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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

Withdrawal assessment report for Equilis EHV 1+4 (EMEA/V/C/006147/0000)

Vaccine common name: Equine herpesvirus vaccine (inactivated)

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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Introduction **4**
Summary of the Pharmacovigilance System Master File 4
Manufacturing authorisations and inspection status 4
Overall conclusions on administrative particulars 5

Part 2 - Quality **5**
Quality documentation (physico-chemical, biological, and microbiological information) 5
Qualitative and quantitative composition 5
Container and closure system 5
Product development 6
Description of the manufacturing method 7
Production and control of starting materials 9
Starting materials listed in pharmacopoeia 9
Starting materials not listed in a pharmacopoeia 10
Control tests during the manufacturing process 13
Control tests on the finished product 13
Batch-to-batch consistency 15
Stability 15
Overall conclusions on quality 16

Part 3 – Safety documentation (safety and residues tests) **17**
General requirements 17
Safety documentation 18
Pre-clinical studies 18
Safety of the administration of one dose 18
Safety of one administration of an overdose 18
Safety of the repeated administration of one dose 18
Examination of reproductive performance 20
Examination of immunological functions 21
User safety 21
Study of residues 22
MRLs 22
Withdrawal period 22
Interactions 22
Clinical studies 23
Environmental risk assessment 28
Overall conclusions on the safety documentation 28

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials) **29**
General requirements 29
Challenge model 30
Efficacy parameters and tests 30
Efficacy documentation 31
Pre-clinical studies 31
Clinical trials 41
Overall conclusion on efficacy 42

Part 5 – Benefit-risk assessment 44
Introduction 44
Benefit assessment 45
Risk assessment 45
Risk management or mitigation measures 46
Evaluation of the benefit-risk balance 46
Conclusion 47

Introduction

The applicant Intervet International B.V. submitted on 26 February 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Equilis EHV 1+4, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 12 October 2022 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

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

Active immunisation of horses to reduce the severity and duration of clinical signs of respiratory disease (rhinopneumonitis), amount and duration of virus excretion and viraemia due to infection with equine herpesvirus 1 and/or equine herpesvirus 4.

Equilis EHV 1+4 is an inactivated vaccine containing equine herpesvirus 1, strain RAC-H and equine herpesvirus 4, strain 2252 as active substances and Iscom-matrix (containing purified saponin) as adjuvant. The target species is horse. The route of administration is intramuscular.

Equilis EHV 1+4 is presented as a suspension for injection in Type I vials of 1 ml (1 dose) or Type I glass pre-filled syringes of 1 ml (1 dose) in packs containing 10 vials or 10 pre-filled syringes with needles.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 19 July 2024, Intervet International B.V. withdrew the application during the clock-stop at day 120 of the procedure. In its letter notifying the Agency of the withdrawal of application, the applicant stated that the reason for the withdrawal is that the currently available resources are not sufficient to solve the issues.

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

A manufacturing authorisation was issued by the competent authority for the manufacturer of the active substance.

A GMP certificate confirming compliance with the principles of GMP for active substances was provided.

A declaration was 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 3 -7/10/2022 by the EU batch release site.

Finished product

Manufacture of the finished product, primary packaging, secondary packaging quality control, batch release and storage and/or distribution take place at Intervet International B.V., Wim de Koverstraat 35, 5831AN Boxmeer, The Netherlands.

The site has a manufacturing authorisation issued on 19/12/2022 by the Dutch competent authority covering the manufacturing activities at the site at Boxmeer.

A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued on 23/7/2020, referencing an inspection on 16/7/2020, by the Dutch 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 substances 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)

Qualitative and quantitative composition

Equilis EHV 1+4 is an inactivated vaccine containing two active substances: inactivated equine herpesvirus 1 (EHV-1) and inactivated equine herpesvirus 4 (EHV-4). The formulation also includes an Iscom-matrix adjuvant containing purified saponin, cholesterol and phosphatidyl choline, and phosphate buffer to form a ready-to-use suspension for injection, with 1 ml of the vaccine representing one dose.

The product is filled into 3 ml type I glass vials containing a single dose of 1 ml, or 2.5 ml type I glass syringes pre-filled with 1 ml in cardboard boxes of 10 vials or syringes.

Container and closure system

There are 2 presentations proposed for the finished product. The vaccine is either filled into 3 ml type I glass vials (in accordance with Ph. Eur. 3.2.1) containing a single dose of 1 ml. These are closed with halobutyl rubber stoppers (in accordance with Ph. Eur. 3.2.9) and aluminium crimp caps. Or the vaccine is filled into 2.5 ml type I neutral glass syringes (in accordance with Ph. Eur. 3.2.1) with a Luer-Slip cone with assembled halobutyl rubber tip cap and closed with a halobutyl rubber stopper/plunger (all rubber components are in accordance with Ph. Eur. 3.2.9). Appropriate

technical drawings and representative certificate of analysis (CoA) are provided demonstrating compliance with the appropriate chapters of the Ph. Eur.

Containers and closures are sterilised by heat treatment or ionising radiation; however, further details were requested and there were some inconsistencies that should have been clarified to ensure compliance with Ph. Eur. 5.1.1 and also regarding the size of the container volumes.

Product development

A description of the product development has been provided addressing the choice of vaccine strains, the manufacturing method and the choice of adjuvant. The EHV strains, EHV type 1 strain RAC-H-2020 and EHV type 4 strain 2252-2020, were chosen based on the prior use in other vaccines manufactured by the applicant demonstrating proven safety and efficacy.

The manufacturing method is a standard procedure used routinely by the applicant and a satisfactory description is provided. The vaccine is formulated with antigen units (U) EHV-1 and U EHV-4, which, upon release, is verified to be in accordance with the dose indicated by the efficacy studies. However, a major objection was raised with regard to the adjuvant formulation used in the vaccines generated for the efficacy studies.

The formulation of the finished product is similar to other equine vaccines manufactured by the applicant and comprises the inactivated EHV-1 and EHV-4 antigens, blended with the adjuvant, Iscom-matrix, and a phosphate buffer. A description of the adjuvant is provided, which is comprised of fraction-C saponins combined with cholesterol and phosphatidylcholine to form matrix particles. The adjuvant was selected based on previous safety and efficacy profile in other MSD products. Two Iscom-matrix preparations (Matrix V and Matrix V2) are proposed for use as an adjuvant, both of which are described by the supplier. While the saponin component remains fixed in the finished product, the quantities of cholesterol and phosphatidylcholine vary between the two formulations.

In previous products, the final quantity of Iscom-matrix is quantified by HPLC by the amount of saponin component in the finished product. However, this was not possible for this product. Since the three Iscom-matrix components (saponin, phosphatidylcholine and cholesterol) are in ratios to one another, the adjuvant content is determined based on one of them. However, the details of the method used were not clear and the ratio between the two different adjuvant formulations not constant. This was considered a major concern and was part of the major objection regarding the adjuvant.

There were a number of concerns related to the method of quantification of the Iscom-matrix in the finished product, and ensuring the quality and consistency of the finished product is maintained when using two different formulations of the adjuvant. These included a request for the justification for using two different formulations, the clarification of the formulation used for the validation of the adjuvant content test and safety and efficacy batches, further information on the other excipients that may be present due to the extraction and manufacturing processes of the saponin component and a clarification regarding the suitability of the quantification of saponin active component. Due to the potential impact on the consistency of the product, which may impact on the safety and efficacy of the vaccine, an additional finished product test regarding the identification or quantification of the adjuvant, e.g. by electron microscopy (EM) was requested. All the above concerns were raised as a major objections.

Two different versions of the development report on the analysis of Matrix V and Matrix V2 are submitted in sections 2A and 2C respectively, further questions regarding this report were raised in

section 2C.

An overview of the batches used in the safety and efficacy studies is provided, with batch protocols provided for each batch. The formulation is equivalent to that intended for marketing. However, there was a major objection regarding the formulation of the adjuvant that is used to generate the batches used for safety and efficacy studies.

With reference to the submitted batch protocols, an explanation on the correlation between the actual release limits for antigenic content and the limits expressed as ranges in the batch protocols was missing. The relationship between units expressed as log_{10} and log_2 was also requested to be elucidated. Additional concerns were raised in this regard in sections 2B and 2G.

All of the batch protocols provided pertain to finished product batches filled in glass vials. Representative batch protocols of R&D and/or production scale batches filled in syringes should have been also provided.

Description of the manufacturing method

The process is considered to be a standard manufacturing process.

The manufacturing process to generate the antigens consists of 8 main steps for each antigen, as described below. Some clarifications were requested in terms of hold times and additional detail regarding the cell and virus propagation. The applicant was also requested to provide the typical batch volume for antigen production. General issues were also identified on manufacture related to product- and process-related impurities.

Step 1 - Production of the cells (PS-2020 for EHV-1 and Vero Marburg-2020 for EHV-4)

Cells are taken from stocks stored at -140 °C or harvested during a clean production round and cultured in the appropriate media in roller bottles. Cells are incubated until forming a confluent monolayer. Cells are passaged until sufficient cells are obtained for virus production ensuring cells do not exceed MCS+20, in accordance with Ph. Eur. 5.2.4. While the passaging procedure for PS-2020 cells is adequately described, further information was requested to describe the passaging procedure for Vero Marburg cells. A definition of "clean cell production round" was requested together with a description how these cells are controlled for their applicability prior to use. Clarification was asked for the control of a confluent cell monolayer prior to detachment.

Step 2-3 - Virus production (EHV-1 and EHV-4)

Roller bottles of the appropriate cells are seeded with EHV-1 RAC-H-2020 and incubated. The working seed virus (WSV) is not more than 5 passages from the master seed virus (MSV) in accordance with Ph. Eur. 0062. The virus is harvested by shaking the roller bottles and the harvest is stored. Validation for this hold time was not provided and was requested. Further information was also requested regarding the preparation of the viral stock prior to seeding the cells.

Steps 4 - 6 - Downstream processing of the virus harvest (EHV-1 and EHV-4)

The harvest is concentrated by ultrafiltration and clarified by filtration or centrifugation. The harvest is stored for up to one week. Validation for the hold time is provided for up to 5 days, further validation was requested. Information was missing on centrifugation duration.

Steps 7 - 8 - Viral inactivation and storage (EHV-1 and EHV-4)

The viral harvest is inactivated and inactivation occurs under continuous stirring. Inactivation is stopped. The inactivated antigen is stored. There were some outstanding queries regarding the

stability of the stored antigen that were raised in Part 2G. Further, information on the control of residual was requested.

The inactivation test method and kinetics are adequately validated and comply with the requirements of Ph. Eur. 0062.

Blending of the finished product

To generate the finished product the thawed EHV-1 is added to the EHV-4 antigen in a sterile blending vessel to achieve the fixed amount of U/dose for EHV-1 and EHV-4. The appropriate amounts of Iscom-Matrix and PBS are added to the blending vessel, the vaccine is blended by continuous stirring. Clarification was requested regarding the amount of Iscom-matrix used for blending. Additional information on stirring speed and temperature was required.

The vaccine bulk is stored prior to filling into the final containers, which, while not specifically validated, can be considered acceptable as the finished product testing is performed on filled vials.

Major steps of the manufacturing process have been validated by three consecutive antigen and finished product batches. However, there were several questions raised in Part 2F regarding the batch data provided and therefore no conclusions could be made regarding the validation of the manufacturing process.

Validation of the titration tests for EHV-1 and EHV-4

Validation of the viral titration tests for EHV-1 and EH-4 was performed in line with VICH GL1 and GL2 with all parameters assessed and acceptable with the exception of accuracy and specificity. The omission of testing for the accuracy of the validation was considered acceptable, however, as there were outstanding concerns regarding the extraneous agent testing of the media and growth supplements, the omission of testing for specificity was not considered acceptable unless these concerns were addressed. Information was needed on reference standards in the context of the omission of accuracy.

Validation of the residual substance stopping inactivation testing

Validation of the method was performed in line with VICH GL1 and GL2 with all parameters assessed with the exception of specificity, which is not relevant and therefore its omission is acceptable. All parameters tested were within the stipulated acceptance criteria, however, further information was requested regarding a deviation from the protocol with respect to the acceptance criteria for the immediate precision as well as an explanation for the omission of robustness in the validation.

Validation of the sterility testing of the antigens

The sterility testing of the antigens is performed by direct inoculation in accordance with Ph. Eur. 2.6.1. EHV-1 can also be tested by direct inoculation with automated growth detection, which the applicant states is in accordance with Ph. Eur. 5.1.6. However, additional information was requested from the applicant regarding the primary validation of the technique to include further information on the principle of detection.

Validation of the antigenic mass ELISA for the quantification of EHV-1 and EHV-4 inactivated antigens

The validation of the antigen mass ELISA tests for detection of inactivated EHV-1 and EHV-4 antigens were performed following VICH GL1 and GL2. The applicant assessed specificity, robustness, precision (repeatability and intermediate precision), linearity and range of the assays.

The antigenic mass of test samples is determined against the antigenic mass of the reference standard with an assigned antigenic mass. The antigenic mass of the reference batch was the same as used in the efficacy studies, however how the antigenic units were assigned to the efficacious and reference batches would have required further clarification and was considered a major concern. Further information on the manufacturing process for the reference, internal control and sample batches and details of the antibodies used in the validation studies was requested. The robustness, precision and linearity were sufficiently demonstrated, however the results of the specificity of the assays and relevance of the validated range of both assays required further clarification.

Validation of the potency tests on the finished product

Validation of the method was performed in line with VICH GL1 and GL2 with all parameters assessed with the exception of accuracy, which is acceptable in line with VICH GL2 considering the precision, linearity and specificity are sufficiently demonstrated. Queries regarding the adjuvant used to validate specificity of the assay and replacement of the critical assay reagents, must have been addressed. The applicant was also requested to harmonise the nomenclature used to determine the potency to ensure consistency throughout the documents.

Validation of the adjuvant content

HPLC is used to measure the cholesterol component of the Iscom-matrix adjuvant. Considering the three components of the adjuvant system (saponin, cholesterol and phosphatidylcholine) are present in a constant ratio, providing a specific HPLC peak pattern, the cholesterol component can be used to quantify the other constituents of the Iscom-matrix. Validation of the method was performed in line with VICH GL1 and GL2 with all parameters assessed. However, the applicant was requested to clarify which of the two Iscom-matrix formulations proposed was used to perform the validation studies. Clarification was required for the tests for specificity, stability and robustness prior to any conclusions regarding the validation of the test method.

Validation of the sterility testing of the finished product

The sterility test is performed by direct inoculation in line with Ph. Eur. 2.6.1 with automated growth detection. Therefore, satisfactory response to the queries relating to the sterility testing of the EHV-1 antigen using automated growth detection (Bactec method) were required for conclusions to be drawn regarding validation of the sterility testing of the finished product. Additional clarification was required regarding the finalised method to ensure that there is no inhibition of growth of any of the microorganisms listed in Ph. Eur. 2.6.1. Clarification was needed on why sterility validation was only performed with glass vials but not with prefilled syringes.

Sterility testing of the finished product may also be performed by membrane filtration in line with Ph. Eur. 2.6.1.

Production and control of starting materials

Starting materials listed in pharmacopoeia

Representative CoA have been provided for all starting materials listed in the pharmacopoeia.

