND-IBD, Innovax-ND-ILT and Innovax-ILT-IBD, and it was concluded that these excipients were not pharmacologically active at the doses used. Since the dosages used in Innovax-ND-H5 are identical than those used in Innovax-ND-IBD, Innovax-ND-ILT and Innovax-ILT-IBD, it can be considered that these three excipients are not pharmacologically active when used at the amounts contained in Innovax-ND-H5.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

The mixed use of Innovax-ND-H5 with Nobilis Rismavac has been investigated in a specific study (Overdose safety study mentioned above) previously assessed.

The results of this study have been considered satisfactory. Therefore, the safe use of Innovax-ND-H5 when mixing with Nobilis Rismavac has been demonstrated and it is indicated in section 3.8 of the SPC.

Clinical studies

In line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances, no field studies are required.

However, the applicant provided 10 safety and efficacy clinical trials performed with other Innovax vaccines. None of them has been performed with Innovax-ND-H5.

The results of the studies provided were very similar. No differences in morbidity or mortality between test and control groups were observed and no local reaction were detected.

Although the safety of Innovax-ND-H5 has not been investigated in clinical studies, the safety of similar vaccines with the same backbone as Innovax-ND-H5 has been demonstrated. This is considered acceptable.

Environmental risk assessment

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

The natural host of HVT is the turkey, and the virus is non-pathogenic for the target species and other avian non-target species. Based on study results carried out with other Innovax vaccines, the insertion of different genes has not modified the host range, the pathogenicity or spreading capacity of the parent strain.

The excipients contained in the vaccine do not contain any toxic or pharmacologically active components for the environment. In relation to the antibiotics used during the production of the vaccine, the maximum residue concentrations of antibiotics that may be present per dose in the final product are below the MRL as it has been demonstrated in the risk assessment.

A Phase II environmental risk assessment is not considered necessary for Innovax-ND-H5, since it is not expected that the vaccine poses a risk for the environment when used according to the SPC.

Section 3.5 of the SPC contains the following sentence that is considered to mitigate the risk of spreading of the vaccine strain: "*As this is a live vaccine, the vaccine strain is excreted from vaccinated birds and may spread to turkeys. Safety trials have shown that the strain is safe for turkeys. However, precautionary measures have to be followed in order to avoid direct or indirect contact between vaccinated chickens and turkeys.*"

Considerations for the environmental risk assessment

Based on the data provided the ERA can stop at Phase I. Innovax-ND-H5 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

The product 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, as well as a brief summary of Innovax-ND-H5 and other vaccines containing the same backbone carrier HVT FC-126.

Reports of the safety studies performed with vaccines containing the same parent strain and genes encoding for HVT, NDV, IBD, and/or ILT, are also attached.

The applicant states that copies of the written consent of competent authorities for the deliberate release in the environment are not provided since field trials are not required for Innovax-ND-H5 according to Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021). This approach is appropriate.

A technical dossier supplying the information requested in Annex IIIA of Directive 2001/18/EC has been provided. The characteristics (origin and date of isolation) of the parenteral HVT strain FC-126 are described appropriately. The scientific references describing the non-pathogenic characteristics of the natural strain are included. There is no taxonomic relationship between HVT and the original virus of the inserts (NDV and AIV).

The genetic stability of HVT is supported by the use of more than 40 years of the strain in different vaccines without reports on genetic alterations. The pathological, ecological and physiological

characteristics are indicated in the technical dossier as follows: it is not considered a zoonosis, the natural host are turkeys, the generation time in turkeys can be estimated between 12 and 48 hours and animals are permanently infected. In relation to human, animal and plant health, the dossier states that HVT only infect avian species.

The method used for the production of the GMO is a standard procedure for the construction of the recombinant herpesvirus and is supported by scientific literature.

The vector used to insert the expression cassette contains the sequences of the NDV F and AIV H5 genes with promoter and terminator sequences. These sequences are flanked by HVT regions to enable homologous recombination.

The activity of the two expressed proteins is described. The fusion protein (F) of the NDV mediates the fusion of the viral envelope with the plasma membrane. The hemagglutinin protein (H5) of AIV is responsible for the binding of the virus to the cell receptors of the host.

Overall conclusions on the safety documentation

The applicant has provided 1 pivotal pre-clinical study to investigate the safety of 10 fold overdose of Innovax-ND-H5. This study covers the study for the safety of administration of one dose. Both categories (one-day-old chickens and 18-day embryonated SPF eggs) were vaccinated using the recommended administration route. Batches used in these studies were GMP batches.

On the basis of the results, it was concluded that the safety of the targeted animals when the product is administered according to the recommended schedule and via the recommended route is acceptable. This safety test has been performed in line with Ph. Eur. monograph 0589 (Marek's disease vaccine – live), and the test for Residual pathogenicity of the strain has been specifically carried out. The results of this study are satisfactory.
Reproductive safety was not investigated. The SPC contains the appropriate warning.

In relation to the specific requirements for live vaccines, the applicant addressed the potential for spread and dissemination of the vaccine strain based in the results from studies performed with other similar vaccines. No specific reversion to virulence study has been performed however, the results from supportive studies carried out with similar vaccines are considered acceptable to cover this gap as this procedure is assessed under an Article 25 marketing authorisation application.

