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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Equilis Prequenza (EMEA/V/C/000094/X/007/G)

Common name: Vaccine against equine influenza in horses

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

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Introduction

A grouped application for an extension and variations of a Community marketing authorisation of Equilis Prequenza has been submitted to the European Medicines Agency on 28 September 2011 by Intervet International BV in accordance with Articles 19 and 16 of Commission Regulation (EC) No 1234/2008 and Annex I point 1 (d) and Annex III point 1 thereof.

The CVMP adopted an opinion and CVMP assessment report on 7 February 2013.

On 10 April 2013, the European Commission adopted a Commission Decision for this application.

The proposed composition for Equilis Prequenza is to contain inactivated equine viruses A/equine-2/South Africa/4/03 50 AU (antigenic units) and A/equine-2/Newmarket/2/93 50 AU per 1 ml and is presented in boxes of 10 glass vials or 1, 5 or 10 pre-filled syringes. It is indicated for active immunisation of horses from 6 months of age against equine influenza to reduce clinical signs and virus excretion after infection. The route of administration is intramuscular use. The target species is horses.

Part 1 - Administrative particulars

No change compared to the originating vaccine.

The applicant has revised the SPC, labelling and package leaflet in the light of the subject of the present line extension with grouped variations.

Overall conclusions on administrative particulars

No change compared to the originating vaccine.

Part 2 - Quality

Composition

The proposed vaccine Equilis Prequenza represents an inactivated vaccine (suspension for injection) for the active immunisation of horses against equine influenza.

The conventionally produced vaccine contains the equine influenza virus (EIV) strains A/equine-2/Newmarket/2/93 and A/equine-2/South Africa/4/03, which were originally isolated from infected horses from Newmarket (United Kingdom) and South Africa. These virus strains are inactivated using beta-propiolactone solution (BPL). It is however noted that these strains are not fully in line with the latest OIE recommendations and additional justification for the composition was provided.

Container

There were no changes compared to the originating vaccine.

Development Pharmaceutics

The vaccine originally contained subunits consisting of purified haemagglutinin (HA) and neuraminidase (NA) glycoproteins from three strains of equine influenza virus:

- A/equine-1/Prague/1/56- H7N7

- A/equine-2/Newmarket/1/93- H3N8 (= American lineage)
- A/equine-2/Newmarket/2/93- H3N8 (= European lineage)

This strain selection was in line with the "*Consultation of OIE and WHO experts on progress in surveillance of equine influenza and application to vaccine strain selection*" (Newmarket, 1995).

In 2004 the OIE Expert Surveillance Panel on Equine Influenza Vaccine Composition recommended a strain update. The American lineage H3N8 component should be replaced by an A/equine-2/South Africa/4/2003-like virus.

In addition, in 2008 the panel no longer recommended the inclusion of an H7N7 virus.

In accordance with the recommendation of 2008 the applicant has decided to remove the H7N7 strain (A/equine-1/Prague/56) and to replace the American lineage H3N8 component (A/equine-2/Newmarket/1/93) by A/equine-2/South Africa/4/2003.

As a result of the changes the influenza composition is as follows:

- A/equine-2/ Newmarket/2/93 (H3N8: "European" lineage)
- A/equine-2/ South Africa/4/03 (H3N8: "American" lineage Florida sub-lineage clade 1).

In addition, for harmonisation purposes of Intervet's equine vaccine range, the applicant has decided to replace the master seed of the viruses A/Equine-2/Newmarket/2/93 strain (derived from legacy Intervet) by the legacy Hoechst Roussel Vet master seed (already included in another equine influenza vaccine). The two master seeds originate from the same isolate and share the same premaster seed. In order to confirm the equivalence of the A/equine-2/Newmarket/2/93 master seeds the sequence of both was determined. Despite the presence of two quasispecies in the master seed, no difference is found in the antigen harvests since only the quasispecies already known from the current product is propagated.

An overview of the main changes to the equine influenza virus composition of Equilis Prequenza and to the manufacturing process and control testing, including replacement of A/equine2/Newmarket/2/93 Master Seed is presented below.

