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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. (Orbyk EHD) (EMEA/V/C/006804/0000)

Vaccine common name: Epizootic haemorrhagic disease vaccine (recombinant protein)

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

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Introduction

The applicant Laboratorios Syva S.A. submitted, on 27 June 2025, an application for a marketing authorisation to the European Medicines Agency (The Agency) for Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. (the final product name was approved and changed into Orbyk EHD before the publication of this EPAR), 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 11 April 2025 as Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. has been developed by means of a biotechnological process, i.e. using recombinant DNA technology (Article 42(2)(a)(i)).

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. emulsion for injection for cattle is a vaccine containing ≥ 100 mcg of VP2 protein of epizootic haemorrhagic disease virus, serotype 8 (EHDV8) as active substance, and Montanide ISA 28 R VG as adjuvant. The target species is cattle.

The primary vaccination schedule to be given to cattle from 3 months of age consists of two doses of 2 ml to be administered 4 weeks apart by the intramuscular route.

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

For active immunisation of cattle to reduce viraemia and fever caused by epizootic haemorrhagic disease virus serotype 8.
Onset of immunity: 2 weeks after completion of the primary vaccination scheme
Duration of immunity: Has not been established

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is presented in HDPE vials containing 40 ml (20 doses), 50 ml (25 doses) or 100 ml (50 doses).

The rapporteur appointed is Esther Werner and the co-rapporteur is Jacqueline Poot.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances.

The CVMP considered that the outbreaks of epizootic haemorrhagic disease (EHD) caused by the serotype 8 in cattle in Europe, the significant impact on animal health and the limited availability of authorised vaccines in the Union to respond to these outbreaks constituted exceptional circumstances related to animal health as per Regulation (EU) 2019/6.

In Europe, outbreaks of the disease were first confirmed in several cattle farms in Italy in October 2022. Since then, outbreaks of the disease caused by the serotype 8 of the virus have been confirmed in other Member States (Spain, Portugal and France). For example, in France, between 1 June 2024, and 6 March 2025, 3,819 outbreaks of EHD were recorded.

Data collected from the field show that the morbidity is highly variable but can reach 100% in some farms. Clinical signs observed include hyperthermia, anorexia, abatement, muzzle ulcers, nasal discharge and lameness, requiring extensive and prolonged treatment. Severe symptoms can be observed in adult cattle (from 2 years of age) which may lead to mortality (M. Gondard *et al.*, 2024).

In the light of the animal health situation, some EU Member States (e.g. Belgium, France, Portugal and Spain) have allowed the use of the vaccine under Article 110 of Regulation (EU) 2019/6, by which 'a competent authority may, in the interest of animal health and welfare and public health, allow the use of an immunological veterinary medicinal product not authorised within the Union on a case by case basis'. As of March 2025, Belgium has implemented mandatory vaccination programs to combat EHD in

cattle.

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 EHD virus serotype 8, currently circulating in the European Union (EU), was recognised by the CVMP.

On 4 December 2025, the CVMP adopted an opinion and CVMP assessment report.

On 29 January 2026, the European Commission adopted a Commission Decision granting the marketing authorisation for Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A.

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

Active substance

The active substance manufacturing site (Laboratorios Syva S.A) manufacturing authorisation number 0760 was issued on 28 March 2025 by the Spanish competent authority.

The GMP certificate (available in EudraGMDP), confirming compliance with the principles of GMP for active substances, is provided. The certificate was issued on 29 August 2024 referencing an inspection on 29 February 2024 by the Spanish competent authority.

A declaration has been provided for the active substance manufacturer from the QP at the proposed EU batch release site stating that the active substance is manufactured in compliance with EU GMP. This was verified based on an audit performed on 23 September 2024 by the quality assurance team of Laboratorios Syva S.A.

Finished product

Laboratorios Syva S.A.
Parque Tecnologico De Leon
Calle Nicostrato Vela, M15-M16 León
24009 León, Spain.

Activities performed: manufacture of finished product, quality control testing (chemical/physical, microbiological, biological), primary packaging, secondary packaging, batch release, storage, and distribution.

Manufacturing authorisation number 0760 was issued on 28 March 2025 by the Spanish competent authority.

A GMP certificate (available in EudraGMDP), confirming compliance with the principles of GMP, is provided. The certificate was issued on 29 August 2024 referencing an inspection on 29 February 2024 by the Spanish competent authority.

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 is in line with legal requirements.

Part 2 - Quality

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

Qualitative and quantitative composition

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is a biotechnology-derived subunit marker vaccine developed for the active immunisation of cattle against serotype 8 of the epizootic haemorrhagic disease virus (EHDV-8). The vaccine is presented as an emulsion for injection and contains as active substance VP2 protein of EHDV 8 at a quantity of at least 100 mcg per 2 ml dose. The vaccine contains Montanide ISA 28 R VG as adjuvant and phosphate buffer solution (PBS) as excipient. The vaccine is intended to be available in multidose presentations and consequently contains thiomersal as a preservative. The vaccine does not contain any live virus.

The product is available in high-density polyethylene (HDPE) vials containing 40 ml (20 doses), 50 ml (25 doses) or 100 ml (50 doses) packed in a cardboard box as described in section 5.4 of the SPC.

The pack sizes are consistent with the dosage regimen and duration of use.

Container and closure system

The product is filled into 40 ml, 50 ml and 100 ml HDPE vials (in accordance with Ph. Eur. chapters 3.1.3 and 3.1.5) containing 20, 25 and 50 doses, respectively. The vials are closed with bromobutyl rubber stoppers (type 1 in accordance with Ph. Eur. chapter 3.2.9) and aluminium seals.

The containers and stoppers are adequately sterilised. The sterilisation methods comply with Ph. Eur. 5.1.1.

Product development

Adequate justification for developing the vaccine has been given. As already acknowledged by the CVMP in granting the request for application under exceptional circumstances and agreeing to an accelerated timetable for assessment of the procedure, there is an unmet medical need for this kind of

product. A positive impact on animal health and on EHDV-8 outbreak management could be expected based on the efficacy of the product.

An explanation and justification for the composition and presentation of the vaccine have been provided. The development of the vaccine was based on the baculovirus expression vector system (BEVS) to express the VP2 capsid protein of EHDV-8 in insect cells. The BEVS has been selected for the high level of gene expression and cost-effective production. It is a common and widely established expression system, which is particularly useful for producing properly-folded proteins including post-translational modifications, thus, more closely resembling the native protein with its immunogenic properties.

Reasonable justification is provided regarding the relevance of the chosen strain within the EU, on which the VP2 sequence is based. The VP2 gene sequence has been generated synthetically and is identical to the VP2 gene of an EHDV-8 strain that was isolated in Sardinia (Italy) in 2022. The identity of the gene sequence was confirmed by conventional sanger sequencing.