The recombination and the genomic re-assortment of the strain was justified based on the scientific literature and the fact that vaccines containing live HVT have been used worldwide for more than 40 years. No reports on recombination with field strain have been reported. This is considered acceptable.

As this product contains a GMO active substance, the safety requirements of Directive 2001/18/EC must be met. In accordance with CVMP "Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021), the applicant has thereby provided data from other vaccines containing the same backbone carrier, in addition to having supplied the expected information for vaccines containing a GMO. This is considered acceptable. Since field trials are not required according to Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021), copies of the written consent of competent authorities for the deliberate release in the environment should not be provided in this procedure.

The product is not expected to adversely affect the immune response of the target animals or of its progeny. Studies with other Innovax vaccines have been provided. This is acceptable for vaccines

authorised in exceptional circumstances.

A user safety assessment in line with the relevant guidance document has been presented and is considered satisfactory. Based on the assessment presented, the product does not pose an unacceptable risk to the user when used in accordance with the SPC. The appropriate warnings for the user have been included in the product literature.

An appropriate environmental risk assessment was provided. Innovax-ND-H5 is not expected to pose a risk for the environment when used according to the SPC.

According to the CVMP "Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021), when an IVMP contains a GMO, the safety requirements of Directive 2001/18/EC must be met. In line with the latter directive, it is acceptable for an applicant to submit data, which has been generated for similar GMO constructs already authorised to fulfil part of the requirements for safety. The data presented from other similar vaccines with the same parent strain have been accepted.

The final conclusion on safety is considered favourable under an Article 25 marketing authorisation procedure as the applicant has fulfilled the requirements for avian influenza vaccines stated in the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021), specifically the reduced data included in the table 2 of the mentioned Guideline.

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)

General requirements

The vaccine, as per initial request from the applicant, modified later on in the procedure, is intended for a single application, *in ovo* to 18-19-day old embryonated eggs or subcutaneous to one-day-old chickens.

The vaccine is claimed to reduce mortality and clinical signs caused by avian influenza of the H5 subtype, clade 2.2.1; and to reduce viral transmission, replication and shedding after infection with avian influenza of the H5 subtype, clade 2.2.1.

Cross-protection has been established against avian influenza of the H5 subtype, clades 2.3.2.1c, 2.3.4.4 and 2.3.4.4b.

The onset of immunity is established at 2 weeks post-vaccination whereas the duration of immunity is established at 12 weeks post-vaccination.

The assessment of the efficacy of the vaccine has been carried out taking into account the exceptional circumstances under article 25.

Challenge model

Pre-clinical studies performed by the applicant include challenge with 4 HPAIV strains containing H5:

- clade 2.2.1
- clade 2.3.2.1c
- clade 2.3.4.4

- clade 2.3.4.4b

Efficacy parameters and tests

There is no specific Ph. Eur, monograph available for avian influenza. The recommendations from the World Organisation for Animal Health (WOAH) are followed.

The efficacy parameters chosen for the evaluation of efficacy are as follows:

- General health (clinical signs and mortality) was monitored.
- The serological responses after vaccination by collecting blood from all study animals on the day before challenge was measured. Blood samples were tested by means of haemagglutination inhibition (HI) and AIV H5 ELISA.
- The reduction of virus replication and shedding was measured by collecting choanal and cloacal swabs at one-day post-challenge from unvaccinated birds and at different days post-challenge from all vaccinated birds. Samples were processed by means of RT-qPCR.

The parameters chosen are considered appropriate for evaluating the efficacy of the product.

Efficacy documentation

An overview of the key efficacy studies submitted in the dossier is presented below.

Six studies were conducted to demonstrate the efficacy of the product.

According to the guideline for authorisation under exceptional circumstances (article 25), extrapolation of data can be acceptable, if justified, for different studies when different routes of administration are used. Although the absence of MDA and DOI studies is permitted for this type of procedures, the applicant has nevertheless submitted some documentation.

Pre-clinical studies

Dose determination

The applicant has not presented any specific study for dose determination. The proposed dose of Innovax-ND-H5 was established based on the experience with other vaccines based on the same platform. This is considered acceptable.

Onset of immunity

Three studies were performed with Innovax-ND-H5 in order to demonstrate the onset of immunity for AIV. The studies were designed in line with WOAH manual of diagnostic tests and vaccines for terrestrial animals 2015, chapter 2.3.4. Avian Influenza.

Innovax-ND-H5 was tested according to the recommended routes of administration, which is the subcutaneous route for chicken at one day of age (0.2 ml) (in all 3 studies) and/or the *in ovo* route for 18/19 days of embryonated eggs (0.05 ml) (in one of the studies). The control groups remained untreated.