Bovine serum

Bovine serum is used as a component in the culture media for both EHV-1 and EHV-4 cells and virus propagation. There are a number of suppliers proposed for bovine serum, and it is noted that CEP

have been provided for bovine serum, adult bovine serum, donor bovine serum, foetal bovine serum, foetal calf serum, newborn bovine calf serum and newborn calf serum, however, the nomenclature in the dossier is 'bovine serum'. Therefore, it is assumed that each of these categories of serum can be used interchangeably as 'bovine serum'. The raw material for the production of serum is acquired from New Zealand, Australia, USA, Canada and Mexico. Some further information was requested regarding the CEPs provided.

A certificate of analysis is provided for one supplier of bovine serum, which describes the testing performed, including testing for a number of extraneous agents, sterility, mycoplasma and includes a certificate of irradiation. However, no further CoA are provided from the other suppliers and no risk assessment has been provided with regard to extraneous agent contamination for the bovine serum, or information regarding the irradiation of the bovine serum by the applicant. This information was requested.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

EHV-1 strain RAC-H-2020

EHV-1 strain RAC-H-2020 was originally isolated from an aborted equine foetus in 1957, used to infect golden hamsters and subsequently seeded to porcine kidney cells. MSD Animal Health obtained it from the University of Munich in 1986, where it was transferred to the PS porcine kidney cell line and passaged further to generate the MSV. The MSV is appropriately labelled and stored.

The identity of the MSV is confirmed by immunofluorescence using monoclonal antibodies against EHV-1, however, no method could be located in the dossier, and this was requested. The MSV is tested for sterility in compliance with Ph. Eur. 2.6.1, mycoplasma in compliance with Ph. Eur. 2.6.7, and relevant extraneous agents. Testing for extraneous agents (EA) relevant for each of the species outlined is in compliance with Ph. Eur. 5.2.5, with satisfactory justification provided for those agents not tested, including the provision of appropriate supportive literature.

A TSE risk assessment was provided describing the risk of contamination as negligible, which is acceptable. However, some discrepancies are noted between the risk assessment and a summary document on EA testing and needed therefore to be clarified, also for EHV-4 strain 2252-2020.

The WSV is produced from the MSV by passaging in PS-2020 cells. The WSV is tested for sterility in accordance with Ph. Eur. 2.6.1, and mycoplasma in accordance with Ph. Eur. 2.6.7. The preparation and testing of the WSV is described in sufficient detail and is in compliance with the requirements of Ph. Eur. 0062.

EHV-4 strain 2252-2020

EHV-4 strain 2252-2020 was originally isolated from the upper respiratory tract of an adult horse in the UK in 1973, and subsequently seeded to primary equine cells, Vero cells and primary pig kidney cells at MSD Animal Health to generate the MSV. The MSV is appropriately labelled and stored.

The identity of the MSV is confirmed by immunofluorescence using monoclonal antibodies against EHV-4, however, no method could be located in the dossier, and this was requested. The MSV is tested for sterility in compliance with Ph. Eur. 2.6.1, mycoplasma in compliance with Ph. Eur. 2.6.7, and relevant extraneous agents. Testing for extraneous agents relevant for each of the species outlined is in compliance with Ph. Eur. 5.2.5, with satisfactory justification provided for those agents not tested, including the provision of appropriate supportive literature.

A TSE risk assessment was provided describing the risk of contamination as negligible, which is acceptable.

The WSV is produced from the MSV by passaging in Vero Marburg-2020 cells. The WSV is tested for sterility in accordance with Ph. Eur. 2.6.1, and mycoplasma in accordance with Ph. Eur. 2.6.7. The preparation and testing of the WSV is described in sufficient detail and is in compliance with the requirements of Ph. Eur. 0062.

PS-2020 cells used for EHV-1 antigen production

PS-2020 (porcine stable) cells are a continuous porcine kidney cell line, which were obtained in 1986 by MSD Animal Health from the University of Berlin, who originally obtained the cells from the Robert Koch Institute, Berlin. Mycoplasma eradication was performed and the MCS derived after passages on PS cells. The MCS is appropriately labelled and stored.

No specific WCS is prepared; PS-2020 cells are sub-cultured up to MCS+20. Clarification was requested to ensure the maximum number of passages does not exceed 20 from the MCS.

Testing of the MCS and MCS+20, where appropriate, is performed in accordance with Ph. Eur. 5.2.4, with the exception of tumorigenicity, which is considered unnecessary for this product considering the manufacturing process and inactivation ensures no whole or viable cells are present in the finished product. Testing for extraneous agents is performed in accordance with Ph. Eur. 5.2.5, with sufficient justification provided for any agents omitted from testing. A TSE risk assessment was provided in line with Ph. Eur. 5.2.8 and demonstrates a negligible TSE risk.

Vero Marburg-2020 cells used for EHV-4 antigen production

The Vero Marburg-2020 cell line is derived from kidney tissue isolated from an African Green Monkey. It was obtained in 1977 by MSD Animal Health and the MCS derived after few passages. The MCS is appropriately labelled and stored.

No specific WCS is prepared; Vero Marburg-2020 cells are sub-cultured up to MCS+20. Some clarification was requested regarding the maximal passage generated.

Testing of the MCS and MCS+20, where appropriate, is performed in accordance with Ph. Eur. 5.2.4, with the exception of tumorigenicity, which is considered acceptable. Testing for extraneous agents is performed in accordance with Ph. Eur. 5.2.5, with sufficient justification provided for any agents omitted from testing. A TSE risk assessment was provided in line with Ph. Eur. 5.2.8 and demonstrates a negligible TSE risk.

Iscom-matrix

Iscom-matrix is a mixture of saponin, cholesterol and phosphatidylcholine and is supplied ready to use in one of two formulations, Matrix V and Matrix V2, with CoA provided for both formulations. There were a number of concerns regarding the Iscom-matrix that were raised as major objections.

A risk assessment has been provided for both extraneous agents and TSE, both are considered acceptable.

Tryptose phosphate broth

A suitable CoA is provided for TBP indicating that the components include milk fit for human consumption and material of porcine origin. With respect to the TSE risk, in accordance with the Notice for guidance (NfG) EMEA/410/01-rev3, milk fit for human consumption is considered negligible risk, and pigs are not a TSE-relevant species, therefore the TSE risk is considered negligible. The TBP is sterilised for ≥15 minutes at ≥121 °C, in accordance with Ph. Eur. 5.1.1.

Tryptose

A suitable CoA is provided for tryptose indicating that the components include milk fit for human consumption and material of porcine origin. With respect to the TSE risk, in accordance with the NfG EMEA/410/01-rev3, milk fit for human consumption is considered negligible risk, and pigs are not a TSE-relevant species, therefore the TSE risk is considered negligible. The TBP is sterilised for ≥15 minutes at ≥121 °C, in accordance with Ph. Eur. 5.1.1.

Sterilisation as described would not be considered sufficient to inactivate all viruses, and therefore a risk assessment for the contamination of all materials of animal origin was requested, in accordance with the requirements of Ph. Eur. 0062 and 5.2.5.

Lactalbumin hydrolysate

A suitable CoA is provided for tryptose indicating that the components include milk fit for human consumption. With respect to the TSE risk, in accordance with the NfG EMEA/410/01-rev3, milk fit for human consumption is considered negligible risk, therefore the TSE risk is considered negligible. The TBP is sterilised for ≥15 minutes at ≥121 °C, in accordance with Ph. Eur. 5.1.1.

Trypsin

Trypsin is sourced from porcine pancreas and produced in a process using bovine lactose. A suitable CoA is provided. With respect to TSE, in accordance with the NfG EMEA/410/01-rev3, milk fit for human consumption is considered negligible risk, and pigs are not a TSE-relevant species, therefore the TSE risk is considered negligible. The certificate of irradiation quoted in the CoA should have been provided including details of the irradiation process.

Veggie media

A suitable CoA for Veggie-media is provided. Veggie media does not contain any material of human or animal origin and is sterilised prior to use. Further information was requested regarding the qualitative and quantitative composition of the media as well as the preparation of the media.

Veggie protease

A suitable CoA for papain is provided. Papain is extracted from the *Carica papaya* and does not contain any material of human or animal origin.

Starting materials of non-biological origin

Certificates of analysis have been provided for 2-bromoethylamine hydrobromide and leupeptin, with both conforming to the required specifications. However, there were some outstanding questions regarding the use of antibiotics in the virus culture media, and the provision of missing CoA.

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

Detailed qualitative and quantitative composition, method of preparation and storage of the media and solutions prepared in-house are 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. Several CoA for components used in the preparation of media could not be located and were requested.

Control tests during the manufacturing process

The applicant presented in-process data for the manufacture of two batches of EHV-1 and three EHV-4 batches. During the manufacture of the antigen the following in-process control (IPC) tests are carried out on each antigen: infectious EHV titration test, inactivation control, test for residual thiosulphate, sterility and antigenic mass determination. The results of the IPC tests provided by the applicant for these batches were consistent and within the specifications. However, the proposed manufacturing scale for the antigen batches is not specified and batch specific records for one of the EHV-1 antigen batch should have been provided before the conclusion on consistency of manufacture of the antigens could be made. Additionally, the applicant provided data for three consecutive batches of each antigen manufactured at the R&D scale where the final bulk was less than 1L each. Results of these batches were comparable, however no tests for residual thiosulphate were performed. Also, it is not clear whether these batches were manufactured using the same manufacturing process/equipment as for the production scale manufacture. Therefore, these data were considered as supportive only.

The description for the IPC tests were provided. The infectious EHV titration test is carried out on every antigen batch before inactivation of the harvested virus with BEI to determine the infectivity titre by means of cytopathogenic effect (CPE) on SP cells (EHV-1) or Vero Marburg cells (EHV-4). The inactivation test is performed on every antigen batch after inactivation by inoculating the cell cultures with inactivated and neutralised antigen and checking for the presence of CPE during several subcultures over the period of 2 weeks. A qualitative test for residual thiosulphate is performed on a representative sample of each antigen batch after inactivation to confirm the presence of residual sodium thiosulfate by iodine titration. Sterility is performed on every inactivated antigen batch to detect contamination. Samples are tested for presence of contaminating microorganisms by direct inoculation according to Ph. Eur. 2.6.1. As backup, an automated growth detection system (BD BacTec System) can be used for sterility testing of EHV-1, however further clarification was required on what instances would require the backup testing and questions on sterility test validation are raised in Part 2B. The antigenic mass determination test is performed on every inactivated antigen batch to determine the antigen content of the batch by EHV-1 or EHV-4 specific sandwich ELISA. Validation of the EHV-1 and EHV-4 antigen mass ELISA methods for detection of inactivated EHV-1 and EHV-4 antigens were performed following the VICH GL1 and GL2. The applicant assessed specificity, robustness, precision (repeatability and intermediate precision), linearity and range of the assay. The antigenic mass of test samples in Units (U)/mL is determined against the antigenic mass of the reference standard with an assigned antigenic mass. The linearity, robustness and precision were sufficiently demonstrated for both assays. However, it is unclear how the antigenic mass units were assigned to the reference standard batches, the quality of the batches used for validation is questioned, the choice and origin of the antibodies used and the validated ranges required further clarification, and the specificity of the assays were not sufficiently demonstrated.

Overall, the in-process tests can be considered sufficient to control all the critical steps in the manufacturing, however the questions raised in relation to the validation of the test methods raised needed to be satisfactorily addressed. A number of questions were raised on the quality of the SOPs provided for the IPC tests, including the details and amounts of standards and reagents used and absence of the defined standards/reagents replacement procedures and protocols.

Control tests on the finished product

The description of the methods used for the control of the finished product (appearance, pH,

identification and potency, determination of the adjuvant content, sterility and filling volume) and the specifications were provided; however, some minor information was missing and should have been provided by the applicant. Validation of the finished product (FP) tests is in accordance with VICH GL1 and GL2 although questions were raised as discussed in Part 2B.

The appearance test is a macroscopic observation performed on a representative sample of finished product to check appearance, container and volume. Limits of specifications defined as translucent, pink to colourless opalescent fluid. The determination of pH is carried out on a representative sample of finished product in accordance with the Ph. Eur. 2.2.3. The specification for the pH of the finished product is within an acceptable range 6.5-7.5.

Identity and potency of the active substances' tests are performed on a representative sample of finished product by ELISA. The identity of the antigens is confirmed by virtue of specificity of the ELISA antibodies to a particular antigen, although the details of the antibodies used in the ELISA assays were not provided and were requested. Potency is established by determining the antigenic mass of test samples and is determined against the antigenic mass of the reference standard, with a predefined antigenic mass, and is expressed in $\log_{10}$ U/ml. The limits of specification for EHV-1 is ≥ 3.0 $\log_{10}$ U/ml and for EHV-4 is ≥ 3.5 $\log_{10}$ U/ml and is based on the minimum antigen content used in the preclinical and clinical efficacy studies performed with Equilis EHV 1+4 at 3.0 $\log_{10}$ U/dose of EHV-1 and 3.5 $\log_{10}$ U/dose of EHV-4. The vaccine is manufactured at a fixed amount of EHV-1 and EHV-4 antigen, and the acceptable threshold for batch release is set. This ensures that only efficacious batches will be released to the market. The antigen mass ELISA tests were validated in line with VICH GL1 and GL2. The following parameters were investigated: specificity, robustness, precision (repeatability, intermediate precision, sample size and reproducibility), linearity and range. The quantitation and detection limits are not relevant for the purpose of these tests.

The specificity was demonstrated in line with VICH GL2 taking into consideration presence of high concentration of the adjuvant (the matrix effect) and another compound with closely related structure, such as EHV-4 or EHV-1 accordingly, however the applicant was requested to clarify which Iscom-matrix (V or V2) was used in the specificity samples. The robustness, linearity and precision, by means of intermediate precision and repeatability, were sufficiently demonstrated. However, the validated range of the assay required further clarification in terms of relevance to the finished product release specifications.

Overall, the antigenic mass ELISA for EHV-1 and EHV-4 titration could be considered suitable to detect batches with lower antigen content and ensure consistency of manufacture provided the issues raised in relation to the validation, details of the SOP and replacement protocols were addressed satisfactorily.

The adjuvant determination in the finished product is performed on a representative sample of finished product by measuring concentration by HPLC according to an isocratic reversed phase method by using UV detection. Final product control tests regarding the identification or quantification of the adjuvant, e.g. by electron microscopy was requested. A major objection was raised in relation to the proposed method of adjuvant content determination as discussed above.

No identification or assay of excipients component is provided. Due to presence of residues in the antigen bulk as result of the inactivation process a method for determination of residual concentration should have been introduced for finished product testing, unless a robust justification for omission would have been provided.

Sterility testing is performed on each filling lot to ensure sterility of each vaccine batch according to Ph. Eur. 2.6.1, by performing either a direct inoculation method in line with Ph. Eur. 2.6.1 "Sterility" or an automated growth detection system based on detection of CO_2 produced by the

microorganisms in line with Ph. Eur. 5.1.6 "Alternative methods for control of microbiological quality". Validation of both methods is discussed in Part 2B. However, it is not clear whether these methods are used interchangeably or sequentially and further clarification was required on the technique description in the SOP provided.

The filling volume test is performed on the final product as part of IPC testing during filling at about 30 minute-intervals to check the volume in the filled vials / syringes, however no SOP or the method of calculating the volume from the weight of the syringes is provided. Limits of specifications for vials are 1.08 – 1.35 ml and for syringes 1.00 – 1.25 ml of deliverable volume and considered acceptable. For consistency reasons, the filling volumes have only been tested in vials, not in syringes. This should have been justified by the applicant.