The rationale for establishing the quantity of the active substance at ≥ 100 mcg of VP2 protein per dose is based on a sub-potent vaccine batch that was claimed to be efficacious in the target species. Antigen quantification in vaccine batches used in the clinical safety and efficacy study has been done by densitometry, which was used as developmental test. Meanwhile, a sandwich ELISA assay has been developed that is deemed fit-for-purpose as in-process and finished product control test, based on original and supplementary data submitted with this marketing authorisation dossier. The method uses two monoclonal antibodies that specifically recognise conformational epitopes on EHDV-8 VP2 protein, which indirectly confirms structural integrity of the active substance.

The choice of adjuvants and excipients has been adequately described. Sufficient justification has been given for the use of the preservative, with satisfactory demonstration of preservation efficacy.

The production process is based on the seed lot system. A risk assessment with regard to absence of TSE and extraneous agents in the virus and cell seeds has been performed in line with Ph. Eur. 5.2.8 and 5.2.5, respectively, and is satisfactory. All other starting materials are free of animal components, and their origin and sterilisation have been adequately described.

The manufacturing process including the process control tests has been developed based on the requirements of Ph. Eur. 0062 while allowing for data gaps as outlined in the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021).

Inactivation kinetics and an inactivation control test have been developed to ensure that the recombinant baculovirus encoding the VP2 gene is adequately inactivated. The respective validation reports are included in the dossier. In-process and finished process control tests are implemented to ascertain consistency and homogeneity of produced batches.

Representative product batches produced according to the current manufacturing process have been used in the pre-clinical studies submitted with the dossier for marketing authorisation. The formulation of these batches is the same as that intended for marketing.

Description of the manufacturing method

The manufacturing process consists of three main steps: (1) production of the active substance, (2) formulation of the bulk vaccine and (3) filling and packaging. Batches can be manufactured according to the following process:

(1) For production of the active substance, *Spodoptera frugiperda* rhabdovirus-negative (Sf-RVN)

insect cells are amplified to a desired quantity and subsequently infected with the recombinant baculovirus. The required inoculum was prepared by previously propagating the viral working seed on insect cells. The inoculum can be stored in a refrigerator. Data on potential loss of infectivity in the inoculum are not presented.

Infected Sf-RVN cells are maintained in a production bioreactor during the time needed for the production of the VP2 protein. At the end of the incubation, cells and supernatant are harvested and a sample for determining the baculovirus titre and sterility is taken. The harvest is kept and then processed by mechanical cell lysis in the presence of a non-ionic surfactant.

After cell lysis and solubilisation of the antigen are completed, the baculovirus is inactivated by addition of binary ethylenimine (BEI). BEI is later neutralised by sodium thiosulfate.

An inactivation kinetics have been performed demonstrating that six batches of baculovirus were inactivated within 67% of the total inactivation time allowed during the process, and thus, complies with Ph. Eur. 0062.

(2) The antigen is stored in sterile containers for up to 24 months at 2-8 °C. Samples for inactivation control, residual thiosulfate, sterility and VP2 quantification are taken. Even though the proposed intermediate storage period is not supported by sufficient data, this is deemed an acceptable risk considering this is an Article 25 application and since the risk is controllable by testing potency on the finished product. Nevertheless, a specific obligation on providing stability data on the active substance is raised (**specific obligation**). Preparation of the bulk vaccine requires mixing of the antigen with the preservative and then with PBS, followed by addition of the sterile-filtered adjuvant. The antigen bulk is maintained under constant agitation under controlled conditions. Before filling, samples for pH and density control tests are taken from the homogenous emulsion.

(3) Filling is carried out in an automatic dosing tank. The specified volume allowing for overages is described for each presentation. This is considered acceptable. Filling of the product is performed under agitation. The volume is tested periodically.

Labelling and packaging are also carried out automatically. Finished product control tests according to Ph. Eur. 0062 are performed on the filled product.

The process is considered to be a standard manufacturing process, and the in-process control tests are considered adequate. Based on batch data from three production scale batches, it has been demonstrated that the current process is capable of producing the finished product in a reproducible and consistent manner.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Sufficient information is presented with regard to starting materials listed in a pharmacopoeia and their purpose during the manufacturing process of Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. The specifications of the materials are in accordance with the European Pharmacopoeia. Representative certificates of analysis (CoA) from a supplier are included in the dossier for each starting material.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

The only starting materials of animal origin are the recombinant baculovirus (rBV) and the SF-RVN cell line. Both are of insect origin and comply with the current version of Ph. Eur. 5.2.8 and the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01 version 3). The product's risk with regard to transmitting BSE/TSE is therefore considered negligible.

(1) Recombinant baculovirus Bv-EHDV-VP2

The recombinant baculovirus Bv-EHDV-VP2 was constructed using a commercial baculovirus expression vector system. This system is based on the *Autographa californica* nucleopolyhedrovirus (AcMNPV) genome, in which the gene of interest - VP2 gene from EHDV-8 strain EHDV-8/Cattle Guspini SAR2022 – is inserted by homologous recombination using a synthetically produced transfer vector. The baculovirus has an essential gene deletion. As a result, recombinant virus cannot persist in the environment and survive between hosts. The recombinant baculovirus does not contain any antibiotic resistance gene.

Details on the origin and generation of the recombinant virus, the control of the inserted DNA sequence, genetic stability and biological properties are described in a specific report included in the dossier. Overall, the information on rBV generation by recombinant DNA technology is considered sufficient.

The master seed virus (MSV) is a defined number of passages after initial transfection of insect cells and homologous recombination between a bacmid containing the BV genome and a helper plasmid containing the EHDV-8 VP2 gene. The seed designation, including name and date of preparation, have been provided. The MSV stocks are stored at -80 °C. The MSV is tested for sterility in accordance with Ph. Eur. 2.6.1; mycoplasma in accordance with Ph. Eur. 2.6.7; identity by PCR and sequencing; viral titre by $CCID_{50}$ (immunofluorescence); and extraneous agents by risk assessment, PCR or PERT in accordance with Ph. Eur. 5.2.5.

Information on the working seed virus (WSV) including preparation, designation, characterisation (purity, identity, titre), and storage has been provided. The WSV is no more than five passages form the master seed lot in compliance with Ph. Eur. 0062. The information regarding WSV is complete and satisfactory.

Insert stability of the VP2 antigen has been verified from the working seed by PCR and sequencing of the PCR product. No mutations could be identified in any passage compared to the MSV, hence, integrity of the VP2 gene sequence has been confirmed. Moreover, protein production in infected insect cells was demonstrated to be stable. This is acceptable as vaccine production involves a number of passages after the working seed within the demonstrated stability profile of this recombinant baculovirus.

(2) Sf-RVN cell line

Sf-RVN insect cells are used for propagating the recombinant baculovirus and for expressing the EHDV-8 VP2 antigen. The origin and passage history of the cells was sufficiently described. The cells originate from a cell clone that is confirmed to be free of insect rhabdovirus by deep sequencing and PCR. Literature reference and the PCR test result are included in the dossier.