In all 3 studies, SPF birds were challenged with challenge strains of either homologous or heterologous clades of the H5 serotype of avian influenza, at 2- or 3-weeks post-vaccination. The chickens were subsequently observed daily for at least 10 days for clinical signs related to AIV infection or death. The percentage of protection at the end of the observation period was

established. The percentage of protection was defined as the percentage of reduction in mortality of the vaccinated group as compared to the control group (= (Pcontrols group – Pvacc group)/(Pcontrol group))*100) where P is the percentage mortality). The same calculation was made for number of birds displaying clinical signs. Animals were observed twice a day to detect clinical signs/dead birds. In addition, other efficacy parameters checked were viral load and shedding, as well as serological response. For that purpose, choanal and cloacal swabs as bold samples were taken.

First study: the objective of this study was to evaluate the efficacy of *in ovo* or subcutaneous (SC) vaccination with Innovax-ND-H5 against heterologous challenge at 2 or 3 weeks of age with a currently circulating avian influenza virus (clade 2.3.4.4b). For *in ovo* vaccination, sixty-two 19-day-old embryonated SPF eggs were vaccinated with Innovax-ND-H5 ($10^{3.3}$ PFU/egg) and divided in two groups (groups 1 and 4) containing 31 eggs each. At one-day of age, the chicks that met the inclusion criteria were assigned to their groups (23 birds per group). On the same day, a total of 72 healthy one-day old SPF chickens were divided in four groups. Group 2 and 5 were subcutaneously vaccinated with Innovax-ND-H5 ($10^{3.3}$ PFU/dose) and contained 23 chickens each. Group 3 and 6 remained unvaccinated to serve as challenge controls and contained 13 chickens each. At either 2 or 3-weeks of age, a total of 20 vaccinated and 10 challenge control birds in groups 1-3 or 4-6, respectively, were challenged with HPAI H5N1 heterologous strain/chicken/Netherlands/21038165-006010/2021 (H5N1-NL21, clade 2.3.4.4b). Chickens were monitored for the development of clinical signs of disease for a period of 11 days post-challenge. Serological responses after vaccination were also assessed by collecting blood from all study animals on the day before challenge. Finally, to evaluate the reduction of virus replication and shedding, choanal and cloacal swabs were collected at one-day post-challenge from unvaccinated birds and at 1-, 3-, 5-, and 7-days post-challenge from all vaccinated birds.

After challenge, all the unvaccinated animals died. Only 10% of the animals vaccinated *in ovo* were affected, regardless the time of challenge (2 or 3 weeks post-vaccination). All the animals vaccinated subcutaneously (SC) survived after challenge 2 weeks post-vaccination. 5% of the SC vaccinated birds died after 3 weeks post-vaccination challenge.

The serological evaluation of the blood samples taken post-vaccination confirmed that the unvaccinated controls of groups 3 and 6 were all seronegative for NDV and AIV H5. Furthermore, a good correlation between clinical protection and the antibody levels detected in the AIV H5 ELISA was observed as early as two weeks post-vaccination.

In relation to the virus load a stronger reduction in virus replication and shedding was observed after the challenge at 2 weeks of age in comparison with the one at 3 weeks. One day after the 2-week challenge, the viral load in the choana of the *in ovo* vaccinated birds was significantly reduced (p-value = 0.0119) when compared to the unvaccinated controls. Subcutaneous vaccination with Innovax-ND-H5 resulted in a 1.0 $\log_{10}$ reduction of virus replication. Choanal swabs collected from unvaccinated control birds challenged at 3 weeks of age had a mean titer of 5.5 $\log_{10}$ EID_{50} equivalents/ml. According to these data, appears that vaccination with Innovax-ND-H5 (*in ovo* or subcutaneously) did not result in a significant reduction of the viral load in the choana of the birds vaccinated. The SPC has been modified accordingly.

A significant reduction of virus shedding via the cloaca was observed in the *in ovo* and subcutaneously vaccinated birds when compared to the controls (p-value < 0.0001), reaching almost undetectable levels.

This is the only study in which both routes of administration were used. The indications proposed are based on the results obtained in this pivotal study.

Another study was performed to evaluate the efficacy of subcutaneous (SC) vaccination with Innovax-ND-H5 against homologous challenge at 2 or 3 weeks of age in SPF layers vaccinated at one day of age. A total of 40 healthy one-day old chickens were allocated to three groups: group 1 and 3 were vaccinated (0.2 ml; SC) with Innovax-ND-H5 at one day of age and contained 15 birds each. Group 2 remained unvaccinated to serve as challenge controls and contained 10 birds.

The birds in group 2 and 3 were challenged with HPAI H5N1 strain A/turkey/Turkey/01/2005 (homologous challenge, clade 2.2.1) at 2 weeks of age, whereas the birds in group 1 were challenged at 3 weeks of age. Chickens were monitored at least twice daily for the development of clinical signs of disease for a period of 10 days post-challenge. To assess the reduction of virus shedding, choanal swabs were collected at one day post-challenge from the unvaccinated birds (group 2) and at 1-, 2-, 3-, 5-, and 7-days post-challenge from all vaccinated birds in groups 1 and 3. Finally, serological responses after vaccination were assessed by collecting blood samples from all study animals before challenge.

After challenge at 2 weeks, none of the unvaccinated controls survived the challenge and died within two days after challenge. In contrast, vaccination with Innovax-ND-H5 resulted in 100% survival when challenging at either 2 or 3 weeks. No clinical signs were recorded along the study.