Batch-to-batch consistency

The applicant presented finished product data for the manufacture of three consecutive finished product batches manufactured at R&D scale and two batches manufactured at a lower limit of the production scale proposed. The batches were tested for filling volume, pH, appearance, identity/potency, adjuvant content and sterility. The results for the five batches provided were within the specifications and comparable, except for the adjuvant content. The adjuvant content was tested on the two production scale batches only with OOS results due to human error, as lower quantity of Iscom-matrix was added during blending of the finished product. The applicant was requested to elaborate these OOS results in more detail and to explain whether any corrective actions have been taken. In line with the Guideline on process validation for finished products (EMA/CHMP/CVMP/QWP/749073/2016) data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches corresponding to at least 10% of the production scale batch, and a justification outlined in the Guideline is provided. Data from R&D batches however can only be considered supportive. Therefore, results of the FP testing for two additional production scale batches should have been provided before the end of the procedure to support the data for consistency of manufacture. Additionally, the BRP should have included reference to the test methods used for batch analysis. No data to support consistency of manufacturing at the upper limit of the manufacturing scale has been provided. This could have been considered acceptable if the data for three consecutive batches at lower limit of the production range was provided.

However, since consistency of the manufacturing process is not proven and no reliable data regarding the adjuvant content are available, this issue was considered a major objection unless appropriate data, as requested above, were provided by the applicant.

During the manufacture of the active substance the following tests are carried out: the corresponding virus titration, inactivation, residues, sterility and antigenic mass of the corresponding virus. Results of all tests were within the limits of the defined specifications and comparable between the batches of each antigen. Test descriptions and the limits of acceptance were presented. The in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing provided the issues raised on the IPC testing are addressed satisfactorily.

Stability

<u>For the bulk antigen</u>

The shelf life proposed for the two antigens is 1 year when EHV-1 stored at ≤-35°C and EHV-4 stored at 2 - 8°C. The antigen stability for 1 year was studied by blending two R&D scale batches of finished product. One batch was blended with fresh antigens, while the other batch was blended

with the antigens stored at their proposed storage temperatures for 1 year before blending. The batches were tested at T0, T12 and T23/26 for identity and potency and the results were comparable between the batches. The results for the R&D batches were within the specifications and comparable. However, the description of the containers used for the stability study was not provided. To conclude on the acceptability and comparability of the stability data of the antigen, data for the production batches manufactured at full or at least a pilot scale, providing this mimics the full-scale production described in the Part 2B, must have been provided in line with the Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010-Rev.2).

In particular, stability studies should have been performed with three different batches for each antigen (production scale or representative pilot scale). Test results of antigen batches, information on precise storage conditions (including containers used) as well as a shelf life specification for stored active substance batches were requested to be provided in order to be able to substantiate a shelf life claim for stored active substance batches.

For the finished product

The shelf life proposed for the finished product is 2 years stored at 2-8 °C. The results of stability study for three R&D scale production batches (low pH blend, medium pH blend and high pH blend) were provided up to some months of storage. All results were within the set specifications, except results for pH testing for one batch blended with high pH. Three more batches were also placed on the stability programme for which no stability data was provided for two batches and results were provided for one batch (same bulk vaccine blend as another batch, only filled in syringes), which were within the set specifications. Results of R&D stability testing for additional 7 Equilis EHV 1+4 R&D batches stored at 2-8 °C were provided for various storage duration. All results were within the specifications; however, no sterility testing was performed for any batches presented to support the proposed stability data. The sterility of the product must be proven at the end of the shelf life in line with the Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010). The proposed shelf life of 24 months based on the results from the R&D stability testing is not acceptable. No conclusion on the duration of the shelf life could be made for this immunological product. The applicant could have provided additional results of the on-going stability study on full production scale batches by the end of the procedure in line with the Guideline on requirements for the production and control of IVMPs (EMA/CVMP/IWP/206555/2010-Rev.2) to support a claim for shelf life of the finished product, however the sterility of the antigen batches filled into both vials and syringes at the end of the shelf life proposed must have been demonstrated.

Overall, due to lack of acceptable stability data for this IVMP, a major objection was raised concerning submitted stability data.

Overall conclusions on quality

The quality part of the dossier complies with the Annex II to Regulation (EU) 2019/6. General and where relevant specific Ph. Eur. monographs have been followed and the data are generally adequate in support of a consistent and well controlled manufacturing process. Nevertheless, some issues needed to be clarified and/or justified further.

The composition of the product is described in sufficient detail. The development of the product has been adequately described and justified. A major objection was raised regarding the adjuvant. There were concerns regarding the potential use of two formulations of the Iscom-matrix adjuvant interchangeably. A robust justification was required before this could be accepted; or a single

formulation was proposed. Furthermore, the method of quantitation of the Iscom-matrix was considered a major objection, with robust justification required to demonstrate that the method proposed is fit for purpose to accurately quantify the active components of the adjuvant. A suitable method of ensuring the quality of the adjuvant complex in the finished product was also required. All excipients are well known pharmaceutical ingredients and there are no novel excipients used in the finished product formulation.

The manufacturing process consists of eight main steps for each antigen, followed by blending of the finished product and filling into final containers. The manufacturing process has generally been described in adequate detail.

Starting materials have been listed and shown to comply with pharmacopoeial or in-house requirements. The extraneous agents risk assessment needed to be updated to include all starting materials of biological origin. Description of the media and working solutions is adequate, however, a number of CoAs could not be located and were requested.

Control tests performed during the manufacturing process have generally been adequately described and appropriately validated. However, further detail or clarification were required for a number of the validation studies including sterility. A major objection was raised regarding the antigenic mass ELISA tests requiring clarification of the units of measurement, which are not consistent throughout the dossier or validation documents.

Finished product control tests have generally been adequately described and in general appropriately validated, although further details/clarification regarding potency test validation were required.

Consistency of manufacture has not been adequately supported and additional data were requested to demonstrate the consistency of manufacture. This was considered a major objection. Data on stability of the active substances and the finished product have been provided for R&D batches only and is considered insufficient. A major objection was raised concerning the stability data.

In the presence of major objections, no conclusions could be taken on the quality documentation of the application.

Part 3 – Safety documentation (safety and residues tests)

General requirements

Safety studies were conducted in accordance with the requirements of Regulation (EU) 2019/6, and in addition, the relevant guidance documents Ph. Eur. 1613 (for inactivated equine herpesvirus vaccines) and Ph. Eur. 5.2.6 were taken into account.

Batches of vaccine used in the safety studies were stated to have been manufactured in accordance with the description in Part 2 of the dossier. However, noting that there are major issues raised with respect to the adjuvant under the quality part of the dossier, the applicant was requested to confirm the composition of the adjuvant proposed for inclusion in the final formulation of Equilis EHV 1+4 and to clarify if it is the same (qualitatively and quantitatively) as that in the batches used in the pivotal safety studies. If there were any differences in the adjuvant used in the safety studies compared to that which is proposed for marketing, the applicant should have justified how the safety data

presented in Part 3, could be considered representative of the safety profile of the vaccine formulation proposed for marketing.

It is noted that questions are raised under Part 2 concerning the conversion factor for the antigen content in AU/dose to antigen content in log 10 U/ml. Although the applicant has stated the antigen content per dose in log 10 U/ml in Part 3 of the dossier for each vaccine batch, together with information regarding AU/dose in the final study reports for the studies concerned, this point should have been resolved and the applicant was requested to confirm the stated antigen content in log 10 U/ml for the batches used in the safety studies.

Safety documentation

Safety of the primary vaccination schedule in 5 – 7-month-old foals, in pregnant mares (during different periods of gestation), and safety of the booster vaccination in pregnant mares was investigated in 4 GLP-compliant pre-clinical safety studies. Safety of a fourth (second booster) administration was investigated in adult horses in a GLP-compliant pre-clinical efficacy (duration of immunity) study. Safety of the primary vaccination schedule in 5 – 7-month-old foals, and safety of the primary course plus the booster vaccination in pregnant mares was investigated in a GCP-compliant clinical safety (combined with efficacy) study. Compatibility of use is claimed with three equine vaccines (Equilis Prequenza Te, Equilis Prequenza, and Equilis Te), for use at the same time but not mixed with Equilis EHV 1+4. The safety of non-mixed associated use of Equilis EHV 1+4 with Equilis Prequenza Te and Equilis Prequenza was investigated in pregnant mares in a pre-clinical (laboratory) study and with Equilis Prequenza Te in 5–7-month-old foals and pregnant mares in the clinical safety study.

The vaccine was administered by the intramuscular route, as recommended in the SPC.

Pre-clinical studies

In the pre-clinical safety studies the following parameters were used to establish the safety of Equilis EHV 1+4 in the target species, horses:

- Clinical observations, including rectal temperature measurement for 14 days post-vaccination.
- Virus neutralisation (VN) assay to determine virus neutralising antibodies for EHV-1 and EHV-4.
- Determination of presence of EHV-1 and/or EHV-4 in peripheral blood leucocytes (PBL).
- Determination of presence / excretion of EHV-1 and/or EHV-4 in nasal swabs.

Safety of the administration of one dose

Refer to Safety of the repeated administration of one dose, below.

Safety of one administration of an overdose

As Equilis EHV 1+4 is an inactivated vaccine, investigation of the safety of an overdose is not required. Notwithstanding this, in three studies, vaccine batches that were blended to contain 5-fold higher antigenic content than the targeted fixed content at batch release were used.

Safety of the repeated administration of one dose

One pivotal study and three supportive repeated dose pre-clinical studies were provided.

In study **1,** 10 5–7-month-old foals were administered Equilis EHV 1+4 (blended to contain the minimum antigenic content at batch release), and 14 days later, were revaccinated with Equilis EHV 1+4 (blended to contain 5 times the fixed antigenic content at batch release). Four foals were included in the study as negative controls. The time interval between vaccine administrations is compliant with relevant guidance. Whilst the study is considered a pivotal study for the safety of the vaccine following single and repeated use, significant concerns were raised concerning the data presented. The use of a vaccine batch of minimum antigenic content for the first vaccination is not in compliance with Ph. Eur. requirements. Furthermore, the pre-study serological status of the foals used in the study is not in accordance with Ph. Eur. 1613, as on the day of the first vaccination, 6/14 and 13/14 of foals did not have 'a low antibody titre not indicative of recent infection' for EHV-1 and EHV-4 respectively, although it was confirmed that study animals were not excreting EHV-1 or EHV-4 throughout the study. The observations of note in this pivotal preclinical safety study were elevated rectal temperature and local injection site reactions. Serous to mucopurulent ocular and nasal discharge were also recorded throughout the course of the study. The applicant was requested to re-evaluate the rectal temperature data in this and other pre-clinical safety studies such that the adverse event 'elevated temperature' could be accurately reported in the SPC. Justification for the use of a below maximum potency batch for the administration of the first dose and evidence that the serological status of the foals used in this pivotal study did not impact of the evaluation of vaccine safety was required before safety of Equilis EHV 1+4 in the most sensitive category of animals could be considered to have been suitably demonstrated.

In studies **2** and **3,** 9 (both studies combined) foals were administered with one dose of Equilis EHV 1+4, 2 weeks apart. Both doses were manufactured to contain 5 times the targeted fixed antigenic content at batch release. This study has been performed in animals younger than the proposed minimum age of 6 months. A contemporaneous age-matched control group was not included. Based on the study design, and the age of animals, this study is considered a supportive (non-pivotal) study for safety of the vaccine following single and repeated use in foals. While a similar adverse event profile to that in older foals was observed, the specific results would have not been captured in the SPC of Equilis EHV 1+4. The applicant was requested to remove the following statement from section 3.2 of the SPC: 'Safety has been demonstrated in foals.' In addition, appropriate efficacy data to support use in foals younger than 6 months of age were not provided.

Study **4** is a pre-clinical efficacy study, which was also used to evaluate the safety of administration of a 4th dose of Equilis EHV 1+4 (administered 1 year after the first revaccination (booster) dose). Six horses were administered a 4th dose of Equilis EHV 1+4 (formulated to contain the minimum antigen content at batch release). One control animal was included. While the antigenic content of the vaccine batch used and the number of animals studied (6 rather than 8) are not compliant with pharmacopeial requirements, it is also noted that safety of repeated doses of the vaccine at up to 5-fold the fixed antigenic content has been evaluated in other laboratory safety studies, and at 3-fold the targeted fixed antigenic content in a clinical field trial. Furthermore, the safety profile of the vaccine has been established (and appears relatively consistent) across other laboratory safety studies and one clinical field trial. As such, this investigation of safety of a 4th dose is considered supportive of the safety of administration of a booster dose of Equilis EHV 1+4. Observations of note in this study included elevated rectal temperature and injection site swellings.

Overall, repeated administration of Equilis EHV 1+4 in 5–7-month-old foals (considered suitably representative of the age of the most sensitive group of animals for which the vaccine is intended for use, i.e., from 6 months of age) appears to be safe, with the adverse events of elevated temperature and local, injection site reactions occurring very commonly, along with observations of nasal and ocular discharge. However, there were significant concerns raised in respect of the pivotal pre-clinical safety study, namely the use of seropositive animals in the study, and the use (on one occasion) of a

vaccine batch blended to contain the minimum fixed antigenic content at batch release. Therefore, a final conclusion on the safety of the administration of one dose and the repeated administration of Equilis EHV 1+4 could not be made.

Based on the results of a supportive study investigating the safety of administration of a 4th dose of the vaccine (12 months after administration of the first booster) in young, adult horses, a similar safety profile was observed and administration of a 4th dose to the target species, horses, is considered safe.

Data concerning administration of the vaccine to very young foals are not considered directly relevant to this application.

Examination of reproductive performance

Safety of Equilis EHV 1+4 in pregnant mares was investigated in one pre-clinical safety study, and also in a clinical safety (and efficacy) trial.

In Study **1,** 6 pregnant Shetland mares (approximately 5 – 6 months pregnant at first vaccination) were vaccinated 3 times during pregnancy with Equilis EHV 1+4, 4 animals were included as a control group. The study design was not in compliance with Ph. Eur. 5.2.6 requirements, as the same 6 animals were re-administered the vaccine (rather than 24 mares, 8 in each gestational stage). In addition, the batch used for vaccination contained the minimum antigenic content at batch release, administered twice in the second trimester / term, and once in the third trimester / term of gestation. As such and noting also the conclusions reached in respect of safety of use of Equilis EHV 1+4 during pregnancy in the clinical field trial, this study is considered supportive (but not pivotal) for demonstration of safety of vaccination during the second and third trimester of pregnancy (only).

Considering that there were a number of deficiencies regarding the presented study (e.g., data on the animals used in the study are missing, including data on which day of the study the mares were vaccinated, in order to verify the month of gestation and thus the trimester of pregnancy when the vaccines were administered, as well as the interval between each vaccine application (V1, V2, V3)) together with the use of a minimum antigenic content batch, it is not considered that the data are sufficiently robust to evaluate safety during pregnancy. Therefore, the applicant was not requested to provide further information in respect of the study.

At the second and third vaccination timepoints the horses were all vaccinated (at a separate injection site) with commercial batches of Equilis Prequenza and Equilis Prequenza Te, respectively. The results of this study are considered relevant for the safety of the associated (but not mixed) use of these vaccines at the same time as Equilis EHV 1+4 in pregnant mares.