A seed lot system for Sf-RVN cells was established and characterised according to Ph. Eur. 5.2.4. Master cell seeds (MCS) and working cell seeds (WCS) were tested for sterility (Ph. Eur. 2.6.1),

mycoplasma (Ph. Eur. 2.6.7) and extraneous agents (Ph. Eur. 5.2.5). The risk with regard to presence of extraneous agents was adequately assessed and considered to be negligible based on a risk assessment and PCR testing.

The applicant proposed to use cells below the 20th passage from the MCS as substrate for antigen production and provided adequate data regarding species identity and karyology. The test reports for the MCS, WCS and MCS+21 are included in the dossier.

The cell stocks are stored in liquid nitrogen. DMSO is used as cryoprotectant. A new vial of master seed is only used when a new lot of working seed is required.

(3) Montanide ISA 28R VG

Montanide ISA 28 R VG is used as adjuvant and is part of the final formulation. It contains pharmaceutical grade oil from mineral origin. Sufficient information on the source, components, purpose and sterilisation method is provided. A certificate of analysis by the supplier is included in the dossier confirming that this starting material is animal-component free, and thus, outside the scope of Ph. Eur. 5.2.8.

Starting materials of non-biological origin

Starting materials of non-biological origin that are not listed in a pharmacopoeia are 2-bromoethylamine hydrobromide (BEA), β-naphthol violet and Insect cell culture media. Sufficient information is provided on the source, sterilisation and purpose of these materials. Certificates of analysis stating respective specifications and storage conditions are included in the dossier.

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

The following media and solutions were used: BEI solution, cell culture medium, sodium hydroxide solution, sodium thiosulphate solution and thiomersal solution.

Information regarding the qualitative and quantitative composition of all culture media and solutions, their treatment processes and their storage conditions is provided in the dossier. All components are either tested for or treated to ensure that there are no contaminants, or further assurance is given that there is no potential risk.

Control tests during the manufacturing process

The applicant presented in-process data for the manufacture of four representative antigen bulks. During the manufacture of the antigen the following tests are carried out: appearance of the cells, passage number check, cell count, sterility (Ph. Eur. 2.6.1), viral titration, inactivation control, residual thiosulfate (Ph. Eur. 0414), antigen quantification by ELISA, density (Ph. Eur. 2.2.5), pH and filling control. Short test descriptions and the limits of acceptance were presented. The in-process tests are deemed to be sufficient to control the critical steps in the manufacturing process.

The inactivation control test has been validated and is considered sufficiently sensitive to detect any remaining infective baculovirus in the antigen bulk.

Control tests on the finished product

1) General characteristics of the finished product

The appearance is assessed by visual inspection. The vaccine must be a white or white to greyish homogeneous emulsion in which phase separation is not observed.

Viscosity is determined as a parameter to confirm the stability of the emulsion.

Density is tested according to Ph. Eur. 2.2.5.

The stability of the emulsion is further controlled by applying centrifugal force. If the vaccine solution returns to "normal" after manual shaking and no more than a % of oil is noticed at the top, the emulsion is considered stable.

The pH is determined by potentiometric evaluation in accordance with Ph. Eur. 2.2.3.

Packaging controls are performed by visual inspection to ensure the correct capping, labelling and insertion of package leaflets. The batch number and expiry date are also checked.

2) Identification of the active substance

Identity of the active substance is confirmed by the ELISA potency test that uses monoclonal antibodies against VP2 protein of EHDV-8. Preliminary data confirmed specificity of these antibodies for the active substance.

3) Batch titre or potency

Potency is tested by quantification of the active substance in the finished product via a double sandwich ELISA using two different monoclonal antibodies that recognise the VP2 protein of EHDV-8. An internal standard that has been quantified based on a reference vaccine that was claimed to be efficacious in the target species is included in the assay as control.

Validation of the potency test is not mandatory according to the "Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021). Based on original and supplementary data submitted with this marketing authorisation dossier, it can be concluded that the ELISA test is fit-for-purpose to distinguish between sub-potent and potent batches. However, this conclusion should be further supported by a complete validation report that should be provided post-authorisation (**specific obligation**).

4) Identification and assay of adjuvants

Confirmation of the correct amount of adjuvant, as well as of the suitability of interaction between the active substances and the adjuvant in the finished vaccine, is supported by the physico-chemical controls performed on the final product.

5) Identification and assay of excipient components

The test for quantification of thiomersal is performed by absorption spectrometry according to Ph. Eur. 2.2.23.

6) Sterility and purity tests

Sterility in the finished product is determined by direct inoculation in accordance with Ph. Eur. 2.6.1 '*Sterility*'.

7) Filling volume

The filling control test performed at the QC department is carried out by measuring the vaccine volume

in a graduated test cylinder.

A short description of the methods used for the control of the finished product and the specifications were provided.

Batch-to-batch consistency

The applicant presented finished product data for the manufacture of three production-scale finished product batches. During the manufacture of the active substance the following tests are carried out: appearance of the cells, passage number check, cell count, sterility, viral titration, inactivation control, residual thiosulfate, antigen quantification by ELISA, density, pH and filling control. Test descriptions and the limits of acceptance were presented. The in-process tests are deemed to be sufficient to control the critical steps in the manufacturing process.

As all three production-scale batches meet the specifications of the in-process and finished product control tests, consistency of the currently described manufacturing process is demonstrated.

Stability

The active substance is proposed to be stored for up to 24 months at 5 ± 3 °C. Even though the proposed intermediate storage period is not supported by sufficient data, this is deemed an acceptable risk considering this is an Article 25 application and since the risk is controllable by testing potency on the finished product. Nevertheless, real-time stability data should be provided to confirm the 24-month shelf life for the active substance. This is raised as a specific obligation.

Stability data of up to 12 months are provided for one production scale vaccine batch stored at 5 ± 3 °C. Furthermore, stability data up to 9 months and 6 months, respectively, are provided for two more production scale batches. Potency results for these three batches suggest that the active substance, EHDV-8 VP2 protein, remains stable during the course of 1 year. Thus, a shelf-life of 1 year can be accepted at this point for the finished product. However, the results of the ongoing real-time stability studies should be provided to confirm the 12-month shelf life of the vaccine. Any out of specification result should be communicated immediately to the Agency (**specific obligation**).

An in-use stability of 10 hours is proposed for the product. Preservative efficacy has been tested in accordance with Ph. Eur. 5.1.3 and monograph 0062. Data on the efficacy of the preservative at the end of the proposed in-use shelf life are available and are considered satisfactory. However, due to the nature of the product, it is considered appropriate that data based on the potency of the finished product should be provided to support the in-use shelf life. These data will be submitted post-authorisation (**specific obligation**).

New active substance (NAS) status

The applicant requested the active substance, VP2 protein of epizootic haemorrhagic disease virus, serotype 8 contained in Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. to be considered a new active substance. The applicant's rationale is that in comparison to the known active substance 'Epizootic haemorrhagic disease virus, serotype 8, strain EHDV8 SPA 2022/LCV_03 LCV Cod.:O78, Inactivated' previously authorised in the European Union, VP2 protein of epizootic haemorrhagic disease virus, serotype 8 differs significantly in nature and properties from the above-mentioned substance already authorised in the EU.

