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medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

HIPRABOVIS-BALANCE

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0166/001/MR
Name, strength and pharmaceutical form	**HIPRABOVIS BALANCE** Lyophilisate and solvent for suspension for injection
Applicant	**Laboratorios HIPRA, S.A.** Avda. la Selva, 135 17170- Amer (Girona) Spain
Active substance(s)	**Parainfluenza-3 virus, inactivated, strain SF4** …HAI* ≥ 16 (≥ 480 HAU before inactivation) **Bovine viral diarrhoea virus, inactivated, strain NADL** …SN** ≥ 20 (≥ 10^6 $TCID_{50}$ before inactivation) **Bovine respiratory syncytial virus, live, strain Lym-56** ... ≥ 10^4 $TCID_{50}$*** * HAI: mean haemagglutination inhibition titre induced in rabbits. * SN: mean serum neutralisation titre induced in rabbits. *** $TCID_{50}$: Tissue culture infective dose 50
ATC Vet code	QI02AH (live and inactivated viral vaccines for the bovine species)
Target species	Bovine (cows, heifers and calves; as of 4 weeks old)
Indication for use	Adult cattle (cows and heifers): prevention of bovine viral diarrhoea (including the disease of the mucosas) (BVD). Calves: prevention of the Parainfluenza 3 (PI3) virus, disease of the mucosas or bovine viral diarrhoea (BVD) and pneumonia by bovine respiratory syncytial virus (BRS). Immunity starts three weeks after the first of administration and lasts 12 months.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 29/09/2010
Date product first authorised in the Reference Member State (MRP only)	21/07/2008
Concerned Member States for original procedure	PT

I. SCIENTIFIC OVERVIEW

For public assessment reports for the first authorisation in a range*:*

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a renewal authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains per dose of 3 ml the following active substances:

Parainfluenza-3 virus, inactivated, strain SF4…… IHA*≥16

Bovine viral diarrhoea virus, inactivated, strain NADL ……..SN** ≥ 20

Bovine respiratory syncytial virus, live, strain Lym-56 ……≥ 104 $TCID_{50}$***

* HAI: mean haemagglutination inhibition titre induced in rabbits.

* SN: mean serum neutralisation titre induced in rabbits.

*** TCID50: Tissue culture infective dose 50

The vaccine contains Aluminium hydroxide (Al 3+) as adjuvant and Thimerosal as preservative.

The product is presented in separated fractions, a lyophilisate and a solvent for suspension for injection and is packaged with different formats, i.e. box with 1 vial of lyophilised fraction (5 doses) + 1 vial of 20 ml of liquid fraction (containing 15 ml), box with 1 vial lyophilised fraction (30 doses) + 1 vial of 100 ml of liquid fraction (containing 90 ml) and box with 1 vial of lyophilised fraction (80 doses) + 1 vial of 250 ml of liquid fraction (containing 240 ml) and box with 1 vial lyophilised fraction (25 doses) + one 100-ml vial of liquid fraction (with 75 ml).

The bottles are European Pharmacopoeia (Ph.Eur.) type I amber coloured glass vial for the 20-ml and 100 ml (5 and 30 doses respectively) and type II 250-ml (80 doses) for the liquid fraction. For the lyophilisated fraction the bottles are 10-ml colourless type I glass vial. The vials are closed with their corresponding bromobutyl elastomer closures classified as Type I (in accordance with the current edition of the Ph.Eur), and anodized aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation, the inactivation process and the presence of Thimerosal as preservative are justified. The inactivation process and the detection limit of the control of inactivation are correctly validated.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site and in accordance with the European Pharmacopoeia and relevant European guidelines.

The manufacturing method is a classical vaccine manufacturing process involving growth on well established cell lines. Three main steps are concerned: 1) preparation

of the active substances, 2) preparation of the mixing and filling of the vaccine for each fraction and 3) packaging of the finished product. The process is well described.

C. Control of Starting Materials

The active substances are Parainfluenza-3 virus, inactivated, strain SF4; Bovine viral diarrhoea virus, inactivated, strain NADL and Bovine respiratory syncytial virus, live, strain Lym-56. The specifications of the active substances are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications have been provided.

Certificates of analysis are provided for all starting materials used in the manufacture of the vaccine. These materials are tested according to the Ph.Eur. or in-house specifications as appropriate. Sterilisation of some materials is performed by filtration instead of by steam sterilisation, as this would either alter their properties or is technically not feasible. Adult and foetal bovine serum is tested according to the CVMP guideline on requirements and controls applied to bovine serum used in the production of immunological veterinary medicinal products (EMEA/CVMP/743/00)

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur.; any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.
The company has provided an EDQM certificates for the foetal and adult bovine serum. The other components that can represent a risk for the transmission of animal spongiform encephalopathies are assessed satisfactorily.

E. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular aspect, pH, Aluminium concentration and identification, identification and titration of PI3V,

identification and titration of BVDV, identification and titration of BRSV, volume control, humidity, solubility, sterility, mycoplasms absence, extraneous agents and packaging.

The demonstration of the batch to batch consistency is based on the results of 2 batches produced according to the method described in the dossier.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Three pilot batches with the bigger and smaller presentations (5 and 80 doses) were used to support the stability data up to 18 months.
The 3 hours in-use shelf-life of the reconstituted vaccine is supported by the data provided with two batches produced according to the method described in the dossier. Batch 8Q1J-3 and batch 8Q1K-3 control tests results have been included.