Observations of note include elevated rectal temperature and local injection site reactions at the site of administration of Equilis EHV 1+4, both of which occurred very commonly. It was also noted that injection site reactions occurred very commonly and for a longer duration (up to 13 days) at the site of vaccination with Equilis Prequenza in the control group. This is a higher frequency and longer duration for injection site reactions than currently described in the SPC of Equilis Prequenza, however it did not occur under conditions of associated use with Equilis EHV 1+4. In respect of safety aspects specific to gestation, although one vaccinated mare aborted at 39 weeks gestation, extensive investigations on the mare and foetus ruled out EHV-1 and EHV-4 as a cause of abortion. All other mares and foals were considered to have normal gestations and post-partum / neonatal periods, respectively.

The effect of vaccination on lactation has not been monitored in safety studies in pregnant mares,

therefore it should be noted in the SPC.

The clinical safety study is considered pivotal for the demonstration of safety of vaccination during the second and third trimesters / terms of pregnancy (only). Please refer to section 'Clinical studies' below for further detail regarding study design. In brief, this study investigated the safety of repeated administration (3 times at approximately 5-, 7- and 9-months gestation) in 22 pregnant mares (n=24 control mares), and the third administration of Equilis EHV 1+4 during pregnancy was under conditions of associated use with Equilis Prequenza Te. Further detail regarding exact gestational stage at the time of first vaccination would have been sought, however it does not appear that mares were vaccinated before approximately 5 months gestation. As such, an exclusion statement in the SPC for vaccination before 5 months gestation would have been required.

The safety profile in pregnant mares was similar to that observed in foals and other, pre-clinical safety studies. Rectal temperature elevations were very commonly reported, as were local injection site reactions. It is noted that although some observations were under conditions of associated use, these data comprise the pivotal safety data in pregnant mares. In respect of the associated use (at the third vaccination timepoint) with Equilis Prequenza Te, little difference between groups (in respect of adverse events, and specifically injection site reactions) was observed.

In summary, it is concluded that in the target animal species, horses, the vaccine is safe for use in pregnant mares in the second and third trimesters of pregnancy, but that safety before 5 months gestation (with the exact timing to be confirmed) has not been demonstrated, and such use should have been restricted in the SPC.

Examination of immunological functions

Equilis EHV 1+4 is an inactivated whole virus vaccine, and as such, vaccine virus will not replicate in cells of the immune system of a vaccinated animal. Therefore, no impairment of the immune system is anticipated.

User safety

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

In identifying and characterising hazards, the applicant states that the virus strains contained in the vaccine are both inactivated, and that the excipients contained in the vaccine are either salts of the phosphate buffer (which do not constitute a hazard) or are listed in Table 1 of the annex to Commission Regulation (EU) 37/2010 with a 'No MRL required' classification (choline -included in the buffer as phosphatidylcholine- and *Quillaia* saponin). Neither virus has zoonotic potential. Both choline and cholesterol are naturally and widely occurring substances in the body, and along with the components of the phosphate buffer can be considered to present no hazard to a user. Although saponin has a 'No MRL required' classification, this does not necessarily equate to a substance having no hazardous potential to users. Notwithstanding this point, it is accepted that none of the excipients are expected to pose a risk to the user, and it is acknowledged that the same excipients are included in other animal vaccines. It is accepted that no hazards were identified.

It is concluded that skin contact with Equilis EHV 1+4 (following accidental breakage of a vial or syringe) is very unlikely to occur, which is accepted. In respect of accidental self-injection, the vaccine will be administered by personnel who are trained / experienced in injection technique, and therefore, the risk of accidental self-injection is also very low.

As there are no live micro-organisms present in the vaccine, and all vaccine components are not known to cause topical adverse effects, and are considered 'safe', it follows therefore that there are no known consequences of exposure to the vaccine via either skin contact or accidental self-injection. This is considered consistent with the outcome of the hazard characterisation, above.

It is accepted that no further risk management / communication steps are required in respect of skin contact. The applicant has proposed the following user safety warning for inclusion in section 3.5 of the SPC:

'In case of accidental self-administration, seek medical advice immediately and show the package leaflet or the label to the physician.'

Although the statement proposed by the applicant is in keeping with a standard statement in the QRD template v9, it is not considered to reflect of the outcome of the risk assessment carried out by the applicant. In the absence of a known risk following accidental self-injection, it is considered that a requirement to 'seek medical advice immediately' following accidental self-injection is unnecessary, and that no specific user safety warning is required for Equilis EHV 1+4. As such it was proposed that the warning in question is replaced with the word 'None.'

Study of residues

No studies on residues have been performed. This is considered acceptable.

MRLs

The active substances being principles of biological origin intended to produce active immunity are not within the scope of Regulation (EC) No 470/2009.

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 antimicrobial substances polymyxin B sulphate and neomycin sulphate used in the manufacturing process are present at low residual levels (theoretical calculations of 42 µg/ml and 840 µg/ml respectively) in the finished product, and are not considered to constitute a risk to the consumer.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

The applicant has proposed that Equilis EHV 1+4 can be used at the same time, but not mixed with Equilis Prequenza Te, Equilis Prequenza and Equilis Te. In support of the safety of the proposed associated use, the applicant has provided data from one pre-clinical laboratory safety study and one clinical field trial.

In the pre-clinical safety study, pregnant mares were vaccinated once in the second trimester / term of pregnancy with Equilis EHV 1+4 (containing the minimum antigenic content at batch release), and

a commercial batch of Equilis Prequenza at a separate site, and the same mares were vaccinated again in the third trimester / term of pregnancy with Equilis EHV 1+4 (minimum antigenic content), and a commercial batch of Equilis Prequenza Te at a separate site. Control mares were vaccinated with Equilis Prequenza, and Equilis Prequenza Te at the same timepoints. In the clinical field trial, pregnant mares were vaccinated in the third trimester / term of pregnancy with Equilis EHV 1+4 and Equilis Prequenza Te (at a different site). 5–7-month-old foals were vaccinated with Equilis Prequenza Te at the same time as Equilis EHV 1+4 on two occasions, 4 weeks apart.

Based on the results of the preclinical safety study the safety profile of Equilis EHV 1+4 (albeit using a batch manufactured to contain the minimum antigenic content) was not affected when Equilis Prequenza, or Equilis Prequenza Te were administered at the same time. Local reactions in 2 control mares at the site of injection with Equilis Prequenza were noted (up to 5 cm in diameter, lasting for 13 days). This is a higher frequency (very common) and a longer duration than the 2 days described in section 4.6 of the SPC of Equilis Prequenza, however, this did not occur under conditions of associated use with Equilis EHV 1+4.

Based on the results of the clinical safety and efficacy study, the safety profile of Equilis EHV 1+4 was unaffected by associated use with Equilis Prequenza Te. The text proposed for section 3.6 of the SPC (taking into account proposed updates consequent to results from all safety studies) is considered therefore to represent the worst-case, whether the vaccine is used under conditions of associated use, or not. However, reactions at the site of Equilis Prequenza Te vaccination were more severe in foals administered Equilis EHD 1+4 at the same time compared to the control group that received Equilis Prequenza Te alone. Crust and warmth at injection site are not included in the SPC of Equilis Prequenza Te, and the frequency of injection site reactions to Equilis Prequenza Te was "very common" following associated use with Equilis EHV1+4 with a maximum duration of 5 days (as compared to 2 days when used alone).

If the associated use claim for the vaccines Equilis Prequenza Te, Equilis Prequenza and Equilis Te would have been approved, an update to section 4.8 of the SPCs of these vaccines would have been required. It is considered that the following statement captures the extent of the local reactions observed in the studies presented for the purpose of investigating the safety of associated non-mixed use of Equilis Prequenza Te, and the fall-out vaccines Equilis Prequenza and Equilis Te with Equilis EHV 1+4, and should have therefore been applied to all three vaccines that are the subject of the proposed associated used claim:

'When used at the same time as Equilis EHV 1+4, injection site swellings occur very commonly, may be warm and/or crusted, and last up to 5 days.'

While the applicant is considered to have suitably investigated safety of the associated but not mixed use of Equilis EHV 1+4 and Equilis Prequenza Te (inclusive of the fall-out vaccines Equilis Prequenza and Equilis Te), it is noted that based on evaluation of efficacy data, the associated use claim is considered to have been insufficiently supported. See Part 4.

Clinical studies

One pivotal clinical study, conducted to evaluate safety (and efficacy) of Equilis EHV 1+4 in 5–7-month-old foals and pregnant mares under field conditions was presented.

Clinical study in the Netherlands to assess the safety of Equilis EHD in foals and pregnant mares and serological response to vaccination in foals.	
Objectives	To assess the safety of Equilis EHD under field conditions in foals and pregnant mares.

<table>
<tr><td></td><td>In foals also the serological response to vaccination was determined.</td></tr>
<tr><td>Study sites</td><td>3 sites in the Netherlands.</td></tr>
<tr><td>Study design</td><td>Controlled, blinded, randomised.</td></tr>
<tr><td>Study status</td><td>GCP-compliant.</td></tr>
<tr><td>Animals</td><td>Client-owned foals (n=38, male and female) and pregnant mares (n=46), warmblood horses. Clinically healthy animals, foals of 6 (±1) months of age, pregnant mares 5 (±1) months pregnant. The animals were previously vaccinated for EIV and tetanus, and most for EHV-1, EHV-4.</td></tr>
<tr><td>Test product

Control product</td><td>Equilis EHD, blended to contain a 3-fold higher EHV-1 and EHV-4 antigen input than the input used for routine vaccine production
Control product: saline solution
Equilis Prequenza Te, commercial batch.</td></tr>
<tr><td>Vaccination scheme</td><td>Test or control products were administered intramuscularly, 1 ml dose, in the left caudal neck, Equilis Prequenza Te was administered intramuscularly, 1 ml dose, on the right caudal neck.

Foals:
<table>
<tr><th>Group</th><th>N</th><th>V1 at 5 – 7 months of age</th><th>V2,
4 weeks after V1 (±3 days)</th></tr>
<tr><td>Test</td><td>20</td><td>Equilis EHD 1+4
+
Equilis Prequenza Te</td><td>Equilis EHD 1+4
+
Equilis Prequenza Te</td></tr>
<tr><td>Control</td><td>18</td><td>Saline
+
Equilis Prequenza Te</td><td>Saline
+
Equilis Prequenza Te</td></tr>
</table>
Pregnant mares:
<table>
<tr><th>Group</th><th>N</th><th>V1 at 4 – 6 months of gestation</th><th>V2,
2 months after V1 (±1 week)
(6 – 8 months gestation)</th><th>V3
2 months after V2 (±1 week)
(8 – 10 months gestation)</th></tr>
<tr><td>Test</td><td>22</td><td>Equilis EHD 1+4</td><td>Equilis EHD 1+4</td><td>Equilis EHD 1+4
+
Equilis Prequenza Te</td></tr>
<tr><td>Control</td><td>24</td><td>Saline</td><td>Saline</td><td>Saline
+
Equilis Prequenza Te</td></tr>
</table></td></tr>
<tr><td>Safety parameters</td><td>Monitoring of adverse events, feed intake, general health and local reactions from 3 days prior to vaccination until 14 days after each vaccination.
Rectal temperature daily for 3 days before each vaccination, just before and 4 hours after vaccination, and daily for 4 days after each vaccination.
Outcome of pregnancy recorded in pregnant mares.

The parameters measured are appropriate for assessment of safety of vaccination.</td></tr>
<tr><td>Efficacy</td><td>For all foals in the study, blood samples were obtained before each vaccination and 2</td></tr>
</table>

parameters	weeks after each vaccination to determine the serological response to vaccination.
Statistical method	Descriptive statistics were used to summarise the data and compare between treatment groups. For the purpose of evaluation of safety, this is considered appropriate.
Results	
Outcomes-Safety observations	No mortalities or adverse events reported other than those described under the specific safety parameters during the study. <u>General health and feed intake:</u> *Foals:* In the test group, 1/20 foals was less active with elevated temperature of 38.7 °C at 1 day post 1st vaccination; and less active, reduced feed intake with elevated temperature of 38.9 °C at 1 day post 2nd vaccination. *Pregnant mares*: no abnormalities of general health attributable to vaccine administration were reported after vaccination. <u>Local reactions</u> *Foals:* *Local reactions to Equilis EHD (or saline in control group):* After **1st** vaccination, local reactions with maximum duration of 4 days were reported in 2/20 foals (10%) (soft swelling and crust, diameter of 1.0 cm in one foal, pain at site of injection. No local reactions were reported after **2nd** vaccination. *Local reactions to Equilis Prequenza Te:* Injection site reactions were not within the scope of the described AEs in the authorised SPC of Equilis Prequenza Te; after **1st** vaccination 4/20 foals (20%) in the test group had an injection site reaction; two with crust at injection site, one with a warm local reaction and one foal with a soft swelling, maximum size 3 cm and maximum duration 2 days. No reactions to Equilis Prequenza Te were reported in the control group. After **2nd** vaccination, 4/20 foals in the test group (20%) presented with injection site reactions; two with crust, one with hard swelling, one with soft swelling, maximum diameter of 4 cm, maximum duration of 5 days. In the control group 1/18 foals (6%) had a warm local reaction, 3 cm, duration of 2 days. *Mares:* *Local reactions to Equilis EHD (or saline in control group):* After **1st** vaccination, local reactions with maximum duration of 3 days were reported in 9/22 mares (41%) (hard swelling with and without pain, soft swelling with and without warmth, maximum diameter of 8 cm. Local reactions were reported in 5/24 mares (21%) in the control group at site of saline administration; hard swelling or warm local reaction or combination thereof, maximum diameter of 4 cm and duration of 4 days). After **2nd** vaccination, local reactions were reported in 8/20 (40%) mares of the test group (crust, soft swelling, warmth, maximum diameter of 6.0 cm and maximum duration of 3 days) and 1/23 (4%) mares in the control group (warm soft swelling, 6 cm, 4 days). After **3rd** vaccination, local reactions were reported in 8/20 (40%) mares of the test group (warmth, soft swelling, hard swelling, maximum diameter of 5 cm and maximum duration of 5 days) and 1/23 (4%) mares in the

	control group (crust, 0.5 cm, 1 day). *Local reactions to Equilis Prequenza Te:* After vaccination 5/20 mares (25%) in the test group (soft swelling or warmth, maximum size of 4 cm and maximum duration was 5 days) and 7/23 mares (30%) in the control group (crust, hard swelling, soft swelling, warmth, max. size 3 cm, max. duration 2 days) had an injection site reaction. <u>Rectal temperature</u> *Foals:* After 1st vaccination, 8/20 foals from the test group had a transient elevated rectal temperature (>38.5 °C) at least once after first vaccination. The average increase on the day after vaccination in this group was 0.3 °C with an individual maximum of 1.4 °C. In the control group 1/18 foals had a temperature >38.5 °C once at 4 hrs after vaccination. After 2nd vaccination, 7/20 in the test group and 2/18 in the control group had a transient elevated rectal temperature (>38.5 °C). In the test group there was an average increase in rectal temperature of 0.3 °C at both 4 hours after vaccination and the first day after vaccination with an individual maximum of 1.4 °C. In the control group the average increase was 0.2 °C at 4 hours after vaccination and on the first day after vaccination with an individual maximum of 0.8 °C. *Pregnant mares* The highest temperature increases due to Equilis EHD were observed after the **1st** vaccination; 4/22 mares in the test group had a rectal temperature >38.5 °C for 1 day (1-day post-vaccination), with a maximum of 39.2 °C (average increase on the day after vaccination was 0.3 °C, individual maximum increase of 1.6 °C). No mares in the control group had rectal temperature >38.5 °C. After **2nd** vaccination, none of the mares in either group had an increase >38.5 °C. After **3rd** vaccination, none of the test group mares had an increase >38.5°C (average increase in rectal temperature on day 1 was 0.3°C, individual maximum of 1.0 °C). In 3/23 mares in the control group an increase >38.5 °C was reported on day 1 after vaccination (maximum of 39.3 °C, average increase 0.5 °C, individual maximum of 1.9 °C). <u>Outcome of pregnancy:</u> There were no adverse effects on the outcome of pregnancy; all mares delivered a live foal after a normal duration of pregnancy.
Outcomes – efficacy observations	Refer to Part 4.
Discussion	
Discussion/ conclusions further to assessment	Taking into account the study design, number of animals, along with the use of a batch of Equilis EHV 1+4 blended to contain 3 times the targeted fixed antigenic content at batch release (noting that the applicant was requested to confirm that Equilis EHD and Equilis EHV 1+4 are the same vaccine), this results of this clinical field study are considered to support the safety of vaccination of 5–7-month-old foals under field conditions, in addition to contributing pivotal data in support of vaccination during pregnancy (although the safety of vaccination prior to 5 months gestation has not been investigated).