Old EIV composition	**Change**	**New EIV composition**
A/equine-1/Prague/56	Strain removed	-
A/equine-2/Newmarket/1/93 Produced in eggs	Strain updated and change of growth substrate	A/equine-2/South Africa/4/03 Produced in MDCK-ISC cells
A/equine-2/Newmarket/2/93 Produced in eggs	Master seed replaced and change of growth substrate	A/equine-2/Newmarket/2/93 (already used for another EI vaccine - legacy HRVet) Produced in MDCK-ISC cells

General European Pharmacopoeia (Ph. Eur.) monographs like Ph. Eur. General monograph 5.2.7, Ph. Eur. monograph 0249 "Equine influenza vaccine (inactivated)", the Note for Guidance EMEA/CVMP/112/98 "Harmonisation of requirements for equine influenza vaccine: Specific requirements for the substitution or addition of a strain or strains" and other relevant EU requirements and guidelines are taken into account for the assessment of the vaccine quality. However, in view of

the change to the method of production of the influenza virus antigens, the specific reduced data requirements listed in the Note for Guidance EMEA/CVMP/112/98 for substitution or addition of a strain are not applicable in this case and additional data are required to substantiate the strain changes proposed.

ISCOM-matrix adjuvant is added as adjuvant. This adjuvant is based on a complex (ISCOM-matrix) which consists of lipid (cholesterol, phosphatidyl choline), saponin (purified) and the specific antigen(s) that will form spontaneously when the constituents are allowed to interact at correct stoichiometry.

Method of manufacture

The production process of the active ingredient (EIV) as well as the finished product correspond to a classical procedure based on classical starting materials. Madin-Darby canine kidney (MDCK-ISC) cells (as monolayer) used as host system and the EIV used as active ingredient (vaccine antigen) are handled in a type of seed-lot system using master and production seeds.

For mass cultivation, the egg-adapted viruses are propagated once in MDCK-ISC cells. After concentration, sonification and clarification, the virus harvests are inactivated using BPL. Thereafter, the vaccine bulks are prepared by blending with the other components (e.g. adjuvant, PBS buffer) to a homogeneous vaccine suspension. For preparation of the finished product, the vaccine bulk is filled into sterile vials and stored.

Working Seed Virus stocks are produced on embryonated SPF chicken eggs. Working Seed stock that will be used for production will be tested for sterility (Ph. Eur. 2.6.1) and mycoplasma (Ph. Eur. 2.6.7). In addition the infectivity titre will be determined by titration in eggs. Details of WSV used for the antigen production are provided for each batch of final product in the batch protocols.

In general, the description of the production process is comprehensible and gives sufficient confidence that the product will be safe, effective and stable. It was demonstrated that the production process generates consistent vaccine batches.

Control of starting materials

Active substance and excipients

Specifications of active ingredients and starting materials are defined and analytical methods are provided.

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

In general, the starting materials of biological origin comply with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathies agents via human and veterinary medicinal products (EMEA/410/01 rev3). The overall TSE risk associated with the inactivated vaccine is considered negligible.

Control tests during production

During the manufacture in-process controls are carried out to assure the quality parameters. Test methods for in-process controls are satisfactorily validated.

The applicant has presented acceptable in-process data for three consecutive batches.

Control tests on the finished product

The control of the finished product is performed on the finished product and is carried out to assure the quality parameters. Limits of acceptance are presented. The control methods are satisfactorily validated.

The end of shelf life specification limit for the vaccine's saponin fraction C content was revised, based on the results generated with the new statistical method (without a correction factor), and was considered justified.

The applicant has presented acceptable data for three consecutive finished product batches.

Stability

Stability data were gathered for the vaccine of the original and the updated composition. These vaccines contain both EIV bulk antigens. Data are provided for nine batches (vials) for 27 months as well as one batch (pre-filled syringes) at release. All batches have passed the control tests on the finished product. Based on these data, a shelf life of 24 months is considered justified for the vials. An end of shelf life limit for the vaccine's saponin fraction C content was also introduced.