Virus titres measured in choanal swabs collected one day post-challenge revealed a significant decrease in virus shedding in the vaccinated groups when compared to the unvaccinated controls: 1.9 $\log_{10}$ reduction when challenging at 2 weeks post-vaccination or 4.0 $\log_{10}$ reduction when challenging at 3 weeks.

No antibodies against AIV were detected in any of the samples collected from the unvaccinated controls or SPF hatch mates. Vaccination with Innovax-ND-H5 resulted in a significant increase in antibody titres at both 2 and 3 weeks of age when compared with the unvaccinated controls. Seroconversion was confirmed for 13/15 birds (87%) at 2 weeks post-vaccination and 13/14 birds (93%) 3 weeks post-vaccination.

In another study, the objective was to evaluate the efficacy of subcutaneous (SC) vaccination with Innovax-ND-H5 against homologous and heterologous challenge in SPF layers vaccinated at one day of age. In total, 75 healthy one-day-old birds were allocated to six groups. Chickens in groups 2, 4 and 6 (15 birds per groups) were vaccinated with Innovax-ND-H5 (0.2 ml; SC) at one day of age. Chickens in groups 1, 3 and 5 (10 birds per group) remained unvaccinated and served as challenge controls.

All chickens in all groups were challenged at 21 days of age; groups 1 and 2 were challenged with HPAI H5N1 strain A/turkey/Turkey/01/2005 (homologous challenge, clade 2.2.1), groups 3 and 4 were challenged with HPAI H5N8 strain A/duck/Biddinghuizen/NL/2016 (heterologous challenge, clade 2.3.4.4), and groups 5 and 6 were challenged with HPAI H5N1 strain A/duck/Vietnam/NCVD-1584/2012 heterologous challenge, clade 2.3.2.1.c). Chickens were monitored at least twice daily for the development of clinical signs of disease for a period of 10 days post-challenge. To assess the reduction of virus shedding, choanal swabs were collected at one-day post-challenge from up to 5 unvaccinated birds (group 1, 3 and 5) and at 1-, 2-, 3-, 5-, and 7-days post-challenge from 10 vaccinated birds in groups 2, 4 and 6.

Vaccination with Innovax-ND-H5 induced a robust seroconversion 3 weeks after vaccination (all vaccinated chickens were seropositive). Furthermore, the serological data in vaccinated birds correlated well with the nearly 100% protection (survival rate 93,3%) obtained against homologous and heterologous challenge virus strains. Finally, reduction in challenge virus shedding (homologous and heterologous) was demonstrated to be significantly decreased in the vaccinated chickens in comparison with the controls. Homologous virus shedding was reduced to almost undetectable levels.

Based on the results of the above 3 studies, the proposed OOI is therefore established at 2 weeks post-vaccination. The indication has been modified based on the data provided.

Duration of immunity

In study the objective was to evaluate the efficacy of *in ovo* vaccination of Innovax-ND-H5 against a heterologous challenge with a currently circulating avian influenza virus strain (clade 2.3.4.4b), at 12 weeks of age, in SPF layers. Thirty-one 19 day-old embryonated SPF eggs were vaccinated with Innovax-ND-H5 ($10^{3.3}$ PFU/egg). At one-day of age, the chicks that met the inclusion criteria were assigned to group 1 (23 birds in total). On the same day, 13 healthy one-day-old SPF chickens were assigned to group 2 and remained unvaccinated to serve as challenge controls. At 12 weeks of age, a total of 20 vaccinated and 10 challenge controls in groups 1 and 2, respectively, were challenged with HPAI heterologous H5N1 strain A/chicken/Netherlands/21038165-006010/2021 (H5N1- NL21, clade 2.3.4.4b). Chickens were monitored for the development of clinical signs of disease for a period of 10 days post-challenge. The serological responses after vaccination were also assessed by collecting blood samples from all study animals on the day before challenge.

All unvaccinated control animals were affected and died or were euthanised within 1 day post infection, indicating a successful challenge. In the vaccinated group, 16 out of 20 animals showed antibody responses and were protected against challenge with HPAI H5N1 virus (80% survival rate). Four out of 20 animals did not show an antibody response to NDV and AIV. In the applicant´s opinion this might be caused to a failure during the administration of the *in ovo* vaccination. Excluding the birds that did not respond to the vaccination, 100% of the vaccinated birds were protected and were seropositive to both, AIV and NDV.

The proposed DOI is therefore established at 12 weeks post-vaccination. The study was carried out after *in ovo* vaccination and animals were challenged with the currently circulating strain 2.3.3.4.b.

According to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021): "The absence of establishment of the duration of immunity is acceptable and must be clearly indicated in the SPC." Nevertheless, the applicant has provided data to demonstrate a 12 weeks DOI claim. The SPC has been modified accordingly to include the route of administration (*in ovo*) and the claims demonstrated.