Based on the review of the data provided, the CVMP considered that the active substance, VP2 protein

of epizootic haemorrhagic disease virus, serotype 8, contained in the veterinary medicinal product Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is to be qualified as a new active substance considering that it is only a subunit vaccine while the already authorised active substance is the complete inactivated virus. Also, Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is produced by recombinant DNA technology; thus, the manufacturing process and antigenic properties are significantly different.

Overall conclusions on quality

The quality part of the dossier generally follows the Annex to Regulation (EU) 2019/6 taking into consideration that this application is being submitted according to Article 25 'Applications in exceptional circumstances', which allows for certain data gaps as specified in the "Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021).

The composition of the product is described in sufficient detail. The development of the product has been adequately described and justified.

The antigen is produced by recombinant DNA technology using the baculovirus expression vector system. The manufacturing process generally follows the requirements of Ph. Eur. 0062 "Vaccines for veterinary use". The production process can be considered standard for this type of vaccine.

Inactivation kinetics and validation of the inactivation control test have been done as required by EMA/CVMP/IWP/251947/2021. The inactivation time has been validated and complies with Ph. Eur. 0062. The inactivation control test is sufficiently sensitive for detecting residual infectivity in the antigen bulk.

The source, specifications, and storage of all starting materials have been adequately presented. Except for the virus and cell seeds, all materials are free of materials of animal origin. Comprehensive risk assessments with regard to the risk of TSE and extraneous agents have been provided in accordance with Ph. Eur. 5.2.8 and Ph. Eur. 5.2.5, respectively, and are considered acceptable.

The potency test is based on an ELISA method that uses monoclonal antibodies against the VP2 protein of EHDV-8. The ELISA assay is used for quantifying the active substance on the antigen bulk. On the finished product, the ELISA is proposed as a means of quantification and identification of the active substance. The ELISA test has not been fully validated, which is acceptable according to Guideline EMA/CVMP/IWP/251947/2021. Based on original and supplementary data submitted with this marketing authorisation dossier, it can be concluded that the test is fit-for-purpose to distinguish between sub-potent and potent batches. However, this conclusion should be further supported by a complete validation report that should be provided post-authorisation (**specific obligation**).

The control tests performed during production and on the finished product are in line with Ph. Eur. 0062 and suitable to ensure consistent production and formation of a stable emulsion. Data from three production-scale batches suggest that the current manufacturing process yields product batches of equivalent quality.

Limited stability data for the active substance are available, which is an acceptable data gap at this point as potency will be ultimately controlled on the finished product. Nevertheless, real-time stability data should be provided to confirm the 24-month shelf life for the active substance (**specific obligation**). Stability data for one industrial-scale batch for 12 months support a shelf-life of 1 year for the finished product, when stored at 5 ± 3 °C. However, the results of the ongoing real-time stability studies should be provided to confirm the 12-month shelf life of the vaccine. Any out of specification result should be communicated immediately to the Agency (**specific obligation**). An in-use shelf-life of

10 hours is proposed for the finished product and is supported based on the demonstrated effectiveness of the preservative. However, as the vaccine contains a protein as active substance that can be susceptible to environmental factors (e.g. temperature), the in-use shelf life should be supported by potency data as well. These data will be submitted post-authorisation (**specific obligation**).

Overall, it can be concluded that the Quality part of the dossier has several data gaps concerning the potency/identity test and the stability of the product. These data gaps can be accepted under the terms of an Article 25 application and are to be addressed post-authorisation as specific obligations.

Part 3 – Safety documentation (safety and residues tests)

General requirements

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is an inactivated subunit vaccine that contains, as active substance, the recombinant VP2 protein of epizootic haemorrhagic disease virus, serotype 8. Although the VP2 protein is obtained on a baculovirus expression vector system, the recombinant baculovirus is fully inactivated during the antigen production process and, therefore, the vaccine contains no genetically modified organism (GMO) as per legal definition. Montanide ISA 28 R VG is used as adjuvant, thiomersal as preservative and phosphate buffer solution (PBS) as vehicle.

The applicant has considered the relevant current legislative and regulatory requirements in Europe when planning the safety studies.

Safety documentation

One pivotal pre-clinical combined safety and efficacy study was conducted in the target species to evaluate the safety of the administration of a single and a repeated dose of the vaccine. This pre-clinical study was not reported to be GLP-compliant, which is acceptable for an application under Article 25 of Regulation (EU) 2019/6. The study was carried out in cattle of the minimum age recommended for vaccination, using R&D batches containing at least 100 mcg/dose (standard batch) or 75 mcg/dose (sub-potent batch) of the VP2 protein. The use of R&D batches is also acceptable for this type of application.

To further support the results of this pivotal study, a non-GCP clinical study in a non-target species (deer) is also provided.

In both these studies, the product is called EHDV-8 vaccine 1.

Study reference	*Study purpose*
01	Single and repeated dose in cattle
02	Clinical study in non-target species

The assessment has been performed according to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021).

Pre-clinical studies

Safety of the administration of one dose

The safety of a single dose was evaluated together with the safety of the repeated administration of one dose.

Safety of one administration of an overdose

No overdose studies are required for inactivated vaccines.

Safety of the repeated administration of one dose

The pivotal study provided to evaluate the safety of a single dose and a repeated dose is a combined safety and efficacy study, which is acceptable for inactivated immunological veterinary products (IVMP) according to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021). The study was not conducted under GLP requirements. This is also acceptable for an Article 25 procedure according to the above-mentioned guideline.

In this study, three different groups were included, each with eight 3- to 5-month-old female calves. Two groups were vaccinated: one with 2 ml of a standard batch (100 mcg/dose) and one with 2 ml of a sub-potent batch (75 mcg/dose). The third group was kept as control and inoculated with 2 ml of a saline solution. Administrations were performed on D0 and D28 of the study. The animals were vaccinated intramuscularly (IM) in the right (D0) and left (D28) side of the neck. Before the start of the study, the calves were tested negative for bovine viral diarrhoea virus (BVDV) and bluetongue virus (BTV) genomes, were seronegative for BTV VP7, EHDV VP7 (both by ELISA) and EHDV-8 neutralising antibodies (by VNT).

Body weights were measured upon arrival at the BSL1 facility (D-1), on the day of transportation to the BSL3 facility for challenge infection (D35) and also at the end of the study. Systemic reactions were followed up daily during the acclimatisation period. Local reactions were evaluated for five days after each IM injection. Rectal temperature was measured from three days before, at the time of vaccination and until five days after vaccination (no D0 + 4 hours point in time was included).

No statistical differences were found when comparing body weight development between groups.
No animal died during the study period.