Overall conclusions on quality

Overall, the updated strain composition and the switch from a completely egg-produced vaccine to a final step antigen production on cell cultures are supported by the data. Although the proposed new composition is not in line with the latest OIE recommendations, an acceptable justification for the strains proposed is provided.

The production methods as well as the in-process and final product quality control and the stability results demonstrate compliance with the specifications and a reproducible and consistent quality of the vaccine.

The seed lot system for final step cell-based production of the influenza antigens has been explained with emphasis on the so-far elusive working seed virus (WSV) of both antigen strains. Testing of starting materials was overall adequate. Concerning the MDCK-ISC cells, the cell seed production, storage conditions and amount of prepared vials has been described in detail. Control testing was complete. Compliance of starting materials of animal origin used during production with the requirements of the Note for guidance on minimising risk of transmitting animal spongiform encephalopathy agents via human and veterinary products was shown.

In general, controls during manufacture and tests on the finished product ensure compliance with the quality specifications mentioned.

For determination of the antigen quantity before inactivation a titration in embryonated SPF eggs is used. Concerning the determination of the antigen quantity after inactivation the ELISA for strains SA4/03 and NM2/93 is considered suitable.

In principle, regarding determination of the potency the HI test remains suitable also for the new whole virus vaccine; however, the pass criteria have been newly defined.

The CVMP considers the presented analytical dossier as adequate. The quality of Equilis Prequenza is considered to be adequately demonstrated.

Part 3 – Safety

Safety documentation

Safety data are presented taking into consideration Ph. Eur. monograph 0249 "Equine influenza vaccine (inactivated)" and the Note for Guidance EMEA/CVMP/112/98 "Harmonisation of requirements for equine influenza vaccine: Specific requirements for the substitution or addition of a strain or strains". However, in view of the change to the method of production of the influenza virus antigens, additional data to those listed in Note for Guidance EMEA/CVMP/112/98 for substitution or addition of a strain are required to substantiate the strain changes proposed.

However, it is considered that the change of the production method from egg culture to cell culture and the inclusion of whole inactivated virus particles instead of purified HA subunits is such a substantial change that it is necessary to completely re-evaluate the safety of the product. The first study carried out was considered to be insufficient in this regard and a repeated dose safety study fully compliant with Ph. Eur. 5.2.6, i.e. including three doses of vaccine to cover the primary vaccination schedule and the first re-vaccination, was therefore carried out. An additional repeated dose safety study has been performed (three vaccinations with one dose 14 days apart).

In addition safety monitoring has been performed in two efficacy studies (two vaccinations with one dose 4 weeks apart in Shetland ponies and Fjord horses).

Furthermore, it has to be ensured that all reported pharmacovigilance reports are submitted with details of the batch number used and within a short time frame. For that reason, a change of periodic safety update report (PSUR) cycle frequency to 6 monthly reporting is recommended.

Laboratory tests

A laboratory study has been performed using different batches of Equilis Prequenza and Equilis Prequenza Te, which were representative for the production process. Safety aspects were also assessed in the laboratory efficacy study using Equilis Prequenza Te.

Safety of the administration of one dose

A repeated dose safety study including three doses of vaccine to cover the primary vaccination schedule and the first re-vaccination has been performed (please refer to Safety of the repeated administration of one dose).

Safety of one administration of an overdose

The results obtained after the administration of a double dose and repeated single dose demonstrate for horses that adverse reactions are limited to an occasional increase in body temperature. Sometimes transient fever occurred which never persisted for more than 24 hours. Local reactions at the injection site such as swelling were observed temporarily which normally disappeared within a few days.

The outcomes of the study are reflected in the wording of the proposed SPC.

Safety of the repeated administration of one dose

The results obtained after the administration of a double dose and repeated single dose are available (please refer to Safety of the administration of overdose). The outcomes of the study are reflected in the wording of the proposed SPC.