Maternally derived antibodies (MDA)

Two studies were carried out in MDA-positive layers to investigate the onset of immunity by the subcutaneous administration route:

Study: the objective of this study was to evaluate the efficacy of subcutaneous (SC) vaccination with Innovax-ND-H5 against homologous challenge at 4 or 5 weeks of age in layers with maternally derived antibodies (MDA +) against avian influenza virus subtype H5 (AIV-H5) and vaccinated at one day of age. A total of 50 healthy one-day-old chickens were allocated to four groups: group 2 and 4 (15 birds each) were vaccinated (0.2 ml; SC) with Innovax-ND-H5 at one day of age. Group 1 and 3 (10 birds each) remained unvaccinated to serve as challenge controls. The serological responses after vaccination were assessed by collecting blood samples from all study animals before challenge. Basal MDA-levels were determined by measuring the antibody titres against AIV-H5 present in the serum of a total of 20 hatch mates (10 hatch mates per timepoint) at the day of vaccination.

The birds in group 3 and 4 were challenged with HPAI H5N1 strain A/turkey/Turkey/01/2005 (homologous challenge, clade 2.2.1) at 4 weeks of age, whereas the birds in group 1 and 2 were challenged at 5 weeks of age. Chickens were monitored at least twice daily for the development of

clinical signs of disease for a period of 10 days post-challenge infections. To assess the reduction of virus shedding after vaccination with Innovax-ND-H5, choanal swabs were collected at 1-, 2-, 3-, 5-, and 7-days post-challenge from all surviving study animals.

After challenge with HPAI H5N1 at 4 weeks, 70% of the unvaccinated control birds and 54% of the vaccinated birds died or had to be euthanized as a result of the infection. In contrast, at 5 weeks 100% of the unvaccinated birds died as consequence of AIV infection between 4- and 8-days post-challenge. Challenging at 5 weeks post-vaccination with Innovax-ND-H5 conferred 46% protection against challenge with HPAI H5N1, which was proven to be significantly different from the control group.

Virus titres measured in choanal swabs collected at 1, 2-, 3-, 5- and 7-days post-challenge revealed a reduction in virus shedding of approximately 1.0 $\log_{10}$ in the birds vaccinated with Innovax-ND-H5 after challenge at 4 or 5 weeks of age when compared to the controls.

Reduction in virus shedding over time post-challenge was compared between the vaccinated groups and the control birds. The virus shedding post challenge was higher in the control groups compared to the corresponding vaccinated groups. However, the reduction in virus shedding in the vaccinated groups was not significantly different from the controls. Over the 7 days post challenge, group 4 (challenged at 4 weeks) was 1.01 $\log_{10}$ EID_{50} lower than group 3 (p-value, 0.0643), while the reduction in group 2 (challenged at 5 weeks) was 0.77 $\log_{10}$ EID_{50} lower than group 1 (p-value, 0.1089).

At one day of age all serum samples obtained from the hatch mates tested positive for the presence of MDAs against AIV-H5 in the homologous HI assay, declining below the detection threshold in the unvaccinated birds at 4 weeks of age. However, no seroconversion was detected in the serum samples of vaccinated chickens challenged at either 4 or 5 weeks of age. Similarly, no significant differences were found between the titres induced in the vaccinated and control birds.

According to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021): ”lack of data regarding maternal derived antibodies and their effect on IVMP efficacy may be acceptable, however, in such cases a clear statement in the SPC is necessary.” The SPC has been amended according to the results provided.

Study:

The objective of this study was to determine the efficacy of Innovax-ND-H5 to prevent virus transmission by reducing virus replication and shedding after challenge in SPF chickens and in chickens with MDAs against avian influenza virus subtype H5 (AIV-H5). For that purpose, subcutaneous vaccination of Innovax-ND-H5 was administered at one-day of age and the birds were challenged with homologous or heterologous HPAI H5N1 virus (clade 2.2.1 and clade 2.3.2.1c, respectively) at 5 weeks of age in SPF animals or 6 weeks of age in MDA+ animals. A contact challenge model was used in which vaccinated birds were challenged (infected) and housed together with vaccinated non-challenged animals (contact challenge, sentinels). As a control, non-vaccinated birds were also challenged (infected) and housed together with non-vaccinated non-challenged birds (contact challenge, sentinels). Shedding of virus after challenge was determined in cloacal swabs and virus replication in infected/sentinel animals was determined using choanal swabs and serological assays.

A total of 105 healthy one-day-old SPF and 48 healthy one-day old MDA+ layer chickens were allocated to 15 groups, divided over 3 rooms (5 groups per room): groups 1-11 consisted of SPF birds and groups 12-15 of MDA+ birds. Groups 2-4, 7-9 and 12-14 were vaccinated (0.2 ml;

subcutaneous) with Innovax-ND-H5 at one-day of age and each group contained 12 birds each. Groups 1, 6 and 11 each contained 3 birds and remained unvaccinated and unchallenged to serve as airborne sentinel controls within each room. Groups 5, 10 and 15 also remained unvaccinated to serve as challenge controls and each group contained 12 birds. Serological responses after vaccination were assessed by collecting blood from all study animals before challenge. Basal antibody levels were determined by measuring the antibody titres against AIV-H5 present in the serum of 5 SPF animals and 10 AIV MDA+ animals at the day of vaccination.