After the first vaccination in the vaccinated groups, 12 out of 16 animals showed fever for a maximum of five days and 3 out of 16 animals exhibited dullness for two days. However, all calves recovered without treatment. Some controls also displayed fever. After the booster vaccination on D28, no clinical signs related to the vaccination were reported. Eight out of 16 vaccinated calves showed fever for 1-2 days, while no control animal developed fever. In the following days, no fever was noted in any animal. The average body temperature increases observed after the first and second vaccination were significantly different from the control group, even though the base line of the control group was higher due to the inclusion of two animals with fever.

Local reactions were commonly observed promptly after each vaccination (warmth, nodules, firm swellings) but resolved after two days. During necropsies, some histopathological findings were noted at the injection sites of some vaccinated animals. These findings are considered as normal after IM vaccination with an adjuvanted vaccine.

No safety of a third (booster) injection was investigated, which is considered acceptable for an Article 25 procedure.

The study provided has some deficiencies e.g. the suitability of the animals could be questioned (circulation of respiratory disease, mycosis). Moreover, partly contradictory and inconsistent information is provided, no study protocol was provided, the randomisation procedure is not clear and some minor deviations from Ph. Eur. monograph 5.2.6 are noted. Notwithstanding the deficiencies of the study, it can be concluded that the vaccine is safe for 3- to 5-month-old cattle when given at an interval of 4 weeks. The SPC sections 3.6 and 3.9 were adapted accordingly.

Examination of reproductive performance

No study evaluating the safety of the vaccine during pregnancy, lactation or its impact on fertility is provided.

The applicant has provided pharmacovigilance data on the use of Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. in the field under Article 110 (2) of Regulation (EU) 2019/6 in cattle and deer. Approximately one million doses were administrated between November 2024 and June 2025 in Spain, Belgium and Portugal, of which approximately 98% have been used in cattle, including pregnant cows. No notification of adverse reactions concerning the reproductive function have been registered, which indicates that the vaccine does not represent a risk for reproduction.

However, while according to Guideline EMA/CVMP/IWP/251947/2021 such studies may be omitted, either a relevant warning should be included in the SPC or data from a similar vaccine should be provided to prove safety for the reproductive tract. The pharmacovigilance data provided are considered as supportive to assume that no safety issues will arise if the vaccine is accidentally used in pregnant cows or during lactation. It is acknowledged that only the EHDV VP2 protein is included as active substance, that the baculovirus system used for replication of this protein is inactivated during manufacture and that no adverse events were reported concerning pregnancy.
The data provided are not very detailed and no information is given concerning the numbers of pregnant or lactating cattle and their specific pregnancy stage. A comprehensive assessment is therefore not possible.

Based on the above, the original proposed wording of the applicant in the SPC under section 3.7 concerning pregnancy and lactation is not acceptable as no dedicated study was performed and no additional data are available from another IVMP of similar composition and similar vaccination schedule. Therefore, the standard QRD warning sentence was included in the PI.

Examination of immunological functions

No specific studies were conducted to investigate the effects of the product on immunological functions. The adverse effects that were observed in the combined safety and efficacy study were included in the SPC. It is unlikely that this vaccine will have an adverse effect on immunological functions due to the nature of the product (i.e. inactivated vaccine).

The applicant has provided pharmacovigilance data on several adverse events that were reported during the use in the field under Article 110 (2) of Regulation (EU) 2019/6. It is noted that also hypersensitivity reactions like anaphylaxis were reported, which may indicate an involvement of the immune system. It is also noted that no purification or filtration step of the antigen is foreseen during manufacture in contrast to other similar vaccines.

Nevertheless, the incidences reported are very rare (<1 animal / 10 000 animals treated, including isolated reports) and it is unknown if the product was used according to directions. In section 3.6 of the SPC, relevant adverse reactions were included. Therefore, this approach is accepted.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with the "Guideline on user safety for immunological veterinary medicinal products" (EMEA/CVMP/IWP/54533/2006).

The main potential routes of accidental contact with the product have been considered. It was concluded that the most likely ones are those of accidental self-injection and dermal exposure. The active substance is an inactivated protein and is not infectious. The recombinant baculovirus system used for replication of the active substance is inactivated.

The excipients are commonly used in other vaccines and do not pose a risk for the user. Since the product contains an adjuvant consisting of mineral oil, the appropriate standard warning for mineral oil-containing vaccines is included in the product literature.

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

Study of residues

The active substance, being a principle of biological origin intended to produce active immunity, is not within the scope of Regulation (EC) No 470/2009. The recombinant baculovirus system used for replication of the active substance is inactivated.

The excipients, including adjuvants, 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 when used as in this product. The maximum thiomersal content in Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. will be 0.01%, which is acceptable according to Table 1 of the Annex to Commission Regulation (EU) No 37/2010.

The withdrawal period is set at zero days.

Interactions

No data are provided investigating interactions of the vaccine with any other veterinary medicinal product. Therefore, the standard statement has been included in section 3.8 of the SPC:
"No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case-by-case basis.".

Clinical studies

Clinical safety studies in the target species have not been conducted by the applicant because, according to Guideline EMA/CVMP/IWP/251947/2021, clinical trials are not required to be included in a dossier submitted under Article 25 of Regulation (EU) 2019/6.

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. was granted a

temporary authorisation for use under the scope of Article 110 (2) of Regulation (EU) 2019/6 in Spain, Belgium, Portugal and France. The applicant collected pharmacovigilance data, which have been provided.

Additionally, a combined clinical safety and efficacy study carried out in the non-target species deer is provided.

Pharmacovigilance data from temporary authorisation under Article 110 (2) of Regulation (EU) 2019/6

Eight cases were reported in cattle, and two cases were reported in deer. In most cases, it is not known if the product was used according to the directions on the label.

The detailed descriptions of the cases are included in the provided pharmacovigilance report. The adverse events reported (milk production decrease, decreased appetite, death, breathing difficulty and hypersensitivity) have been reflected in the table in SPC section 3.6.

Clinical study in the non-target species deer

The clinical study in 11- to 13-month-old deer (130 animals) was conducted in Spain. Fifty animals were vaccinated with a 100-mcg dose of Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. (ten of them were closely monitored). Another group of 40 deer was vaccinated with 75 mcg/dose and, in one group of 40 deer, only PBS was administered. All groups were vaccinated twice with a four-week interval.

All deer were observed for general health after each vaccination. The separate group was monitored additionally for specific clinical signs, reactions at local injection sites and rectal temperatures. Blood samples were collected from each animal to exclude EDHV infection before vaccination and evaluate antibody development.

No health issues, clinical signs and anomalies at the injection sites were noted throughout the study. Some deer had already elevated temperatures before the first vaccination probably due to stress of handling. Four hours after the vaccination, six animals showed fever that decreased again from the day after vaccination. The same results were more or less seen after the second vaccination.

In summary, the study supports the safety of the vaccine for deer from 11 months of age. However, deer are not the target species and, therefore, it is not acceptable to include such information in the product information.