In addition a repeated dose safety study including three doses of vaccine to cover the primary vaccination schedule and the first re-vaccination has been performed (3 doses given 14 days apart). This study included several 3-year-old Shetland ponies (known to be a sensitive breed). One pony developed local reactions at the injection site up to 15 cm x 20 cm over a period of 5 days after two of three vaccinations. Comparable events are reported in the PSURs of the current vaccine. As the data are limited, especially from sensitive breeds, it is not clear if these observations are exceptional and only related to this pony. Therefore the possible adverse reactions will be mentioned in the product literature and additional safety data, from sensitive breeds in particular, will be collected via the pharmacovigilance system.

Examination of reproductive performance

No additional data are submitted for the updated vaccine.

However, no change to the impact of the vaccine on the reproductive performance is expected due to the kind of changes applied for.

Examination of immunological functions

No additional data are submitted for the updated vaccine.

However, no change to the impact on the immunological function is expected as a result of the changes applied for.

Special requirements for live vaccines

The special requirements for live vaccines are not applicable as Equilis Prequenza vaccine is inactivated.

Study of residues

No changes compared to the originating vaccine.

Interactions

No additional data are submitted. No changes compared to the originating vaccine.

Field studies

No additional studies are submitted for the updated vaccine.

User safety

No additional data are submitted for the updated vaccine.

However, with regard to the user safety, the likelihood, the consequences and the level of risk of human exposure are not expected to be modified as a result of the changes applied for.

Environmental risk assessment

No additional data are submitted for the updated vaccine.

However, with regard to the ecotoxicity, an environmental risk which can be identified through the use of this vaccine is not expected. The likelihood, the consequences and the level of risk are expected not to be modified due to the changes applied for.

The product is an adjuvanted liquid vaccine containing inactivated viral antigens (whole virus) as active components. The adjuvant contains a mixture of a purified fraction of Quillaia saponin (Matrix C), cholesterol and phosphatidyl choline. The vaccine is administered by individual intramuscular injections; direct exposure of the environment to the product does not take place. The vaccine does not contain any component in a concentration that poses a risk to (human) health; residues of the vaccine in animals that may enter the food chain are not a risk to the environment. Excretion of any of the components of the vaccine or of metabolites can be excluded. Any unused product or waste material will be disposed of by the appropriate channels. An appropriate advice is included in the SPC.

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

Not applicable.

Overall conclusion on safety

From the presented data it can be concluded that the vaccine is safe for horses. No increase of temperature was observed compared to the findings of the former vaccine. Most of the observed signs are already adequately indicated in the product literature. In the repeated dose safety study one Shetland pony reacted by developing swellings at the injection site up to a size of 15 cm x 20 cm over a period of 5 days. This finding is reflected in the product literature. A possible reason for this reaction may be that the vaccine was not administrated by deep intramuscular injection. Therefore the wording for the route of administration has been changed to 'strictly intramuscular'.

Due to the important changes between the originating and updated vaccine in production and final product it has to be ensured that all reported pharmacovigilance events are submitted with details of the batch number used and within a short time frame. For that reason, a restart of the PSUR cycle to 6 monthly reporting is recommended.

In light of this recommendation and taking into account the current PSUR periodicity for the product, the MAH is requested to submit a PSUR covering the period between the last PSUR and the time point after which the PSUR cycle restart will come into effect and submission of 6-monthly PSURs will commence.

Part 4 – Efficacy

Efficacy data are presented taking into consideration Ph. Eur. monograph 0249 "Equine influenza vaccine (inactivated)" and the Note for Guidance EMEA/CVMP/112/98 "Harmonisation of requirements for equine influenza vaccine: Specific requirements for the substitution or addition of a strain or strains". However, in view of the change to the method of production of the influenza virus antigens,

additional data to those listed in Note for Guidance EMEA/CVMP/112/98 for substitution or addition of a strain may be required to substantiate the strain changes proposed.

Laboratory trials

A batch of Equilis Prequenza Te was used for testing the efficacy of the vaccine. This batch represents a normal production batch with a standard antigen content and standard adjuvant content.