Half of the SPF birds (6 out of 12) from groups 2-5 were directly challenged with HPAI H5N1 strain A/turkey/Turkey/01/2005 (TT05, homologous challenge, clade 2.2.1) at 5 weeks of age, whereas the other half of the birds were kept separated from the challenged animals and were reunited eight hours later (contact challenge sentinels). Additionally, half of the SPF birds (6/12) from groups 7-10 were directly challenged with HPAI H5N1 strain A/duck/Vietnam/NCVD-1584/2012 (VN12, heterologous challenge, clade 2.3.2.1c) at 5 weeks of age, whereas the other half of the birds were kept separated from the challenged animals and were reunited eight hours later (contact challenge sentinels). Finally, half of the MDA+ birds (6/12) from groups 12- 15 were directly challenged with HPAI H5N1 strain A/turkey/Turkey/01/2005 (homologous challenge, clade 2.2.1) at 6 weeks of age, whereas the other half of the birds were kept separated from the challenged animals and were reunited eight hours later (contact challenge sentinels). Chickens were monitored at least twice daily for the development of clinical signs of disease for a period of 8 days post-challenge (dpc) infections and at least daily from 9 to 14 days post-challenge. From all surviving animals (except sentinels for airborne transmission), choanal swabs were collected between 1 and 10 dpc to determine virus replication.

Additionally, between 1 and 8 dpc, cloacal swabs were collected from all surviving directly challenged animals to determine shedding of the challenge virus. Prior to euthanasia, blood samples were collected from all contact challenged animals (sentinels) and the sera samples were tested to determine transmission of the challenge virus.

The direct challenge was successful for all groups as all SPF control birds died within 2 days post-challenge and all MDA+ control birds died within 6 days-post vaccination. Contact challenge was successful in both SPF and MDA+ as the unvaccinated control birds, which were placed in contact with birds directly challenged with TT05 virus, were all affected (100% died after challenge). However, SPF birds contact challenged with VN12 virus had a transmission rate of only 17% likely due to the prompt death of the directly challenged birds which were inoculated with a relatively high challenge dose of the VN12 virus (5.3 $\log_{10}$ $TCID_{50}$/animal), killing 5 out of 6 birds within one-day post-challenge.

Vaccinated SPF birds were 100% protected against homologous and heterologous HPAI H5N1 challenge at 5 weeks post-vaccination and resulted in 100% reduction of transmission. Vaccination in AIV MDA+ chickens resulted in 23% survival rate and 56% reduction of transmission against homologous HPAI H5N1 challenge at 6 weeks post-vaccination. Virus titres measured in choanal swabs revealed a reduction in virus replication of 2.5 $\log_{10}$ egg infective dose 50% (EID_{50}) equivalents/ml (1 dpc) in vaccinated SPF chickens that were directly challenged with TT05 (5w) and a reduction of 0.5, 1.8 and 4.9 $\log_{10}$ (2, 4 and 6 dpc, respectively) in vaccinated SPF chickens that received contact challenge with TT05 (5 weeks). Directly challenged (VN12, 5 weeks) SPF chickens vaccinated revealed a reduction in virus replication of 3.3 $\log_{10}$ at one-day post-challenge, whereas no significant differences were observed in the contact challenged groups. Finally, virus replication reduction was shown in AIV MDA+ animals that were vaccinated and directly challenged (1.3, 1.2 and 2.3 $\log_{10}$ reduction at 1, 3 and 5 dpc, respectively) or contact challenged (2.1, 2.9 and 4.2 $\log_{10}$ reduction at 6, 8 and 10 dpc, respectively) with HPAI H5N1 TT05 at 6 weeks post-vaccination.

Virus titres measured by RT-qPCR in cloacal swabs revealed a significant reduction in virus shedding of 3.9 $\log_{10}$ EID_{50} equivalents/ml (1 dpc) after vaccination with Innovax-ND-H5 and direct challenge with TT05 virus (5w) and similarly, a significant reduction of 4.1 $\log_{10}$ EID_{50} equivalents/ml (1 dpc) after vaccination with Innovax-ND-H5 and direct challenge with VN12 virus (5w) was observed. Reduction of shedding in vaccinated and directly challenged (TT05, 6w) AIV MDA+ birds was also demonstrated with a significant reduction of 1.0, 1.9, 1.9 and 2.3 $\log_{10}$ at 2, 3, 4 and 6 dpc, respectively.

At one-day of age, all serum samples obtained from the SPF hatch mates tested negative for influenza antibodies, and all serum samples from the AIV MDA+ hatch mates tested positive for the presence of MDAs against AIV-H5 in the homologous HI assay (TT05), with an average HI titer of 7.6 $\log_2$. Serological analyses of the serum samples collected before challenge at 5- and 6-weeks post-vaccination revealed a statistically significant difference between the HI titres of the SPF vaccinated and SPF control groups. HI titres of the SPF control groups remaining negative, while average titres of 7.1 $\log_2$ (TT05 challenge group) and 7.2 $\log_2$ (VN12 challenge group) were obtained in the vaccinated SPF groups. No antibodies against AIV-H5 were detected in the sera of unvaccinated and Innovax-ND-H5 vaccinated MDA+ chickens at 6 weeks post-vaccination. Sera were also collected from all surviving sentinel animals prior to euthanasia at the end of the study for ND antibody analysis to differentiate vaccine-related antibodies from challenge virus antibodies. However, the results were not included in the analysis as only 4.7% of the sera derived from sentinels were positive, which is most likely caused by the quick death of AIV-affected birds after challenge.