Environmental risk assessment

An environmental risk assessment has been provided in accordance with the CVMP "Note for Guidance on the environmental risk assessment of immunological veterinary medicinal products" (EMEA/CVMP/074/95). Based on the data provided, the ERA can stop at Phase I. Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The applicant has provided one pivotal pre-clinical study to investigate the safety of one dose and a repeated administration of a standard dose to cattle, of 3 months of age, using at least 100 mcg or 75 mcg via intramuscular injection. The batches used in these studies were R&D batches. No GLP conformity is claimed, which is acceptable for an Article 25 procedure and according to the Guideline

EMA/CVMP/IWP/251947/2021.

On the basis of the results, it is concluded that the safety of the vaccine in the target animals is acceptable when the product is administered according to the recommended schedule and via the recommended route of administration.

The applicant did not provide any data on overdose testing. This is in accordance with Annex II of Regulation (EU) 2019/6 as amended and is considered acceptable.

Reproduction safety was not investigated. In the SPC the standard warning sentence was included.

The product is not expected to adversely affect the immune response of the target animals, and, therefore, no tests on the immunological functions were carried out.

A user safety assessment in line with the relevant guidance document has been presented. Based on it, the product does not pose an unacceptable risk to the user when used in accordance with the SPC. The worst-case scenario for user safety is self-injection. The appropriate warnings for the user have been included in the product literature.

Interactions with other products were not investigated. The warning in the SPC is considered adequate.

No clinical trials were performed with Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A., which is in accordance with Article 25 of Regulation (EU) 2019/6. As supportive information, a clinical trial performed in deer was provided. Additionally, pharmacovigilance data on the use of the vaccine under Article 110 (2) were provided for the time period from November 2024 until September 2025. SPC section 3.6 was updated to mirror the complete data.

An appropriate environmental risk assessment was provided. Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is not expected to pose a risk for the environment when used according to the SPC. The active substance was manufactured biotechnologically, but no GMO is included in this vaccine. A withdrawal period of zero days is considered appropriate.

The data provided in the dossier are supportive of the safety of the vaccine in cattle when the vaccine is administered according to the recommended schedule and route of administration.

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

General requirements

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is a recombinant subunit vaccine including the VP2 protein of serotype 8 of EHDV as the active substance. It is intended to be used for the active immunisation of cattle to reduce viraemia and fever caused by the epizootic haemorrhagic disease virus (EHDV) serotype 8 (EDHV-8).
The nature of the vaccine allows distinction between vaccinated and infected animals.

The product is presented as an emulsion for injection. The vaccination scheme is proposed as two intramuscular injections of a 2 ml dose, 4 weeks apart in cattle from the age of 3 months.

The applicant provides a very reduced set of efficacy data, as the application for marketing authorisation is submitted under Article 25 from Regulation (EU) 2019/6.

One pre-clinical study is provided, which covers safety and efficacy data in calves from the age of

3 months, vaccinated according to the proposed vaccination scheme and challenged two weeks later.

Studies on duration of immunity and the effect of the presence of maternally derived antibodies were not performed yet. Clinical studies were also not performed. This is accepted as the vaccine is to be authorised under Article 25 of Regulation (EU) 2019/6.

The proposed indication as included in the SPC is as follows:

- For active immunisation of cattle to reduce viraemia and fever caused by epizootic haemorrhagic disease virus, serotype 8
- Onset of immunity: 2 weeks after completion of the primary vaccination scheme
- Duration of immunity: has not been established.

The assessment has been performed according to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021).

Challenge model

No separate study on the establishment of the challenge model was performed, but the challenge was directly included in the combined safety and efficacy study.

For the design of the challenge part of the study, the applicant referred to a publication from Spedicato et al. (2023), which analyses the kinetics of EHDV infection in calves and lambs of sheep and goats. The study design for the challenge was based on this publication but was slightly modified.

On D42 of the study all animals of all treatment groups (Control group, Vaccine 1-100 mcg EHDV-VP2, Vaccine 2-75 mcg EHDV-VP2) were challenged with virus inoculum with a target concentration of $10^{6.0}$ $CCID_{50}$/ml subcutaneously in the neck (2 ml left and right).
The modified study design for the challenge is considered satisfactory.
Natural infection occurs via Culicoides biting midges, which transmit the virus; therefore, subcutaneous administration is considered appropriate.

The virus strain used for the challenge was EHDV-8/SPA-LBC/24, which was isolated by Laboratorios Syva and stemmed from an EHD outbreak in Spain in 2023. The used strain is considered relevant, as it is relatively recent and isolated from a territory where the disease is currently endemic.

Efficacy parameters and tests

As primary efficacy parameter, vaccine efficacy was intended to be shown by demonstrating a significant reduction in the level and duration of viraemia determined by RT-qPCR in blood samples of vaccinated animals, compared to mock-vaccinated controls. The employed RT-qPCR was developed in-house by the applicant, and a validation report is provided. The validation report does not cover all parameters as described in the VICH guideline for validation of analytical procedures; however, the test method is considered suitable to determine the level of EDHV viraemia in EDTA blood samples from calves included in the combined safety and efficacy study.

The Ct-values obtained were then transformed into $CCID_{50}$/ml values by interpolation from a standard curve prepared with the EDHV challenge strain at 5.7 $\log_{10}$ $CCID_{50}$/ml (Spearman-Kärber). The assay is considered linear for the investigated range and therefore the calculation of viral titres is considered acceptable.

The applicant states that viral loads in blood samples from vaccinated animals were below the threshold ($<10^{2.3}$ CID_{50}/ml) required for an effective vector-mediated transmission, as described in literature, while they were above this threshold in the control group.

The literature reference is a study of Mendiola et al, 2019[1]. This threshold is not investigated in this study; however, the figure is copied from a study by Jennings et al, 1987[2]. The authors investigated the variation in the responses of *Culicoides variipennis* to oral infection with bluetongue virus.
Study of the response of individual susceptible *C. variipennis* to BTV infection demonstrated considerable variation in the level of virus multiplication that individual females are able to support. Virus concentrations varied from less than 1.1 to 5.1 $\log_{10}$ $TCID_{50}$/fly up to 10 days post infection. 43.6 per cent of females contained less than 2.5 $\log_{10}$ $TCID_{50}$ virus. It is suggested that such insects would have a mesenteron escape barrier to infection and would be incapable of transmitting BTV.
It should be noted that the threshold refers to the virus concentration in the vector, and not to the virus concentration in the sheep's blood.