	The applicant was requested to confirm the age of foals at time of first vaccination, and the exact stages of gestation at which pregnant mares were vaccinated. In foals, elevated rectal temperature was observed very commonly, and 1 affected foal was observed to be less active with a reduced appetite at four hours post vaccination. Local injection site reactions were commonly (10%) observed (soft swelling, crust, pain, max. size 1 cm, max. duration 4 days). In pregnant mares, whilst the safety of vaccination during the second and third trimesters of pregnancy was investigated in this study, mares were not vaccinated during the first trimester. The data support the safety of use during pregnancy from approximately 5 months of pregnancy as no adverse impact of vaccination on pregnancy, parturition or on the offspring was observed. In the absence of sufficient reassurance of safety at this stage of gestation, an exclusion statement in the SPC for vaccination in the earlier stages of pregnancy was required. The safety profile in pregnant mares was similar to that observed in foals and other, pre-clinical safety studies. Rectal temperature elevations >38.5 °C were very commonly reported with a mean increase of 0.3 °C, individual maximum increase 1.6 °C). Local reactions were reported very commonly, lasted a maximum duration of 5 days, were a maximum size of 8 cm and encompassed swellings which were hard/soft, warm, painful or crusted, or a combination thereof. It is noted that although some observations were under conditions of associated use, these data comprise the pivotal safety data in pregnant mares. Safety of the associated (but not mixed) use of Equilis EHV 1+4 with Equilis Prequenza Te in 5–7-month-old foals and in pregnant mares is also considered to have been demonstrated. Reactions at the site of Equilis Prequenza Te vaccination were more severe in foals administered Equilis EHV 1+4 at the same time (compared to the control group that received Equilis Prequenza Te alone). In pregnant mares, little difference between groups was observed. It is noted that crust or warmth at injection site are not reported in the description of local reactions in the SPC of Equilis Prequenza Te. Furthermore, the frequency of injection site reactions to Equilis Prequenza Te was "very common" following associated use with Equilis EHV 1+4 (rather than "rarely" as per the authorised SPC) and the maximum duration is longer at 5 days than when used alone. The description of the safety profile following associated use should have been included in section 4.8 of the SPCs of Equilis Prequenza Te, and the fall-out vaccines Equilis Prequenza and Equilis Te. It is concluded that based on the results of this well designed and conducted clinical study, in the target animal species horses, the vaccine appears safe for use in foals from 6 months of age, and in pregnant mares in the second and third trimesters of pregnancy. Furthermore, safety of the associated use of Equilis EHV 1+4 at the same time as (but not mixed with) Equilis Prequenza Te, Equilis Prequenza and Equilis Te has been demonstrated. It is noted however that the efficacy of compatible use is not accepted based on the data presented in Part 4.

Environmental risk assessment

The applicant has presented an environmental risk assessment conducted in accordance with the relevant guideline, Environmental risk assessment for immunological veterinary medicinal products (EMEA/CVMP/074/95).

Under normal conditions of use (by trained / professional users), there will be no exposure of the environment to the vaccine. The vaccine antigens (EHV-1 and EHV-4) are completely inactivated. The product does not contain any live organisms that could be transmitted to or pose a risk to non-target organisms. The excipients include Iscom-matrix as the adjuvant, and PBS. Excretion of any compounds or metabolites of the vaccine will be in minute amounts, if at all and are not anticipated to pose any risk to the environment.

Disposal of unused vaccine should be performed in accordance with national requirements.

Potential hazards include:

- contaminant micro-organisms with pathogenic potential.
- toxic effects of any of the product components, via the target animal or when released directly into the environment.
- toxic effect of residues/metabolites of the product components via the target animal or in other animals.

The likelihood of exposure to the hazards listed above is considered negligible, which is accepted.

The overall level of risk to the environment is considered effectively zero, and as such, no Phase II assessment of environmental risk is considered necessary.

Based on the data provided the ERA can stop at Phase I. Equilis EHV 1+4 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 the administration of one dose and the safety of the repeated administration of one dose to the target animal species of the minimum recommended age via the recommended route of administration. There was a concern that based on the presence of (high) antibody titres in the animals used in the pivotal study, and the use of a batch of vaccine that contained the minimum antigenic content at batch release, the safety in the most sensitive category of the target animal species has not been suitably investigated (major objection).

On the basis of this study, it could not be 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.

Four supportive preclinical studies, and one pivotal clinical field study were also provided.

Reproduction safety was investigated in a supportive pre-clinical study and one pivotal clinical study. The product was found to be safe when used in pregnant animals in the second and third trimesters of pregnancy. The SPC would have required amendment (with an exclusion statement for the first 5 months of pregnancy) accordingly.

The effect of vaccination on lactation was not monitored in safety studies in pregnant mares and therefore should have been noted in the SPC.

The safety of associated (but not mixed) use of Equilis EHV 1+4 with Equilis Prequenza Te, Equilis Prequenza and Equilis Te has been suitably investigated and can be considered safe.

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

Based on the results of the preclinical safety studies, and a clinical field trial, it is concluded that the adverse events of note following vaccination are elevated temperature, and local injection site reactions, along with nasal and ocular discharge. The applicant was requested to amend section 3.6 of the SPC in order to accurately reflect the frequency, extent and duration of these clinical signs based on the safety data provided.

The data presented cannot be considered adequate to characterise the safety profile of the vaccine for the target species as acceptable.

A user safety assessment in line with the relevant guidance document has been presented. Based on that assessment, the potential health risk of the product to all users is considered negligible when used in accordance with the SPC.

No residue studies were provided, and the proposed withdrawal period of 'zero days' is accepted.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

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

General requirements

The vaccine is intended for active immunisation to reduce the severity and duration of clinical signs of respiratory disease (rhinopneumonitis), amount and duration of virus excretion and viremia due to infection with equine herpesvirus 1 and/or equine herpesvirus 4, when administered to horses from 6 months of age onwards. A two-dose primary vaccination scheme is proposed, the first dose to be administered from 6 months of age followed by a second dose administered 4 to 6 weeks later. Revaccination is proposed every 6 months for high-risk horses that frequently come into contact with other horses, or every 12 months for low-risk horses.

Although the claims proposed for the vaccine are related to equine viral rhinopneumonitis (no claim for reduction of abortion due to EHV 1), the applicant proposes to include information under section 4 'Immunological properties' of the SPC that the vaccine reduces viraemia which will reduce the risk of abortion and neurological signs.

Compatibility of use of Equilis EHV 1+4 is claimed with three equine vaccines (Equilis Prequenza Te, Equilis Prequenza and Equilis Te), for use at the same time but not mixed with Equilis EHV 1+4. In terms of efficacy data to support this claim, the applicant proposes to include information that virus neutralising antibody response data are available to support the associated use.

Efficacy was demonstrated in compliance with the Regulation (EU) 2019/6, and the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7 as well as Ph. Eur. monograph 1613 Equine herpesvirus vaccine (inactivated).

No justification was provided for the choice of vaccine strains included in Equilis EHV 1+4 in Part 4, although some limited information was presented in Part 2. It is noted that the same vaccine strains were included as live strains in a vaccine authorised in at least one EU MS a number of years ago, with the licence since withdrawn. The applicant was requested to address the relevance of the vaccine strains included in Equilis EHV 1+4 to the current epidemiological situation in the EU.

Challenge model

The challenge model used was in line with the requirements of Ph. Eur. 1613; "At least 2 weeks after the last vaccination, challenge each horse by nasal instillation with a quantity of equid herpesvirus 1 or 4, sufficient to produce, in a susceptible horse, characteristic signs of the disease such as pyrexia and virus excretion (and possibly nasal discharge and coughing)." Three EHV-1 challenge viruses (isolated from the EU) and two EHV-4 challenge viruses (one isolated from the EU, one from the USA) were used in the preclinical efficacy studies; however, justification that the challenge virus strains are epidemiologically relevant for protection against strains currently in the EU should have been provided.

Efficacy parameters and tests

Virus excretion, the efficacy parameter as provided in Ph. Eur. 1613, in addition to clinical signs, rectal temperature, viraemia and the level of virus neutralising (VN) antibody titres, as chosen by the applicant, were investigated in the efficacy studies. The tests performed to evaluate the parameters were detection of virus presence in nasal swabs (virus excretion), detection of virus in peripheral blood leucocytes (PBLs) (viraemia) and VN test for antibody titres. The parameters chosen are considered appropriate for evaluating the efficacy of the product.

Validation results were presented and confirm that the tests chosen are adequately validated to provide reliable results. However, there is some degree of cross-reactivity of EHV-1 and EHV-4. For the VN test, cytopathic effect (CPE) following incubation of serial dilutions of equine sera samples with the relevant virus on VERO-Marburg cells is determined, the titre of the test article is expressed as $\log_2$ and is the highest dilution in which no CPE is observed. A VN titre ≤ 1 $\log_2$ is considered negative.

For the presence of EHV-1 and EHV-4 in nasal swabs, test samples are evaluated for CPE following incubation in RK13 cells for EHV-1 or VERO-Marburg cells for EHV-4. Both virus strains replicate in VERO-Marburg cells, but only EHV-1 replicates in RK13 cells, therefore a combination of the two assays are used to differentiate EHV-1 and EHV-4 positive nasal swabs. Negative samples are considered as ≤ 1.05 $\log_{10}$/ml. Detection of viraemia due to EHV-1 is based on incubation of three different dilutions of PBLs/sample with RK13 cells and examination of CPE (presence or absence). A scoring system is used with score 1, 2 or 3 allocated based on detection of CPE in individual horse serum samples with PBL following culture with RK13 cells. The weighted score was used to take the different PBL dilutions and the impact of these dilutions on the chance of finding positive PBL into account. The total summed score was the summation of the three values (the PBL weighted score) per animal per time period. However, the validation report for detection of EHV-4 in PBL is missing and should have been provided. Furthermore, the respective SOPs for the methods used were not provided (the details of the methods are provided in the validation reports but the SOPs should also have been provided).

A scoring system was developed for clinical signs observations, which encompass the following parameters:

- General health (0; normal, 1; malaise/depression/normal appetite, 2; malaise/depression/reduced appetite, 4; anorexia, 2; dehydration, 1; oedema in one or more legs, 1; diarrhoea, 100; dead), respiratory signs (score 2; hyperpnoea, score 4: dyspnoea, or score 1, 2 or 3 for cough with increased scores depending on number of coughs per 10 minutes).
- Ocular signs (score 1; lacrimation, 2; mild mucopurulent discharge, 4; marked mucopurulent discharge, or score 2; mild conjunctivitis, 4; marked conjunctivitis).
- Nasal signs (score of 1, 2 or 4 for nasal serous discharge, mild nasal mucopurulent, marked nasal mucopurulent, respectively, or score of 1, 2 or 3 for sneezing with increased scores depending on number of sneezes per 10 minutes).
- Neurological signs were monitored but did not occur post-challenge throughout the studies presented with the exception of one animal in the vaccinated group in one study.

Rectal temperature was evaluated separately with scores of 0 (<38.5 °C), 1 (38.50 – 39.09 °C), 2 (39.10 – 39.49 °C), 3 (39.50 – 40.00 °C) or 4 (> 40.00 °C).

Efficacy documentation

Nine studies were conducted to investigate the efficacy of the product and included 8 pre-clinical studies (six pivotal laboratory efficacy studies in the target species and two dose development studies; one in horses, one in ferrets) and one clinical trial. Laboratory studies were well documented and carried out in target animals of the minimum age recommended for vaccination or during pregnancy.

Batches of vaccine used in the efficacy studies were stated to have been manufactured in accordance with Part 2 of the dossier. Equilis EHV 1+4 will be manufactured at a fixed amount of EHV-1 and EHV-4 antigen per dose of 1 ml. Therefore, no minimum or maximum potency batches exist for the product. However, the applicant investigated efficacy under a worst-case scenario with batches intentionally composed with an antigen input below the target input per dose. Similar to the comment raised under Part 3, regarding the adjuvant used in the vaccine, it is unclear if the final formulation of the adjuvant system was used in the batches used to support efficacy. The applicant was requested to confirm the composition of the adjuvant proposed for inclusion in Equilis EHV 1+4. Furthermore, if there are any differences in the adjuvant used in the efficacy studies compared to that which is proposed for marketing, the applicant should have justified how the efficacy data presented in Part 4 may be considered representative of the efficacy profile of the vaccine formulation proposed for marketing.

It is noted that questions were raised under Part 2 concerning the conversion factor for the antigen content in AU/dose to antigen content in $\log_{10}$ U/ml. Although the applicant has stated the antigen content per dose in $\log_{10}$ U/ml in Part 4 of the dossier for each vaccine batch, together with information regarding AU/dose in the final study reports for the studies concerned, this point should have been resolved and the applicant was requested to confirm the stated antigen content in $\log_{10}$ U/ml for the batches used in the efficacy studies.

Pre-clinical studies

Dose determination

Two dose response studies were provided, one conducted in ferrets and one in the target species horses.

In **Study "Evaluation of the dose-response of EHV-1 and EHV-4 in ferrets after subcutaneous administration of a repeated dose"**, seronegative/low seropositive ferrets were vaccinated twice, 3 weeks apart with special purpose Equilis EHV 1+4 batches, blended to contain only EHV-1 or EHV-4 antigen content in varying quantities, or to contain a constant EHV-1 content and varying EHV-4 content (3 – 4 ferrets/group). VN antibodies to EHV-1 increased in a dose-dependent manner in groups vaccinated with EHV-1 only, with increase of EHV-4 VN titres. VN antibodies to EHV-4 increased in a dose-dependent manner in all groups vaccinated with EHV-4 only (and EHV-1 VN titres were also in these groups). In the groups vaccinated with batches with constant EHV-1 antigen content and varying EHV-4 antigen content, the VN antibodies to EHV-1 and EHV-4 increased in all groups and a clear relation between EHV-4 antigen content and the level of induction of EHV-4 VN antibodies was observed. To a lesser extent this was also observed for the EHV-4 antigen content and the level of induction of EHV-1 VN antibodies. It was concluded that vaccination of ferrets with Equilis EHV 1+4 results in the induction of VN antibodies for EHV-1 and EHV-4, and a strong cross-reactivity of the EHV-4 antigen towards the induction of EHV-1 antibodies was observed.