According to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021):" lack of data regarding maternal derived antibodies and their effect on IVMP efficacy may be acceptable, however, in such cases a clear statement in the SPC is necessary. The proposed sentence for section 3.4 in relation to MDA has been modified according to the data provided.

Interactions

There is no specific information for efficacy of AI when the vaccine is used mixed with any other IVMP. The safe use of the vaccine with Nobilis Rismavac was studied and the SPC amended accordingly.

Clinical trials

In line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021) no data of clinical trials was provided.

Overall conclusion on efficacy

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances. This legal base was agreed on the basis of the current epidemiological situation of avian influenza in Europe. Based on article 25, and the guidelines applicable, some requirements are waived for DOI and MDA data, therefore the assessment is focused on the OOI results for the pivotal efficacy study with clade 2.3.4.4.b challenge. As the challenge strain used for this study belongs to the clade 2.3.4.4.b which is a currently circulating strain, the following has been included under section 4.1; "Challenge strain of the circulating clade 2.3.4.4.b has been used in the efficacy studies."

Under this legal base only AI claims can be supported. As the vaccine also contain MD and ND components the following is mentioned in section 4.1 of the SPC:

" The vaccine is a cell-associated live recombinant turkey herpesvirus (HVT) expressing the F protein of Newcastle disease virus (NDV) and the haemagglutinin antigen of avian influenza virus (AIV) of the H5 subtype. The vaccine induces active immunity against Marek's disease, Newcastle disease and avian influenza virus of the H5 subtype in chickens. Antibodies against MDV, NDV and AIV can therefore be detected after vaccination"

The dose determination was based on the previous experience with other vaccines based on the same platform which is acceptable.

The challenge model used for the evaluation of efficacy is robust as four different challenge strains, homologous and heterologous from different clades, were used therefore the PI has been adapted to a general indication for HPAI H5 subtype.

As mentioned above, important to remark that the currently circulating strain belonging to clade 2.3.4.4.b has been used for the pivotal OOI and for DOI studies. This relevant information for the user has been included under section 4.1 of the SPC.

In order to demonstrate the OOI of the vaccine, three different studies were submitted by the applicant. In the pivotal study, both routes of administration and the currently circulating strain 2.3.4.4.b was used for challenge. The outcomes of this study have been used to amend the indications for section 3.2.

In the other two studies for OOI only the SC route of administration was used.

Duration of immunity against AIV was studied in one study. It was demonstrated by challenge up to 12 weeks post-vaccination with Innovax-ND-H5. *In ovo* vaccination was applied and the circulating strain 2.3.4.4.b was used for challenge. Section 3,2 of the SPC has been accordingly modified to also specify that only mortality and clinical signs were assessed as efficacy parameters in the study, as follows:

Duration of immunity: 12 weeks (reduction of mortality and clinical signs demonstrated with *in ovo* administration).

The interference of maternally derived antibodies (MDAs) was assessed in two studies. In the first one, animals were challenged 4 and 5 weeks post-vaccination. The applicant´s conclusions of a delayed response to the vaccine when compared to naïve birds is not supported and therefore the SPC has been modified accordingly.

In the second study, animals were challenged 6 weeks post-vaccination and the mortality rates showed a poor protection (22%). Therefore, the applicant's conclusion is not endorsed by the CVMP as the response was studied challenging the animals 4, 5 and 6 weeks after vaccination, and a clear interference of the MDAs in protection is detected when comparing the results with those in SPF birds. According to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021):" lack of data regarding maternal derived antibodies and their effect on IVMP efficacy may be acceptable, however, in such cases a clear statement in the SPC is necessary." Nevertheless, the applicant did provide data and section 3.4 of the SPC has been amended accordingly, as follows:

"MDA (against H5) can interfere with efficacy of the vaccine".

The safe use of the vaccine with Nobilis Rismavac is included in section 3.8 of the SPC as follows: Safety data are available which demonstrate that Innovax-ND-H5 can be mixed in the same

solvent and administered by the subcutaneous route use with Nobilis Rismavac. "

Part 5 – Benefit-risk assessment

Introduction

Innovax-ND-H5 is a concentrate and solvent for suspension for injection. It is intended for the active immunisation of one-day-old chickens to be administered subcutaneously or 18-19-day-old embryonated chickens eggs *in ovo* to reduce mortality, clinical signs and virus excretion due to infection with high pathogenic Avian Influenza (HPAI) virus of the H5 type.

The active substance of Innovax-ND-H5 is a Turkey herpesvirus, strain HVT-ND-H5 (cell-associated), expressing fusion protein gene of Newcastle disease virus and haemagglutinin gene of avian influenza virus subtype H5. The active substance is considered a new active substance.