The horses (ponies) used in the laboratory trial were not of the minimum recommended age of 6 months. Reduction of clinical signs and virus excretion after the primary course of two vaccine injections (2 x 1 ml) at an interval of 4 weeks is claimed for horses. Onset of immunity (OoI) was proposed at 2 weeks after the primary vaccination course, Duration of Immunity (DoI) for 5 months after primary vaccination course and 12 months after re-vaccination.

A reduction of clinical signs and virus excretion could be demonstrated by challenge 21 days after the primary vaccination course.

OoI was demonstrated via challenge 21 days after primary vaccination course. Serological data are presented to justify the proposed OoI claim (14 days after primary vaccination course). Therefore, a similar OoI can be expected for the originating and updated vaccine.

One additional OoI challenge study has been performed against the challenge strain A-Equi-2 Richmond/1/07. Protection results in line with the indication were demonstrated. The challenge strain belongs to the A-equi-2 Florida lineage clade 2. It was demonstrated that sufficient protection can be expected from the updated vaccine although no vaccine strain of the Florida sublineage clade 2 is included in the vaccine composition.

A DoI study was started and discontinued at an early stage (24 weeks) due to an influenza outbreak in the herd. The serological titre results were available up to week 22. Over this period the titres were similar compared to the titres obtained in the historical DoI studies performed with the current vaccine.

Nevertheless, the DoI and suggested yearly revaccination have not yet been demonstrated completely as sufficient data regarding the updated strain composition have not been generated but CVMP concluded that there is enough data available that it can be expected that the DoI of the originating and updated vaccine are similar with 12 months duration.

Field trials

No additional studies are submitted for the updated vaccine.

Overall conclusion on efficacy

From the data presented it can be concluded the vaccine is efficacious for the proposed indication.

The challenge performed with the "Ohio" strain was considerably weak. Normally severe signs of illness are expected in the control group. The serological responses in the vaccinated horses are comparable to the former vaccine which is known to be a protective level. However, the updated vaccine is a full antigen vaccine.

It was demonstrated by a "Richmond" challenge study that sufficient protection from the updated vaccine can be expected although no vaccine strain of the Florida sublineage clade 2 is included in the vaccine composition.

It is demonstrated that the neutralising antibody levels of these total antibody titres are comparable between former and updated vaccine.

The OoI is demonstrated and justified by serological data.

Based on the available data, it is expected that the DoI of the former and updated vaccine are similar with 12 months duration.

Benefit-Risk Assessment

Introduction

In view of the updated composition as well as of the implementation of an updated vaccine production process, an updated benefit risk assessment is provided. Equine influenza is highly contagious and spreads rapidly between horses causing disease of high morbidity but low mortality.

Equilis Prequenza contains inactivated equine viruses A/equine-2/South Africa/4/03 50 AU (antigenic units) and A/equine-2/Newmarket/2/93 50 AU per 1 ml and is presented in boxes of 10 glass vials or 1, 5 or 10 pre-filled syringes. The vaccine is indicated for active immunisation of horses and ponies against equine influenza to reduce severity and duration of clinical signs and to reduce the amount and duration of virus execration after injection.

Benefit assessment

Direct therapeutic benefit

The benefit of Equilis Prequenza is to reduce severity and duration of clinical signs and to reduce the amount and duration of virus excretion after injection.

Risk assessment

For the target species (horses and ponies) there is a risk of mild fever, local swellings (in very rare cases up to a size of 15 cm x 20 cm over a period of 5 days), discomfort and stiffness after the vaccination. All signs generally disappear within a few days.

For the user there is a low risk of self-injection or injuries from needles and damaged primary packages. However, in the absence of irritating substances such as oil adjuvants, the accidental injection of the vaccine into subcutaneous or muscular tissue does not present any specific risks when accidentally injected.

- The risk to the environment is negligible.
- There are no components which require an MRL. The withdrawal period of zero days is acceptable. There are therefore no consumer safety concerns.