In **Study "Evaluation of the dose-response and stability of an inactivated equine herpesvirus vaccine after intramuscular administration in horses"**, 35 seronegative/low seropositive foals approximately 6 months old were divided into 6 groups (Shetland ponies, 5 groups of 6 foals, 1 group of 5 foals), and were vaccinated by the intramuscular route with a single dose (1 ml) on day 0 and day 28 (week 4) with batches that differed in antigen content or age of the batch. Four ponies were later excluded on the basis of an anamnestic response to vaccination indicating that they were non-naïve to EHV-1 and EHV-4. On day 0, weeks 4, 6 and 9, blood samples for evaluation of VN antibody titres to EHV-1 and EHV-4 were collected. Blood for PBL isolation and nasal swabs were taken before each vaccination and in week 9 for analysis of EHV-1 and EHV-4 to confirm absence of viral presence. Batches were blended at different antigen content levels of either EHV-1 or EHV-4; groups 1 and 2 were vaccinated with batches containing fixed EHV-4 (U/dose) and variable EHV-1 (group 1: low EHV-1; U/dose, group 2: high EHV-1; U/dose), groups 5 and 6 were vaccinated with batches containing fixed EHV-1 (U/dose) and variable EHV-4 (group 4: low EHV-4; U/dose, group 5: high EHV-4; U/dose). Groups 3 and 6 were vaccinated with different batches containing the content of EHV-1 (U/dose) and EHV-4 (U/dose) used in the other efficacy studies presented in Part 4, but the vaccine batch was fresh for administration to group 3 and was aged for administration to group 6.

Result showed that the VN antibodies to EHV-1 and EHV-4 increased in all groups, with peak antibody levels reached at 6 weeks. The differences in antibody levels were minor, however a trend was observed in the both the relationship of EHV-1 antigen content and level of EHV-1 VN antibodies induced and the EHV-4 antigen content and EHV-4 VN antibodies. For example, regarding EHV-1 VN titres, at 6 weeks mean titres of EHV-1 were 7.6 in group 1 (low EHV-1 batch), 8.3 in group 2 (high EHV-1 batch) and 7.5 in group 3 (intermediate EHV-1 batch; dose selected for efficacy evaluation). Similarly, VN titres to EHV-4 increase in a dose proportional manner in the target species, at 6 weeks mean titres of EHV-4 were 8.0 in group 4 (low EHV-4 batch), 10.1 in group 5 (high EHV-4 batch) and 10.9 in group 6 (intermediate EHV-4 batch; dose selected for efficacy evaluation). The antibody response and level of EHV-1 and EHV-4 VN antibodies induced by the vaccine batches used in group 3 and 6 (fresh versus aged vaccine batches) are comparable. No EHV-1 or EHV-4 was detected in the nasal swabs or PBL of any of the foals during the study.

Notwithstanding the trends for a dose-dependent increase in VN titres for both EHV-1 and EHV-4, VN titres are induced in all groups. No specific justification for selection of the proposed dose of U/dose for EHV-1 (with batches for efficacy evaluation 'under-formulated' at U/dose), or EHV-4 content of U/dose (with batches for efficacy evaluation 'under-formulated' at U/dose) was provided.

The proposed dose for EHV-1 and EHV-4 would appear reasonable based on serology data, but as it is unknown from these data if there is a serological threshold for protection, the important aspect is confirmation of the chosen dose in the subsequent studies.

Onset of immunity

Two studies were carried out in horses of the minimum age recommended for vaccination in compliance with Ph. Eur. 1613 requirements to investigate the OOI, by the recommended administration route; one to determine the OOI for protection against EHV-1 and one to determine the OOI for protection against EHV-4. In both studies, and for the DOI studies, it is unclear if general health and clinical observations were conducted on a blinded basis and whether the evaluation of the clinical signs related to EHV-1 / EHV-4 infection was conducted by a veterinarian. The applicant was requested to confirm these points. In addition, in both studies the second dose of the vaccine was administered 4 weeks after the first administration. Noting that the proposed SPC states that the 2nd dose should be administered 4 – 6 weeks after the first dose, the SPC should have been amended to recommend the administration of the 2nd dose 4 weeks after the first dose, as this represents the conditions under which the OOI for EHV-1 and EHV-4 was investigated.

In **Study "Evaluation of the onset of immunity to EHV-1 challenge following intramuscular vaccination with a new inactivated equine herpesvirus"**, 12 foals (Shetland ponies, approximately 6 months of age seronegative / low seropositive to EHV-1 and EHV-4) were allocated to a vaccinated group (n=7) or control group (n=5). Serological pre-screening was used to ensure each treatment group had a comparable number of animals with either low or no antibodies to EHV-1 and EHV-4. Foals in the vaccine group were vaccinated by the intramuscular route with a single dose (1 ml) of Equilis EHV 1+4 (batch IP193388.1) on day 0 and day 28 of the study. Foals in the control group were untreated. Challenge by the intranasal route with virulent EHV-1, strain AB4 was conducted at 7 weeks (3 weeks after the 2nd dose of vaccine). Monitoring of clinical signs and rectal temperature was carried out for 14 days post-challenge. Nasal swabs for evaluation of EHV-1 virus shedding, blood samples for evaluation of serological response and blood samples for PBL isolation and evaluation of presence of EHV-1 (viraemia) were taken at appropriate time points throughout the study and post-challenge.

Results: Prior to challenge, nasal discharge was observed in 5 animals (between 16 – 23 days after first vaccination, confirmed as unrelated to EHV-1 or EHV-4 infection). One horse in the vaccinated group was euthanised 21 days after the first dose for welfare reasons, accepted as non-vaccine related.

After EHV-1 challenge, clinical signs related to EHV-1 infection were observed in all animals; in the vaccinated group until mainly 9 days post-challenge (dpc), with isolated signs (cough) recorded in one animal on 13 dpc and in the control group up to 13 dpc. Signs were generally limited to ocular and nasal discharge, in addition, malaise/depression was observed in 2/5 animals of the control group and a cough (2-5x in 10 minutes) was observed in 2/6 vaccinated and 1/5 control animals. The duration of clinical signs does not appear to have been compared statistically between groups and the descriptive data do not point to a beneficial effect of vaccination on this parameter. The highest mean clinical sign score was observed in the control group on 5 dpc (mean score 4.4) and in the vaccinated group on 2 dpc (mean score 2.8). While the clinical score in the vaccinated group was statistically significantly lower (p=0.0001) compared to the control group, the clinical relevance of the claimed difference is not considered to have been demonstrated. The most frequent signs observed in the ocular and nasal categories of observations were either mild (score 2) or marked (score 4) mucopurulent discharge. There was no score of 3 on this scale, and the main difference between the study groups appears to have been related to a slightly higher proportion of foals with marked

mucopurulent discharge in the control group compared to the vaccinated group on different study days. Thus, the arbitrary weighting to this category (2 vs 4) may have overestimated the difference between groups. Considering that the two categories of observations for which a difference between groups appears to be based upon may be considered essentially the same (oculonasal discharge), and that little clinical difference between groups is apparent based on the raw data provided, the claimed reduction of clinical signs severity is not considered to have been adequately supported. The applicant was requested to justify the approach used for scoring and analysis of clinical signs. Body temperature increased in both groups, peaking at 2 dpc with an average temperature of 40.1 °C and 39.2 °C in the control and vaccinated groups, respectively, and was statistically significantly reduced in the vaccinated group compared to the control group. Whilst it is acknowledged that there would appear to be a beneficial effect of vaccination in terms of reduction of pyrexia following challenge, when excluding this parameter, it is not considered that there is convincing evidence of a reduction of severity of clinical signs due to EHV-1. In the event that further support for this indication could not be provided, the applicant would have been requested to omit this claim from the SPC.

Virus excretion in nasal swabs was detected in all animals of both groups during the post-challenge period. However, significantly less EHV-1 (area under the curve, AUC) (p=0.0018) was shed in the vaccinated group compared to the control group (difference of 4.16 $\log_{10}$ $TCID_{50}$/ml) and the number of days on which EHV-1 was shed was statistically significantly less (p=0.0039) in the vaccinated group compared to the control group (difference of 3.06 days).

Viraemia was observed in both groups from 4 – 8 dpc, peaking at 6 dpc with an average viraemia score of 2.7 and 4.8 in the vaccinated and control groups, respectively. Concerning a reduction in the duration of viraemia, it is noted that in both groups the days on which EHV-1 was detected in PBL was the same (on day 4, 6 and 8 post-challenge). It is unclear how these data are considered to support a reduction in the duration of viraemia. Concerning the amount of viraemia, the viraemia score used to compare differences between groups is based on a sum score for each animal, where a score of 1, 2 and 3 is allocated if CPE is detected in peripheral blood leucocytes. This analysis was not specified in advance in the study protocol (originally a score of 1, 2 or 3 was to be allocated if CPE was detected at different dilutions of PBLs). This change in analysis was added by way of study amendment approximately 4 months after the end of the study and suggests that change to the analysis may have been driven by absence of difference between groups using the originally defined scores. However, assuming that if CPE is detected at a higher dilution, it will also be detected at a lower dilution of the same sample, this change results in an effective score that may have had the effect of disproportionately weighting the score in favour of the vaccinated group. The applicant was requested to justify the reason for this change and to provide the results of the analysis of viraemia using the originally defined scoring system (as a point for clarification). A statistically significant difference in viraemia score is reported (p=0.0420) however, the clinical relevance of the difference in viraemia score is not considered to have been demonstrated. On this point, it is noted that viraemia was detected in foals in both groups on day 4, 6 and 8, and CPE positive samples at the highest dilution of PBL were reported on two days: on day 4 (2/5 foals and 0/6 foals in the control and vaccinated group, respectively) and on day 6 (3/5 foals and 1/6 foals in the control and vaccinated group, respectively). CPE positive samples on the other two dilutions were reported in both groups. Therefore, noting the concerns raised regarding the analysis of results and the relatively similar profile of viraemia between both groups, the claim for protection against viraemia due to EHV-1 is not considered to have been demonstrated.

Mean VN antibody titres of 6.7 $\log_2$ for EHV-1 and 9.3 $\log_2$ for EHV-4 were reported in the vaccinated group at 3 weeks after the second vaccination while the control group animals remained seronegative/low seropositive until after challenge. After EHV-1 challenge, an increase in antibody titre to both EHV-1 and EHV-4 was observed in both groups.

The OOI study for EHV-1 complies with the requirements of Ph. Eur. 1613: "The vaccine complies with the test if the vaccinated horses show no more than slight signs; the signs in vaccinates are less severe than in controls. The average number of days on which virus is excreted and the respective virus titres are significantly lower in vaccinated horses than in controls." The proposed claims for a reduction of virus excretion (amount and duration) would appear to be supported. However although the vaccine is compliant with the requirement that the vaccinated horses show no more than slight signs, and the signs are less severe than in controls, the claim for a reduction of severity and duration of clinical signs is not considered to have been adequately supported due to a number of concerns raised, in addition a reduction of amount and duration of viraemia is not considered to have been adequately supported.

In **Study "Evaluation of the onset of immunity to EHV-4 challenge following intramuscular vaccination with an inactivated equine herpesvirus"**, 12 foals (Shetland ponies, approximately 6 months of age seronegative / low seropositive to EHV-1 and EHV-4) were allocated to a vaccinated group (n=7) or control group (n=5). In the vaccinated group the youngest foal was 8 months (one foal), while the remaining animals were 8.5 – 9.5 months old. Considering that efficacy should be investigated in the minimum age of the target species, the applicant was requested to justify this deviation from requirements. Serological pre-screening was used to ensure each treatment group had a comparable number of animals with either low or no antibodies to EHV-1 and EHV-4. Foals in the vaccine group were vaccinated by the intramuscular route with a single dose (1 ml) of Equilis EHV 1+4 (batch IP193388.1) on day 0 and day 28 of the study. Foals in the control group were untreated. Challenge by the intranasal route with virulent EHV-4, strain T446 was conducted at 7 weeks (3 weeks after the 2nd dose of vaccine). Monitoring of clinical signs and rectal temperature was carried out for 14 days post-challenge. Nasal swabs for evaluation of virus shedding, blood samples for evaluation of serological response and blood samples for PBL isolation and evaluation of viraemia were taken at appropriate time points throughout the study and post-challenge.

Results: On the day of 1st vaccination (day 0), mucopurulent discharge in the eyes or nose, lacrimation and nasal serous discharge were observed in animals of both groups, and cough in one animal of the vaccinated group. The applicant states that these signs were also observed after day 0 and the applicant was requested to clarify the extent of these signs and in which group they occurred after day 0 until day of challenge in week 7.

After EHV-4 challenge, nasal and ocular discharge were observed in both groups but signs were generally milder than those observed after EHV-1 challenge in the previous study. Hyperpnoea was observed in two control ponies on 3 dpc, while a cough (2 – 5x in 10 minutes) was observed in one vaccinated pony on 13 dpc. Clinical signs peaked in the control group on 3 – 4 and 6 – 7 dpc, with an average clinical score of 2.8. In the vaccinated group minor peaks in clinical signs were observed on 3 and 7 dpc, with an average clinical score of 0.9 and 1.1, respectively. Concerning the claim for a reduction in the duration of clinical signs, no data have been provided in support of this aspect of the claim; and the duration was similar between groups. The clinical score in the vaccinated group was statistically significantly lower (p=0.0031) compared to the control group post challenge, however the clinical relevance of the claimed statistically significant reduction is not considered to have been demonstrated. Clinical signs were mild post-challenge, and at the peak of clinical signs, signs are similar to those observed pre-challenge where it was justified that such signs are commonly observed in horses of this age. Apart from hyperpnoea in two animals in the control group on day 3 post-challenge, there would appear to be only a modest clinical difference between the control and vaccinated group in the 14 day post-challenge phase. The same concerns as raised for the EHV-1 OOI study regarding the manner in which clinical signs were scored also apply to these data. Body temperature increased in the control group from 2 – 4 dpc, peaking at 2 dpc with an average temperature of 39.9 °C, compared to a minor increase in the vaccinated group, with an average

temperature of 38.7 °C at 2 dpc, and was statistically significantly reduced in the vaccinated group compared to the control group. Therefore, similar to the issues raised concerning EHV-1, a reduction of duration and severity of clinical signs due to EHV-4 is not considered to have been adequately supported, and the applicant was requested to omit this claim from the SPC.

EHV-4 excretion in nasal swabs was detected in all animals of both groups during the post-challenge period. However, significantly less EHV-4 (AUC) (p=0.0065) was shed in the vaccinated group compared to the control group (difference of 9.11 log_{10} $TCID_{50}$/ml) and the number of days on which EHV-4 was shed was statistically significantly less (p=0.0073) in the vaccinated group compared to the control group (difference of 4.49 days).

Concerning viraemia, no EHV-1 or EHV-4 positive PBL were detected in any of the horses up to time of challenge. After challenge, PBL were isolated for viraemia of EHV-4 however no EHV-1 or EHV-4 was detected in any of the vaccinated or control group animals. This claim should have been omitted from the SPC.

Mean VN antibody titres of 5.5 log_2 for EHV-1 and 8.0 log_2 for EHV-4 were reported in the vaccinated group at 3 weeks after the second vaccination while the control group animals remained seronegative/low seropositive until after challenge. After EHV-4 challenge, an increase in antibody titre to both EHV-1 and EHV-4 was observed in both groups.