This threshold is confirmed/redefined in a further study by Fu et al, 1999[3]. The objective of the present study was to identify and further characterise the barriers to BTV infection, dissemination and transmission in a known *Culicoides* vector species (*C. variipennis*). The insects were experimentally infected by feeding a blood-virus suspension through a parafilm membrane. For oral infection, blood meals were prepared using citrated normal sheep blood, diluted in the ratio of 3:7 with suspensions of BTV in Eagle's medium, so that the final suspension contained 10^{6-7} TCID50/ml of the virus.
This study demonstrated a threshold relationship between the titre of BTV in an individual midge and its ability to transmit virus in its saliva. Midges in which BTV replicated to a final titre that was lower than $10^{3.0}$ $TCID_{50}$ per insect, were unable to transmit the virus, presumably because in these individuals it is restricted entirely to susceptible cells of the gut and a limited number of other cells not including the salivary glands. The cited studies have been performed on BTV and not EHDV, so the evidence is indirect. In the study there was no attempt to recover infectious virus from the blood samples collected. The relevance of the provided data to evaluate the level of actual reduction of vector-mediated transmission after vaccination is considered limited.
With the responses to the list of questions the applicant provided further information, including epidemiological modelling data on the transmission dynamic in vaccinated or unvaccinated animals, which support the conclusion that the efficacy of the product can be considered adequate.

As secondary efficacy parameter, immunogenicity of the product was intended to be evaluated by monitoring an EHDV-8 specific (neutralising) antibody response post vaccination by ELISA and virus neutralisation test.

The ELISA for the detection of antibodies against EHDV-8-VP2 was also developed in-house.
No validation data was provided. The virus neutralisation test used was a classical serum dilution assay for which no validation data was provided. However, as no relevant induction of (neutralising) antibodies after vaccination could be demonstrated, no claim on the induction of antibodies against EDHV-8-VP2 was proposed.

Furthermore, the possible reduction of other clinical parameters such as rectal temperature and EHDV-8 specific clinical signs and lesions was investigated. Post challenge, clinical symptoms were assessed by semi-quantitative clinical scores, rectal temperatures, haematological examinations and finally at the end of the study, gross pathological and histopathological analyses after necropsy of all animals.

Efficacy documentation

One pivotal pre-clinical combined safety and efficacy study in the target species was conducted to

demonstrate the efficacy of the administration of two intramuscular injections of a 2 ml dose, 4 weeks apart in cattle from the age of 3 months and challenged 14 days after the second vaccination, to support an onset of immunity of 2 weeks.

This pre-clinical study was not reported to be GLP-compliant, which is acceptable for efficacy studies. The study was carried out in cattle of the minimum age recommended for vaccination, using R&D batches containing at least 100 mcg/dose (standard batch) or 75 mcg/dose (sub-standard batch) of the VP2 protein of EHDV-8. The use of R&D batches is considered acceptable for this type of application.

With the responses to the list of questions the applicant provided an additional epidemiological modelling study to further support the claim of reduction of viremia after vaccination.

Study reference	Study purposed
01	Onset of immunity after challenge
Impact of the Syva EHDV-8 VP2 subunit vaccine on the basic reproduction ratio for EHDV in cattle	Epidemiological modelling study

Pre-clinical studies

Dose determination

The product is applied under Article 25, therefore no separate study for the determination of the vaccine dose was performed. In the combined safety and efficacy study, 2 different doses (75 mcg/dose and 100 mcg/dose) were tested in calves from 3 months of age.

The vaccine batch containing 100 mcg of the VP2 protein is intended as a standard vaccine batch whilst the vaccine batch containing 75 mcg represents a sub-standard batch.
From the results of the study a slight dose response effect between the two different antigen doses seems apparent.

Onset of immunity

The study provided to evaluate the onset of immunity is a combined safety and efficacy study, which 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 study was not conducted under GLP requirements because this requirement can also be lifted for an Article 25 procedure according to Guideline EMA/CVMP/IWP/251947/2021.

To support the proposed efficacy claims of reduction of viraemia and reduction of fever, with an onset of immunity of 2 weeks, the applicant presents results from a combined safety and efficacy study in vaccinated and control calves with a virulent challenge performed 14 days after the second vaccination.

In this study, three different treatment groups were included, each with eight 3- to 5-month-old female calves: two vaccinated groups, one vaccinated with 2 ml of a standard batch (100 mcg/dose) and one with a sub-standard batch (75 mcg/dose). The third group was inoculated with saline as control. First and second vaccination were performed on D0 and D28 of the study respectively.
The animals were vaccinated intramuscularly (IM) in the right (D0) and left (D28) side of the neck.
Before the start of the study, the calves were tested negative for BVDV and BTV genome, and were seronegative for BTV VP7, EHDV VP7 (both by ELISA) and EHDV-8 neutralising antibodies (by VNT).

Fourteen days after the second vaccination (D42) all animals were challenged with 4 x 5.9 $\log_{10}$ $TCID_{50}$/animal of strain EHDV-8/SPA-LBC/24 subcutaneously in the left and right side of the neck and monitored for 21 days after challenge (DPI).

Post challenge the following parameters were investigated:

- assessment of viraemia by RT-qPCR,
- serology by ELISA and virus neutralisation test,
- assessment of clinical signs and continuous activity monitoring,
- assessment of haematological parameters and
- post-mortem examination by necropsy gross- and histopathology.

Viraemia was detected in all study groups from 3 DPI.

In the control group 8/8 animals showed viraemia, 5/8 animals tested positive until end of study.

In the group vaccinated with the standard batch 5/8 animals showed viraemia, 3/8 animals remained negative, and all animals cleared the virus by 14 DPI.

In the group vaccinated with the sub-standard batch, 6/8 animals showed viraemia, 2/8 animals remained negative, and all animals cleared the virus by 14 DPI.

The obtained Ct-values were transformed into $CCID_{50}$/ml values by interpolation from a standard curve prepared with EDHV challenge strain 5.7 $\log_{10}$ $CCID_{50}$/ml. The assay is considered linear for the investigated range.

A reduced proportion of viraemic animals after challenge, as well as a reduced level and duration of viraemia was observed in vaccinated animals. The difference in duration and intensity of viraemia (AUC) between vaccinated groups compared to the control group was statistically significant ($p<0.05$).

Additionally, the applicant states that the viral loads in blood samples from vaccinated animals were below the threshold ($<10^{2.3}$ $TCID_{50}$/ml) required for effective vector-mediated transmission as described in literature, while they were above this threshold in the control group.

Animals were observed for clinical signs for 21 days after challenge at least once daily.
No clinical signs specific for EHDV were observed in any of the study groups.

Rectal temperatures were recorded at least once daily in all animals. Individual peak values of the animals showed a high variation in timing and range. Timepoints with fever showed an intermittent and irregular pattern over time with a low consistency between calves. Mean rectal temperatures in the control group were mostly higher than in the vaccinated groups from DPI 7 to 10 but only on DPI 9 + 10, simultaneous to the peak of viraemia, a statistically significant difference ($p \leq 0.05$) in average rectal temperature between control and vaccinated groups was demonstrated.

All calves of all groups remained seronegative for EHDV VP7 ELISA antibodies until challenge.
This confirms that no natural infection with EDHV occurred during the study.
Three weeks after challenge all calves but one from the group vaccinated with the standard batch had seroconverted and VP7 antibodies were detected.

Only a minor increase in ELISA optical density (OD) values for antibodies against EHDV-8-VP2 was observed after the first and second vaccination.