The application was submitted under Article 25 of Regulation (EU) 2019/6 (exceptional circumstances). Reduced data requirements therefore apply and have been considered in the assessment. These reductions relate to quality, safety and efficacy.

Benefit assessment

Direct benefit

The proposed benefit of Innovax-ND-H5 is its efficacy in the proposed indications, which was investigated in six well designed pre-clinical studies conducted to an acceptable standard.

Innovax-ND-H5 is the first vaccine against HPAI particularly against the currently circulating clade 2.3.4.4.b in chickens.

Additional benefits

Innovax-ND-H5 is easy to apply.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

Although data gaps are identified, they are considered acceptable under an Article 25 application.

Additionally, specific obligations as post-authorisation measures to the marketing authorisation under exceptional circumstances are established:

- additional information about the combined identity/potency test should be provided;
- further explanation of the management of extraneous agents in eggs/CEF cells should be provided;
- results of real time stability studies for the vaccine up to 39 months should be submitted.

Safety

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal

Administration of Innovax-ND-H5 in accordance with SPC recommendations is generally well tolerated.

The safety of Innovax-ND-H5 in chickens and chicken embryonated eggs was confirmed in a 10x overdose study. No effects were observed in the vaccinated animals administered at the maximum recommended treatment dose.

Risk for the user

The CVMP concluded that the user safety profile of this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment

Innovax-ND-H5 is not expected to pose a risk for the environment when used according to the SPC recommendation. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

No concerns have been identified related to consumer safety.

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 to provide advice on how to prevent or reduce these risks.

User safety

User safety risks have been identified. These risks have been addressed by the safety warnings in the SPC.

Environmental safety

ERA is required as it is a GMO according to Directive 2001/18.

No special precaution for the protection of the environment is included in the SPC.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product is subject to a veterinary prescription.

Specific obligation to complete the post-marketing authorisation measures for the marketing authorisation under exceptional circumstances are detailed in Annex II of the product information and mentioned below.

Description	**Due date**
Combined identity/potency test. The following information should be provided: • Monoclonal mouse-antibodies for AIV-H5 and NDV-F respectively are used for the immunofluorescence staining. A precise description and protocol for the preparation of the monoclonal antibodies is lacking (AIV-H5 MoAb and NDV-F MoAb).	July 2024

Description	Due date
• Potency: An internal reference standard is used as positive control in the potency test. More detailed information should be provided from which batch the internal standard originates and how it was qualified. It should be also detailed how the titre specifications were established.	
CEF cells could be either provided by a supplier or alternatively obtained prepared in- house. Two CoA from two different suppliers are attached for CEF cells as well as for the embryonated chicken eggs: • The applicant should indicate whether the full set of extraneous agents testing is performed for all CEF cells. The list of extraneous agents tested by the supplier does not mention testing for Atadenovirus (Avian Adenovirus Serogroup 3), which is required according to Ph. Eur. 5.2.2. However, in the document "Extraneous agents risk assessment in the final product," the applicant states that the SPF eggs are tested for Atadenovirus. In the CoA from the supplier, no details regarding extraneous agents testing are mentioned. Therefore, the applicant is requested to clearly indicate whether the same extraneous agents testing procedures are performed irrespective of the source of embryonated SPF eggs or CEF cells. • The applicant should confirm that all bovine sera and trypsin used for cell cultivation in all sites are appropriately tested for extraneous agents. • It should be confirmed explained whether the extraneous agents testing programs for all eggs/CEF cells from all possible suppliers are in line with the requirements of Ph. Eur. 5.2.2. • The applicant is asked to further elaborate how absence of Chlamydia spp. In the CEF preparations is guaranteed.	July 2024
The results of real time stability studies for the vaccine, up to 39 months, should be provided to confirm the 3 year shelf-life claim. Any out of specification detected should be communicated immediately to the European Medicines Agency.	June 2026

Evaluation of the benefit-risk balance

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

For active immunisation of one-day-old chicks or 18–19 day-old embryonated chicken eggs:
- to reduce mortality and clinical signs caused by avian influenza of the H5 subtype, clade 2.2.1
- to reduce viral transmission, replication and shedding after infection with avian influenza of the H5 subtype, clade 2.2.1.

Considering the data provided, the claim suggested by the applicant has been modified as follows:

For active immunisation of one-day-old chicks or 18–19 day-old embryonated chicken eggs to reduce mortality, clinical signs and virus excretion due to infection with highly pathogenic Avian Influenza (HPAI) virus of the H5 type.

The provided information on quality, safety and efficacy of the vaccine is considered sufficient to

conclude a positive benefit-risk balance under an article 25 application. Data gaps have been identified which do not preclude to reach a conclusion of the benefit-risk balance. Three specific obligations have been established to be fulfilled post-authorisation.

Conclusion

Based on the original data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Innovax-ND-H5 is approvable since these data satisfy the requirements for an authorisation set out in the legislation in accordance with Article 25 of Regulation (EU) 2019/6.

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

In addition, based on the review of data on related properties of the active substance, the CVMP considers that is to be qualified as a new active substance.