The OOI study for EHV-4 complies with the requirements of Ph. Eur. 1613. The proposed claims for a reduction of virus excretion (amount and duration) would appear to be supported, although justification for deviation from requirements to investigate efficacy in minimum age animal was required. However, whilst vaccinated horses showed no more than slight signs of disease (compliant with Ph. Eur. 1613 requirements), the clinical relevance of any claimed difference in clinical signs between the vaccinated and control groups is not considered to have been adequately demonstrated and, overall, the claims for a reduction of severity and duration of clinical signs and a reduction of viraemia due to EHV-4 infection are not considered to have been adequately supported.

Duration of immunity

EHV-1

The duration of immunity and the efficacy of the administration of the single booster dose were evaluated within the same study for EHV-1, as summarised below.

In **Study EHD-19-48-003 "Evaluation of the duration of immunity to EHV-1 challenge and booster response following intramuscular vaccination with a new inactivated equine herpesvirus"**, 22 foals (Shetland ponies, approximately 6 months of age seronegative / low seropositive to EHV-1 and EHV-4) were divided into 4 groups. On day 0 and 28, group 1 (n=7) and group 3 (n=7) were vaccinated by the intramuscular route with a single dose (1 ml) of Equilis EHV 1+4 (batch IP193388.1). At 6 months after the 2nd dose (in week 31), group 3 received a 3rd dose (booster, batch IP203536.1). Two additional EHV negative horses were included and added to group 4 later in the study (amendment no. 7, resulting in a total of 24 animals finally included in the study). Foals in the control groups 2 (n=5) and 4 (n=5) were untreated. Serological pre-screening was used to ensure each treatment group had a comparable number of animals with either low or no antibodies to EHV-1 and EHV-4. Challenge by the intranasal route with virulent EHV-1, strain M8 was conducted in groups 1 and 2 in week 27 (23 weeks after the 2nd dose of primary vaccination, and at 7 months after the third vaccination in groups 3 and 4 (week 62). Monitoring of clinical signs and rectal temperature was conducted, nasal swabs for evaluation of EHV-1 virus shedding, blood samples for evaluation of serological response and blood samples for PBL isolation and evaluation of presence of

EHV-1 (viraemia) were taken at appropriate time points during the study before challenge and for the 14 days following each of the challenges.

Results:

DOI after primary vaccination course - EHV-1 challenge at 23 weeks (approximately 5 months) after completion of the primary vaccination course.

Clinical signs peaked in the control group on 3 and 6 dpc, with the highest average clinical score of 4.4 on 6 dpc. In the vaccinated group clinical signs peaked on 3, 5 and 7 dpc, with the highest average clinical score of 2.9 on 7 dpc. The clinical score in the vaccinated group was statistically significantly lower (p=0.0248) compared to the control group, however it is noted that a similar spectrum of clinical signs was observed in each group, and the clinical relevance of the claimed difference is not considered to have been demonstrated. Ocular and nasal discharge was observed in both groups between 0 and 14 dpc. Other clinical signs during the study consisted of neurological signs (mild ataxia; score 2) in 1/7 ponies in the vaccinated group (on 5 dpc), malaise/depression; mild to moderate in the vaccinated group (on day 3, 4 and 5 in 2/7, 1/7 and 1/7 ponies, respectively, and mild in the control group (on day 2 in 1/5 ponies) and mild conjunctivitis in 1/7 ponies in the vaccinated group on days 10 and 11. There were no significant differences between groups 1 and 2 for rectal temperature (average rectal temperature on 2 dpc of 40.1 °C and 40.8 °C, respectively). The data presented are not considered to support a reduction of the duration or severity of clinical signs due to EHV-1 challenge at the claimed duration of immunity after primary vaccination.

A statistically significant reduction of the amount of **virus shedding** (p=0.0299) was demonstrated at the DOI timepoint. The duration of EHV-1 shedding was less in the vaccinated group, but not statistically significantly different (difference of 1.34 days). However, this claim is still considered acceptable since it has been adequately demonstrated at OOI, and evidence of protection of this parameter in general (virus shedding) at DOI is demonstrated by the data presented.

A statistically significant reduction in the amount of **viraemia**, but not duration, is claimed based on a statistically significant difference in the AUC for viraemia score. However, as raised for the OOI study, the clinical relevance of the claimed difference is not considered to have been demonstrated. It is noted that the difference between groups may be attributed mostly to a small number of timepoints where the highest of the three dilutions of PBL tested per animal was positive for CPE in the control group, while the duration of viraemia and the proportion of animals positive for viraemia were not different between groups. Thus, similar to the conclusions reached at OOI, this claim is not considered to have been supported by the data presented.

<u>DOI after single revaccination dose – EHV-1 challenge at 7 months after revaccination</u>

The interval between the 3rd vaccination (first booster dose) and the challenge was 7 months instead of 6 months due to study constraints. The applicant recommends the administration of booster doses every 6 months if horses are in frequent contact with other horses. Noting that the interval between booster and challenge is one month longer than the proposed DOI of 6 months, this study can be considered to represent a slightly worse case scenario. Following challenge, clinical signs, virus shedding and viraemia were observed in animals of both the vaccinated and control groups.

Clinical signs were more severe following this challenge, affecting all animals in both groups with signs such as malaise/depression, hyperpnoea, dyspnoea and conjunctivitis. No statistically significant differences in clinical signs were observed between groups for clinical score or rectal temperature. In this study, the average clinical score in the post-challenge period was higher in the vaccinated group 3 compared to control group 4. This is a point of concern and is strengthened also

by the fact that 2/5 control ponies in group 4 were around 8 months of age when challenged, compared to the remaining ponies in group 4 and the vaccinated ponies that were challenged at around 19 months of age. The applicant comments that it is commonly known that EHV infection causes more clinical signs in young foals. Thus, the unequal age-matching in the vaccinated and control group for this challenge would have led to more favourable study conditions for the vaccinated group, and notwithstanding this point, the average clinical score was higher in this group. The applicant was asked to justify the recruiting of additional animals that were not age-matched noting an awareness that younger foals were anticipated to be more susceptible to clinical signs of challenge. Overall, a claim of reduction of severity and duration of clinical signs is not considered to have been adequately supported at 7 months after the administration of the 3rd dose (first booster dose). This strengthens the concern already raised that the clinical signs claim at OOI is weak in general.

A reduction of **virus shedding** (amount [p=0.0056] and duration [p<0.0001], difference of 3.91 days) was demonstrated at 7 months after the administration of the 3rd dose (booster dose).

The overall AUC for **viraemia** score dpc 2 – 13 in the vaccinated group compared to the control group was not different between groups, but a statistically significant difference in the weighted PBL score dpc 4, 6, 8 and 10 between groups is claimed. However, taking into account the concerns previously discussed, the difference between groups is not considered to support a clinically relevant reduction of viraemia at 7 months after the single booster dose.

The serology data provided for the 2 dose basic vaccination scheme and first booster dose show that the VN titres to EHV-1 and EHV-4 are boosted to titres that are higher than those achieved following the administration of the two dose basic vaccination scheme. The titres remain generally high and do not seem to decrease at 7 months post-dose to the level that is observed at 23 weeks after completion of the primary vaccination scheme.

In conclusion, for EHV-1, immunity at 23 weeks after completion of the primary vaccination course and at 7 months after the first single revaccination has been demonstrated for protection against virus excretion, but is not adequately supported for protection against clinical signs or viraemia. It is noted that the DOI was not tested at 6 months after completion of the basic vaccination scheme. It was tested at 23 weeks after the 2nd dose of the basic vaccination scheme. This is closer to a 5 month DOI than 6 month DOI following basic vaccination. Therefore, the SPC should have been updated to state '5 months after completion of the primary vaccination course.'

EHV-4

One study is provided for the evaluation of the DOI for EHV-4. The study provided, summarised below, did not investigate the DOI of the basic vaccination scheme, but instead evaluated the DOI at 6 months after the 3rd vaccine dose (booster dose), which was administered at 5 months after completion of the two-dose basic vaccination scheme, by virulent challenge. This situation arose due to inability to conduct the challenge experiment at 6 months after basic vaccination due to Covid-19 pandemic-related constraints. In addition to the challenge experiment, the serological response to vaccination over the course of the study and the response to a 4th dose, administered at a year interval after the 3rd dose, was evaluated in support of the proposed DOI of 1 year based on serological memory.

In **Study "Multi-site study for the evaluation of the duration of immunity to EHV-4 challenge, booster response after bi-annual and annual revaccination and vaccine safety following intramuscular vaccination with an inactivated equine herpesvirus"**, 18 foals (Connemara ponies, approximately 6 months of age seronegative / low seropositive to EHV-1 and EHV-4) were divided into 3 groups. In week 0 (day 0), week 4 and week 26, group 1 (n=6) and

group 2 (n=6) were vaccinated by the intramuscular route with a single dose (1 ml) of Equilis EHV 1+4 (batch IP193388.1 was used for 1st and 2nd dose, batch IP203536.1 was used for the 3rd and 4th dose). In week 78 (12 months after the 3rd dose), horses in group 2 were vaccinated with a 4th dose. A negative control group (placebo; PBS with Matrix C) was included, group 3 (n=6) with most horses serving as negative control for group 1 (group 3a, n=5) and one horse went on to be used as sentinel/negative control for the remainder of the study (group 3b). Serological pre-screening was used to ensure each treatment group had a comparable number of animals with either low or no antibodies to EHV-1 and EHV-4. Challenge by the intranasal route with virulent EHV-4, strain 122324 was conducted in groups 1 and 3a at 6 months after the 3rd dose/ one year after the first dose of primary vaccination (week 52). Monitoring of clinical signs and rectal temperature was conducted, and nasal swabs for evaluation of EHV-4 virus shedding, blood samples for evaluation of serological response and blood samples for PBL isolation for evaluation of viraemia were taken at appropriate time points during the study before challenge and for the 14 days following challenge. This study also included safety monitoring after the administration of the 4th dose (refer to Part 3) and was conducted on a blinded basis.

DOI after single revaccination dose – EHV-4 challenge at 6 months after revaccination

The challenge resulted in mild **clinical signs** (serous nasal discharge or mild mucopurulent discharge) which were similar in both groups, exceptionally hyperpnoea was reported in one animal in the control group. No statistically significant differences between groups were reported. There were no significant differences between groups 1 and 3a for rectal temperature over time, however the peak temperature was statistically significantly higher (p=0.0112) in group 3a compared to group 1; a peak in temperature of 38.3 and 38.4 °C was observed on day 3 and 5 post-challenge in the control group, but no increases were reported in the vaccinated group. The data presented are not considered to adequately support a reduction of severity or duration of clinical signs due to EHV-4 infection.

A statistically significant reduction of the amount ($p<0.0001$) and of the duration ($p=0.0066$) of **virus shedding** was demonstrated in the vaccinated group at 6 months after the administration of the 3rd dose. This claim is therefore considered to have been adequately supported.

No **viraemia** was detected in PBLs of control or vaccinated animals post-challenge. The data presented do not support a reduction in viraemia due to EHV-4 infection.

Serological response to primary vaccination course, first revaccination at 5 months after 2nd dose of primary course, and first annual booster 12 months later:

At study start, all animals were negative or low positive to equine influenza virus (EIV) and negative or low positive to EHV-1 and EHV-4. The control groups animals remained seronegative/low seropositive until after challenge.

After the 2 dose basic vaccination: a minor increase in titres to EHV-1 and an increase in titres to EHV-4 was observed after the 1st dose and a strong response was observed for both EHV-1 and EHV-4 after the 2nd dose (mean titre of 3.5 $\log_2$ for EHV-1 and 4.6 $\log_2$ for EHV-4 in group 1 and mean titre of 3.2 $\log_2$ for EHV-1 and 6.1 $\log_2$ for EHV-4 in group 3 at 4 weeks after the second dose), after which titres slowly declined.

After the 3rd vaccination: a strong anamnestic response was observed in both vaccinated groups with a higher titre than after the 2nd dose; mean titre of 10.4 log 2 for EHV-1 and 10.3 log 2 for EHV-4 in group 1 and mean titre of 9.3 log 2 for EHV-1 and 10.4 log 2 for EHV-4 in group 3 at week 30 (4 weeks after 3rd dose).

After EHV-4 challenge at 6 months post 3rd dose, an increase in antibody titres to both EHV-1 and EHV-4 was observed (9.2 and 10.6 log_2 for EHV-1 and EHV-4, respectively, at 2 days post-challenge in group 1 compared to 0.8 and 5.6 log_2 for EHV-1 and EHV-4, respectively, in the control group 3a).

After the 4th dose in group 2 (revaccination at 12 months after the 4th dose), a strong anamnestic response was observed for both EHV-1 and EHV-4 (4 weeks after the 4th dose, titres of 8.1 and 9.2 log 2 for EHV-1 and EHV-4, respectively).

In conclusion, for EHV-4, a DOI of 6 months after the first single revaccination has been demonstrated for the viral excretion claim for EHV-4 (reduction of duration and amount), but not for the claims proposed for protection against clinical signs and viraemia. However, the proposed DOI of 6 months after the two dose primary vaccination course for EHV-4 was not investigated. The applicant was therefore requested to provide suitable data to support the proposed DOI for protection against EHV-4 following primary vaccination. However, it would be an expectation that a DOI following primary vaccination for one of the two antigenic components of the vaccine would be suitably demonstrated in order to inform the subsequent revaccination schedule.

The investigation of the efficacy of a single annual booster dose was evaluated at 12 months after administration of the first booster (6 months after completion of the primary vaccination course) by analysis of VN titres to EHV-1 and EHV-4. It can be accepted that the frequency of the proposed annual booster doses is appropriate in terms of maintaining VN titres to EHV-1 and EHV-4 that are higher than those achieved following basic vaccination. Typically, it would be expected that a DOI based on serology would be established using a threshold / cut-off point for antibody titres and protection; however, a correlation between serological response and protection is not supported by the data provided in the OOI studies. The applicant was requested to provide further justification to demonstrate that the increase in VN titres can be considered to be sufficiently representative of protection.

The applicant has worded the information in the SPC relating to DOI as follows:

"Duration of immunity: 6 months after primary vaccination, immunological memory of 1 year, 6 months after revaccination, immunological memory of 1 year."

Immunological memory of one year has not been demonstrated after primary vaccination, since there are no data provided wherein animals received the two-dose basic vaccination scheme and then were revaccinated a full year later. Furthermore, the term "immunological memory" is considered vague, and any reference to protection at 1 year after revaccination should have been more clearly stated as being based on serology data, if it was a case that this has been demonstrated. However, in the absence of a correlation between antibody titres and protection (see above), the applicant was requested to omit the claim for 'immunological memory of 1 year after primary vaccination' and 'immunological memory of 1 year after revaccination' from the description of the DOI.

In summary, the applicant was requested to update this text as follows:

"Duration of immunity: 5 months after completion of the primary vaccination course, 6 months after revaccination.

Maternally derived antibodies (MDA)

No data are presented by the applicant concerning the effect of MDA on vaccine efficacy. However, the applicant justifies that the possible effects of MDA on vaccine efficacy are negligible, due to the proposed minimum age of vaccination of 6 months. This is considered acceptable.

Interactions

A compatibility use claim is proposed for administration of Equilis EHV 1+4 on the same day (different site) but not mixed with Equilis Prequenza Te and its fall-out products, Equilis Prequenza and Equilis Te. The claim is proposed on the basis that VN antibody response data are available to support the associated use. Two pre-clinical studies are presented in support of the efficacy of compatible use. In addition, the associated non-mixed use was investigated in the clinical field trial (S21105).