After challenge a notable antibody response was detected in all three groups, with higher values on D56 in the vaccinated groups compared to controls. At the end of the study OD values in all three treatment groups were comparable.

All calves from all treatment groups remained negative for virus neutralising antibodies until D42 before challenge. All calves from all treatment groups seroconverted three weeks after challenge.

Post challenge, the number of white blood cells, especially neutrophils, dropped on 5 DPI in all groups. The decrease in numbers of white blood cells on 5 DPI and the course of recovery from DPI 7 onwards were comparable in all groups.

No EDHV specific pathological or histopathological alterations were observed in any animal.

Statistical analysis of the data provided is considered satisfactory.

In summary, the study is considered valid, despite a number of shortcomings.

It was concluded that intramuscular injection of 2 doses of the vaccine Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A., administered to cattle from the age of 3 months, at a 4-week interval induced a significant reduction in viraemia (detection of genome copies) after challenge at 14 days after completing the vaccination scheme, since it reduced the proportion of viraemic animals after challenge, as well as the level and the duration of viraemia and reduced the increase of rectal temperature at the time of maximum viraemia.

Epidemiological modelling study

To further support the claim for reduction of viremia, the applicant supplemented the efficacy data with an epidemiological modelling study. In this study, the basic reproduction ratio (R0) and its dependence on environmental temperature is used to quantify transmission of four different strains of EHDV in cattle and deer, and it is defined as the average number of secondary cases that can arise from a single primary case. In conclusion, the modelling study is considered valid, and the results are accepted as supportive for the demonstration of the clinical relevance of the observed reduction of viremia. The claim for reduction of viremia is now substantiated and a considerable reduction of transmission of the disease in vaccinated animals in the field is considered likely. The initially proposed claim for reduction of fever can now also be accepted, as the overall efficacy of the product is now considered demonstrated and significant differences between vaccinated and unvaccinated animals were shown in the challenge study. The major objection is considered solved.

In summary, the CVMP is of the opinion that the presented data including the newly provided epidemiological modelling study demonstrate adequate efficacy of the product in the target species cattle.

Part 5 – Benefit-risk assessment

Introduction

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. emulsion for injection for cattle is a vaccine containing ≥ 100 mcg of VP2 protein of epizootic haemorrhagic disease virus, serotype 8 (EHDV8) as active substance, and Montanide ISA 28 R VG as adjuvant. The target species is cattle.

The primary vaccination schedule to be given to cattle from 3 months of age consists of two doses of 2 ml to be administered 4 weeks apart by the intramuscular route.

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

For active immunisation of cattle to reduce viraemia and fever caused by epizootic haemorrhagic disease virus serotype 8.

Onset of immunity: 2 weeks after completion of the primary vaccination scheme
Duration of immunity: Has not been established

A withdrawal period of zero days is proposed.

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is presented in HDPE vials containing 40 ml (20 doses), 50 ml (25 doses) or 100 ml (50 doses).

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 all dossier parts.

Benefit assessment

Direct benefit

The presented data on efficacy are considered to support adequate efficacy of the product in the target species cattle.

No data are available on duration of immunity. This gap can be accepted under the terms of an Article 25 application and is to be addressed as a specific obligation to the marketing authorisation.

Additional benefits

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. increases the range of available vaccines for the active immunisation of cattle against infections with EHDV.

Risk assessment

The main potential risks are identified as follows:

Quality

Information on development, manufacture and control of the active substance and finished product has been presented. Several data gaps are identified concerning the potency/identity test and the stability of the product. These data gaps can be accepted under the terms of an Article 25 application and are to be addressed as specific obligations to the marketing authorisation:

- The complete validation report for the potency test should be provided to the authorities.
- Stability data for the active substance should be provided to support a storage period of 24 months
- The results of the ongoing real-time stability studies should be provided to confirm the 12-month shelf life of the vaccine. Any out of specification result should be communicated immediately to the Agency.
- Data to confirm the proposed in-use shelf life of 10 hours should be provided.

Safety

Risks for the target animal

The product is generally well tolerated in the target animal when administered intramuscularly in accordance with the SPC recommendations.

The safety of this EHDV vaccine (inactivated) in cattle was confirmed in a study evaluating a standard single dose and a repeated administration of this dose. The main reported adverse reactions include fever and local reactions, which may be observed commonly for a few days.

Pharmacovigilance data provided on the use under Article 110 (2) of Regulation (EU) 2019/6 include some reports in cattle, the adverse reactions provided were included in SPC section 3.6.

Risk for the user

User safety for this product is acceptable when used according to the SPC. Given the nature of the vaccine and its mode of administration, the risk to the user is very low. The main risk is that of accidental self-injection due to the adjuvant containing mineral oil. The standard safety advice is included in the SPC.

Risk for the environment

Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. is not expected to pose a risk to the environment when used according to the SPC recommendations. The nature of the product makes direct exposure to the environment very unlikely. The standard advice on waste disposal is included in the SPC.

Risk for the consumer

A residue study is not required. The withdrawal period is set at zero days.

Special risks

No special risks are indicated.

Risk management or mitigation measures

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

User safety

A low user safety risk due to accidental self-injection has been identified. This risk has been addressed by the safety warnings in the SPC.

The veterinary medicinal product is subject to a veterinary prescription.

Specific obligations 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**
The complete validation report for the potency test should be provided to the authorities.	June 2026

Description	Due date
Stability data for the active substance should be provided to support an intermediate storage period of 24 months.	February 2029
The results of the ongoing real-time stability studies should be provided to confirm the 12-month shelf life of the vaccine. Any out of specification result should be communicated immediately to the Agency.	September 2028
The in-use shelf-life of 10 hours is to be supported by potency data.	June 2026
A study on duration of immunity in cattle should be conducted, and data should be provided.	January 2027

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:
"For active immunisation of cattle to reduce viraemia and fever caused by epizootic haemorrhagic disease virus serotype 8."

Onset of immunity: 2 weeks after completion of the primary vaccination scheme
Duration of immunity: Has not been established

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

The product has been shown to be efficacious for:

Active immunisation of cattle to reduce viremia and fever caused by epizootic haemorrhagic disease virus serotype 8.

Onset of immunity: 2 weeks after completion of the primary vaccination scheme
Duration of immunity: Not established

As the application was submitted under Article 25, certain data on quality, safety and efficacy were not included in the dossier. However, the CVMP considered that the overall benefit of the availability of the veterinary medicinal product would outweigh the risk of absence of these data, also taking into consideration the risk management measures addressed above.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Epizootic haemorrhagic disease vaccine (recombinant protein) Laboratorios Syva S.A. can be approved since these data satisfy the requirements for an authorisation set out in the legislation (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 the quality, recombinant VP2 protein of epizootic haemorrhagic disease virus, serotype 8 (EHDV8), the CVMP considers that recombinant VP2 protein of epizootic haemorrhagic disease virus, serotype 8 (EHDV8) is to be qualified as a new active substance.