Due to the important changes between the originating and updated vaccine in production and final product all pharmacovigilance events reported should include details of the batch number used. Additionally the PSUR cycle should be restarted for submission of 6 monthly reports for two years, followed by yearly reports for the subsequent two years and thereafter at 3 yearly intervals. In light of this recommendation and taking into account the current PSUR periodicity for the product, the MAH is requested to submit a PSUR covering the period between the last PSUR and the time point, after which the PSUR cycle restart will come into effect and submission of 6-monthly PSURs will commence.

Evaluation of the benefit-risk balance

Equilis Prequenza has been shown to have a positive benefit-risk balance. The product has been demonstrated to be efficacious for the indication for active immunisation of horses from 6 months of age against equine influenza to reduce clinical signs and virus excretion after infection. The benefit-risk balance of the updated vaccine is in favour of the product and comparable to the current vaccine. The vaccine is sufficiently tolerated by the target animals and presents a low risk for users and the environment.

Conclusion on benefit-risk balance

Based on the original and complementary data presented it is concluded that the quality, safety and efficacy of Equilis Prequenza can be considered to be in accordance with the requirements of Directive 2001/82/EC, as amended and that the benefit-risk balance is favorable.

Conclusion

Based on the review of the data on quality, safety and efficacy, the CVMP considers that the grouped extension and variations for Equilis Prequenza for treatment of horses (active immunization against equine influenza viruses to reduce clinical signs and virus excretion) is approvable.

Concerning the grouped extension consisting of one extension, six type II variations, three type IB variations and two type IA variations the following can be concluded:

Extension (Condition 1.d of the Annex I of (EC) No 1234/2008) – Change of the growth substrate from commercial SPF eggs to MDCK-ISC cells

This extension, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

Type II (3 variations) No. B.I.a.2.c – Changes in the manufacturing process of the active substance - The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol:

- Change of downstream process (DSP) (treatment with detergents (Triton-X100, deoxycholate), lectin affinity chromatography (subunit formation) to remove egg proteins by virus harvest concentrated, sonified and clarified),
- Change of inactivation procedure - time point inactivation (0.025 % BPL (at least 72 hours at 2-8 °C) (before DSP) by 0.05 % BPL (at least 3 hours at 37 °C) (after DSP)) and
- Replacement of Newmarket/2/93 MSV (passage level: EP4+2 (egg derived) by passage level: EP4+4 (egg derived))

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be acceptable.

Type II No. B.I.b.2.d – Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - Change (replacement) to a biological/ immunological/ immunochemical test method or a method using a

biological reagent for a biological active substance e.g. peptide map, glyco-map, etc.:
Change of adoption IPC (determination infectivity titre by determination antigenic mass).

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be no more relevant. The applicant has withdrawn this variation application and has replaced the proposed determination of the antigenic mass and returned to the current determination of the infectivity titres.

Type IB No. B.I.b.2.z – Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance (by default):
Deletion of test for bacterial endotoxins

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be acceptable.

Type II No. B.II.a.3.b.3 – Changes in the composition (excipients) of the finished product - Change that relates to a biological/immunological product:
Adoption excipient buffer (lactose containing phosphate buffer replaced by phosphate buffered saline)

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be acceptable.

Type IB No. B.II.d.1.a – Change in the specification parameters and/or limits of the finished product - Tightening of specification limits:
Implementation of adapted limits for saponin fraction C content (250–500 µg/ml replaced by 284–394 µg/ml)

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be acceptable.

Type IA No. B.II.d.1.c – Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method:
Introduction of a separate end-of-shelf life limit for saponin fraction C (separate limit for release and end-of-shelf life)

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be acceptable.

Type IA No. B.II.d.2.a – Change in test procedure for the finished product - Minor changes to an approved test procedure:
Omission of correction factor (1.29)

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be acceptable.

Type IB No. B.II.d.2.d – Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition):
Omission of 2nd inactivation control test (during blending)

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be acceptable.

Type II No. C.II.5 – Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza:
Replacement of strains A/equine-1/Prague/56 and A/equine-2/Newmarket/1/93 by strain A/equine-2/South Africa/4/03

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is considered to be acceptable.

Changes to the community marketing authorisation

Changes are required in the following annexes to the Community marketing authorisation:

- Annex I, II and III.