In the first study (**"Evaluation of the efficacy of Prequenza combined with Resp EHV1&4 against EIV-strain Venlo challenge in horses"**), while VN titres to EHV-1 and EHV-4 are shown to increase when Equilis EHV 1+4 is administered at the same time as Equilis Prequenza, due to deficiencies in the study design (lack of adequate control groups vaccinated with Equilis EHV 1+4 alone, animals seropositive prior to vaccination), it is not possible to conclude if the serological response to Equilis EHV 1+4 is affected by associated use with Equilis Prequenza. Furthermore, the efficacy of Equilis Prequenza is also (by necessity for such a claim), required to be demonstrated, however the applicant has elected not to discuss further the efficacy of Equilis Prequenza under conditions of compatible use. Furthermore, it is noted that the timepoint of challenge with EIV in this exploratory study was 3 weeks after the 2nd dose of Equilis Prequenza (when the authorised OOI for this vaccine is 2 weeks after the 2nd dose).

In the second study (**"Evaluation before and after foaling of the potency and safety of a new inactivated equine herpesvirus vaccine used associated with Equilis Prequenza after repeated single dose intramuscular vaccination in pregnant Shetland mares")**, the serological response to vaccination with Equilis EVH 1+4 in pregnant mares was evaluated under conditions of associated use with Equilis Prequenza or Equilis Prequenza Te. The study was primarily designed to investigate safety and it is noted that mares in both the control and vaccinated groups were seropositive for EHV-1 and EHV-4 at study start, and a group vaccinated with Equilis EHV 1+4 alone was not included. Although it can be accepted that vaccination with Equilis EHV 1+4 on three separate occasions during pregnancy, when administered with Equilis Prequenza on one occasion and with Equilis Prequenza Te on one occasion results in an anamnestic response, with statistically significantly higher VN titres to EHV-1 and EHV-4 than those of the control group that received Equilis Prequenza / Equilis Prequenza Te alone, this is not surprising and simply confirms a response to vaccination. Thus, this study is not considered to provide conclusive data concerning the absence of impact of Equilis Prequenza or Equilis Prequenza on the efficacy of Equilis EHV 1+4 when used in association.

In conclusion, the efficacy aspects of the proposed compatible use claim for Equilis EHV 1+4 with Equilis Prequenza Te and its fall-out vaccines are not considered to have been adequately supported by the data presented.

Clinical trials

One field safety and efficacy study was presented, S21105-00. This study investigated the safety and efficacy of primary vaccination in foals and the safety of repeated administration in pregnant mares, and was conducted under conditions of associated use with Equilis Prequenza Te for both doses of primary vaccination in foals, and for the third administration of Equilis EHV 1+4 during pregnancy. Please refer to Part 3 for a summary of the study design. Although this was a combined field safety and efficacy trial (which is acceptable), it is noted that a standard batch was not used (i.e., at the proposed fixed antigenic content for EHV-1 and EHV-4). Instead, an 'over-formulated' batch was used (U for EHV-1 and EHV-4, respectively), thus the clinical trial is considered more relevant to the

safety of use under field conditions since the antigenic dose administered to study animals is higher than the proposed content for commercial batches.

Efficacy of use under field conditions was evaluated by measurement of the serological response (VN titres) in foals. Study animals were seropositive at time of vaccination, which is accepted as representative of field conditions. In the test group, a response to vaccination was observed at 2 weeks after the 1st dose, with VN titres of 6.1 and 7.1 $\log_2$ for EHV-1 and EHV-4, respectively, and higher VN titres of 8.6 and 9.8 $\log_2$ for EHV-1 and EHV-4, respectively, at 2 weeks after the 2nd dose. A single dose of Equilis Prequenza Te was administered at the same time as Equilis EHV 1+4. In the control group administered Equilis Prequenza Te alone, no increase in EHV-1 or EHV-4 antibody titres was observed, demonstrating the absence of field infection during the study. However, this study is not considered to provide meaningful information regarding efficacy under field conditions, other than to confirm a serological response to vaccination in seropositive foals, in associated use with Equilis Prequenza Te. Furthermore, as stated, the fact that vaccination was conducted with an approximately 3-fold higher antigen content for EHV-1 and EHV-4, rather than a standard fixed content batch, also limits any further conclusions which could have been drawn.

Overall conclusion on efficacy

Efficacy was investigated in well documented laboratory studies in the target species using foals of the minimum age recommended for vaccination (from 6 months of age), and the serological response to vaccination was characterised in pregnant mares. The challenge model used to investigate immunogenicity complies with the requirements of Ph. Eur. 1613. Justification that the vaccine strains (and choice of challenge virus strains used to demonstrate efficacy) are currently epidemiologically relevant in the EU should have been provided.

The vaccine is manufactured according to a fixed antigenic content per dose of 1 ml. Batches used in the efficacy studies were formulated to contain less than the proposed antigenic content. In the clinical trial, the batch used was formulated to contain more than the proposed antigenic content. As raised under Part 2, the applicant was requested to provide further clarifications concerning the expression of antigen content in AU/dose compared to $\log_{10}$ U/ml in order to confirm use of minimum content batches for evaluation of efficacy. Concerning the adjuvant used, clarification was required to confirm that the batches used in the efficacy studies can be considered representative of the proposed formulation for marketing with respect to the adjuvant.

The OOI of 3 weeks after primary vaccination is supported by challenge studies conducted at 3 weeks after the second dose of the primary vaccination course, when the first and second doses were administered 4 weeks apart.

At OOI, the data provided are considered to support a claim for a reduction in the amount and duration of viral excretion due to infection for both EHV-1 and EHV-4. A statistically significant difference between vaccinated and control groups for both parameters was demonstrated following challenge.

The claim for a reduction in the severity and duration of clinical signs due to EHV-1 or EHV-4 is not considered to have been adequately supported. Thus, the proposed claim for a reduction of duration and severity of clinical signs due to infection with EHV-1 and EHV-4 should have been omitted.

The claim for a reduction of severity and duration of viraemia due to EHV-1 and EHV-4 is not supported by the data presented. For EHV-4, no viraemia was detected post-challenge in the vaccinated or control groups. For EHV-1, the data provided are not considered to support a reduction of viraemia. The applicant was requested to omit the claim for a reduction in viraemia due

to EHV-1 and EHV-4.

For EHV-1, a DOI of 5 months (23 weeks) after the completion of the primary vaccination course for the claims relating to amount and duration of viral excretion is supported, while the claims relating to clinical signs and viraemia are not considered to have been adequately supported. A DOI of 6 months after the first single revaccination dose is considered to have been supported for protection against virus excretion, but not clinical signs or viraemia. The proposed DOI of 5 months after primary vaccination and 6 months after revaccination is accepted for EHV-1.

The DOI of the primary vaccination scheme for protection against EHV-4 was not investigated, instead the DOI of 6 months after the 3rd vaccine dose (i.e., first booster dose), which was administered at 5 months after completion of the primary vaccination course, was evaluated by challenge. In addition, the serological response to vaccination over the course of the study and the response to a 4th dose, administered at a year interval after the 3rd dose was evaluated in support of the proposed DOI of 1 year based on serological data. A DOI of 6 months after the 3rd vaccine dose was supported only for the claim for a reduction of amount and duration of virus shedding, but not for protection against clinical signs or viraemia. The proposed DOI of 6 months after the two dose primary vaccination course for protection against EHV-4 was not investigated. The applicant was therefore requested to provide suitable data to support the proposed DOI for protection against EHV-4 following primary vaccination. In the absence of appropriate data, the SPC should have been amended accordingly. However, it would be an expectation that a DOI following primary vaccination for one of the two antigenic components of the vaccine would be suitably demonstrated in order to guide the subsequent revaccination schedules.

An inferred DOI of one year based on immunological memory is claimed. The serology data provided to support this claim demonstrates that the frequency of the proposed annual booster doses is appropriate in terms of maintaining VN titres to EHV-1 and EHV-4 that are higher than those achieved following basic vaccination. However, it would be expected that a DOI based on serology would be established using a threshold / cut-off point for antibody titres and protection, and in this case a correlation between serological response and protection is not supported by the data provided in the OOI studies. Furthermore, there are no data available regarding serological levels in a scenario where foals received the two dose primary vaccination course and antibody titres measured a year later (without an interim booster dose). The applicant was requested to provide further justification to demonstrate that the increase in VN titres can be considered to be sufficiently representative of protection. However, given that antibody titres are not correlated with protection, the applicant was requested to omit 'immunological memory of 1 year' from the description of the DOI, both after primary vaccination and after revaccination.

It is noted that the applicant proposes to include information under section 4.1 of the SPC that the vaccine reduces viraemia, which will reduce the risk of abortion and neurological signs. As stated, the claim for a reduction of viraemia is not considered to have been adequately supported. Notwithstanding this point, even if a claim for a reduction of viraemia could be considered to have been demonstrated, the proposed text in section 4.1 should be omitted as the information proposed is, in effect, an additional indication or inferred benefit of using the product, which has not been investigated and is not supported by data.

A compatibility use claim is proposed for administration of Equilis EHV 1+4 on the same day (different site) but not mixed with Equilis Prequenza Te and its fall-out products Equilis Prequenza and Equilis Te. The claim is proposed on the basis that VN antibody response data are available to support the associated use. Whilst two studies are presented in support of the efficacy of compatible use, various deficiencies in the studies provided do not enable a conclusion to be reached whether VN antibody titres to EHV-1 and EHV-4 are adversely affected by concurrent use with Equilis Prequenza

Te, Equilis Prequenza or Equilis Te. Therefore, the efficacy aspects of the proposed compatible use claim for Equilis EHV 1+4 with Equilis Prequenza Te and its fall-out vaccines are not considered to have been adequately supported by the data presented and, information concerning compatible use should have been omitted from the SPC section 3.8.

One multicentre GCP-compliant field trial was performed in foals and pregnant mares in order to assess safety and efficacy under field conditions of use. Efficacy of vaccination under field conditions was evaluated by the serological response to vaccination (in foals only). However, since the batch used for vaccination was formulated to contain an approximately 3-fold higher antigen content for both EHV-1 and EHV-4, from an efficacy perspective, the results obtained are of limited use and simply confirm that a serological response to vaccination took place in seropositive foals under conditions of associated use with Equilis Prequenza Te (with a vaccine batch with higher antigen content than will be present in commercial batches). However, the lack of any further efficacy data from the field trial can be accepted in principle since the efficacy claims for the vaccine were established under controlled laboratory conditions.

In summary, the overall data package to support the efficacy of Equilis EHV 1+4 is not considered to be sufficiently robust in terms of demonstrating a beneficial effect for the reduction of severity and duration of clinical signs of respiratory disease (rhinopneumonitis) or a reduction of viraemia due to infection with EHV-1 and/or EHV-4. These issues are considered to represent major objections. A claim for a reduction of viral excretion (amount and duration) would appear to have been adequately supported by the data presented. However, overall, the proposed indications for use are not considered to have been adequately supported. Finally, it should be noted that should the vaccine be considered efficacious only for a reduction of virus excretion, this may lead to a question on the overall benefit/risk balance, considering that while a reduction in virus excretion is demonstrated, the clinical relevance of that reduction without any other evidence of protection, may be considered questionable.

Part 5 – Benefit-risk assessment

Introduction

Equilis EHV 1+4 is an inactivated vaccine containing equine herpesvirus 1, strain RAC-H and equine herpesvirus 4, strain 2252 as active substances and Iscom-matrix (containing purified saponin) as adjuvant. The target species is horse. The route of administration is intramuscular.

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

Active immunisation of horses to reduce the severity and duration of clinical signs of respiratory disease (rhinopneumonitis), amount and duration of virus excretion and viraemia due to infection with equine herpesvirus 1 and/or equine herpesvirus 4.

The primary vaccination course consists of one 1-ml dose of vaccine followed by a second dose 4 to 6 weeks later. Re-vaccination is recommended every six months for high-risk horses and every 12 months for low-risk horses.

The application has been submitted in accordance with Article 8 of Regulation (EU) 2019/6 (full application).

Benefit assessment

Direct benefit

The proposed benefit of Equilis EHV 1+4 is its efficacy in terms of reducing the severity and duration of clinical signs of respiratory disease (rhinopneumonitis), amount and duration of virus excretion and viraemia due to infection with equine herpesvirus 1 and/or equine herpesvirus 4, which was investigated in a number of well-designed pre-clinical studies conducted to an acceptable standard. However, concerns arised with respect to the scoring and analyses of clinical signs and viraemia. The indications for a reduction of viraemia are not considered to have been supported by the data presented. The indications for a reduction of severity and duration of clinical signs are not considered to have been adequately supported by the data presented.

The onset of immunity is 3 weeks after completion of the two-dose primary vaccination course.

The duration of protection is 23 weeks (approximately 5 months) after the completion of the primary vaccination course for EHV-1 and 6 months after revaccination with a single dose for EHV-1 and EHV-4. The duration of protection after the completion of the primary vaccination course for EHV-4 has not been investigated and this deficiency was raised as a concern. A duration of immunity of one year, based on serological data, for both EHV-1 and EHV-4 following completion of the primary vaccination course and following revaccination with a single dose is claimed, but this is not considered to be adequately supported in the absence of a correlation between antibody titres and protection from infection.

Additional benefits

Equilis EHV 1+4 increases the range of available vaccines for immunisation against EHV-1 and EHV-4.

Risk assessment

Due to concerns regarding the pivotal preclinical safety study, a conclusion on the safety of Equilis EHV 1+4 for the target species cannot be reached. The safety of the vaccine Equilis EHV 1+4 for the user, the environment, and the consumer of foodstuffs from treated animals is considered to have been adequately demonstrated.

Quality

Information on development, manufacture and control of the active substance and finished product has generally been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. However, a number of issues needed to be clarified (including a major objection), regarding the formulation and quantification of the adjuvant, extraneous agent testing of the starting materials, detail provided in the validation studies, and the batches used for consistency and stability studies.

Safety

Risks for the target animal

Administration of Equilis EHV 1+4 in accordance with SPC recommendations appears to be generally well tolerated. The main reported adverse reactions include elevated temperature, local reactions at

the injection site and ocular and nasal discharge. However concerns regarding the pivotal preclinical safety study were raised and a final conclusion on safety of the vaccine in the target animal species, horses, cannot be reached.

The safety of the administration of Equilis EHV 1+4 during pregnancy (after approximately 5 months gestation) has been demonstrated.

The safety of associated (but not mixed) use with Equilis Prequenza Te, Equilis Prequenza and Equilis Te has been suitably investigated, and supported.

Risk for the user

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. No specific safety advice is considered necessary in the SPC.

Risk for the environment

Equilis EHV 1+4 is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

A 'zero days' withdrawal period is considered acceptable.

Risk management or mitigation measures

Appropriate information has been included (or commented upon) in the SPC to inform on the potential risks of this product relevant to the target animal, user, environment and consumer.

User safety

No user safety risks have been identified.

Environmental safety

No specific risk to the environment has been identified.

Consumer safety

A zero day withdrawal period is proposed.

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.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: Active immunisation of horses to reduce the severity and duration of clinical signs of respiratory disease (rhinopneumonitis), amount and duration of virus excretion and viraemia due to infection with equine herpesvirus 1 and/or equine herpesvirus 4.

At the time of the application's withdrawal major concerns had been raised.

In the presence of outstanding major and other concerns, the benefit-risk balance of the application was therefore inconclusive.

Conclusion

Based on the original data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Equilis EHV 1+4 is not approvable as the data presented was not considered to be in accordance with the requirements set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that no conclusions could therefore be taken on the benefit-risk balance in the absence of additional information/data.