III. SAFETY ASSESSMENT

HIPRABOVIS-BALANCE is a smaller combination of an already licensed vaccine. This new trivalent combined vaccine has exactly the same composition as a previously authorised tetravalent vaccine, except for one antigen, which has been removed.

In order to assess the safety and the efficacy of the vaccine the applicant refers to the Note for Guidance on Requirements for Combined veterinary vaccines, CVMP/IWP/52/97-FINAL, according to which the safety and the efficacy of a combined product shall be demonstrated with a vaccine containing the largest number of components. Thus, the results of the safety and the efficacy tests from larger combinations should be acceptable for smaller combinations of the same antigens.

Bearing this premise in mind, the safety and the efficacy of the larger combination HIPRABOVIS-4 dully support those of this trivalent vaccine, HIPRABOVIS BALANCE.

The applicant presents the following studies of the larger combination to support the safety of the administration of the product. Five different batches of vaccine were used for this purpose.

Laboratory trials

Safety of the administration of one dose, an overdose and the repeated administration of one dose.

Laboratory trial no. 1.
This laboratory trial was carried out to demonstrate the safety of the vaccination and revaccination with one dose and an overdose of the liquid fraction of the vaccine administered to calves.

Eight calves were vaccinated, four of them with 1 dose and the remaining four with an overdose. They were compared with 2 non-vaccinated calves. Clinical evolution was analysed by observing local or general clinical signs (rectal temperatures post vaccination and post revaccination, anorexia, swelling, fever, and post-mortem examination of the inoculation site).

Results
A non significant hyperthermic reaction was observed in calves vaccinated with an overdose at 7 to 24 hours post-revaccination. After revaccination, one animal belonging to group B (overdosed) showed a slight local swelling which disappeared at 24 hours post-revaccination, and which was regarded as non-significant. No animals showed anorexia after vaccination and revaccination with a single and with an overdose of the vaccine. Twenty weeks after the first vaccination no animal vaccinated with one dose or an overdose, showed lesions at the inoculation site.

From the results it is concluded that the vaccination and revaccination with an overdose of the vaccine is safe when administered to calves.

Laboratory trial no. 2.
Laboratory trial no. 2 was carried out to evaluate the safety of 1 dose and of an overdose of the freeze-dried component (live BRSV) and the safety of 1 dose of the reconstituted product.

A group of calves were given 1 dose of the freeze-dried component (live BRSV), 10 doses of the freeze-dried component were given to a second group and 1 dose of the reconstituted product was given to another group. They were compared to 2 non-vaccinated calves of the same age. They were observed up to 21 days post-vaccination and the clinical signs as hyperthermia, anorexia and local reactions, were recorded.

Results
No significant hyperthermia, anorexia or local reactions at the inoculation site were observed in vaccinated animals. The obtained results showed that the freeze-dried component administered either at 1 or 10 doses is safe when administered to calves. The reconstituted vaccine administered at a single dose to cattle has also been demonstrated as being safe.

Reversion to virulence

Laboratory trial no. 3. Reversion to virulence
This trial was carried out to demonstrate the absence of reversion to virulence and the stability of the attenuation of the live BRSV (freeze-dried component of the vaccine) by passaging it 5 times in young sensitive animals (calves).

Five serial passages of the live BRSV were carried out in 10 young calves. Each calf was inoculated with ten doses of the live BRS virus. Two control animals were placed together with the vaccinated calves without showing any adverse reactions.

At day 0 two calves were inoculated with 5 doses of the live BRSV (freeze-dried component of HIPRABOVIS-4). The animals were kept under observation for 14 days.
Ten days post-inoculation nasal swabs and blood samples were collected and processed and the supernatants were harvested and used for the following passage. At day 10 the supernatant of the nasal secretions obtained in P1 were inoculated to other two 10-day-old calves. This was considered passage 2 (P.2). Nasal secretions and blood samples were collected and treated as in the first passage. The animals were also kept under observation for 14 days.

This procedure was repeated in the passages 3 and 4. In the 5th passage (the last one) the same procedure was carried out. In addition 2 control animals which had been housed together with the calves from the last passage for 1 month were tested by ELISA serology, to demonstrate that they remained seronegative, and so, no diffussion of the virus to the control animals was produced.

During the observation period (14 days) the following parameters were recorded: temperature, anorexia, dyspnoea, nasal discharge and viral contents of the samples.

Results
No animals showed clinical signs or abnormalities in their behaviour. After 5 passages in young sensitive animals (calves) and after placing together the control and the treated animals no pathogenicity was observed in any of them. These results indicate that there is no reversion to virulence even after 5 passages in target animals and that the attenuation of the BRSV strain is stable.

Laboratory trial no. 4: Study on the spread of the vaccine strain
This trial was carried out to assess the virus shedding of the live freeze-dried component of the vaccine when administered to calves.

The animals were divided in two groups. Calves of Group A were treated with ten doses of live BRSV (freeze-dried component of HIPRABOVIS-4). Calves of Group B were not treated and considered as the control group. All the animals were housed together and observed for 30 days. Nasal swabs samples were taken from all the animals at different days to assess the virus shedding in vaccinated and control animals. Blood samples were also taken from all the animals at different days to assess the humoral antibodies in vaccinated animals and to check the serological status of the control animals.

Results
No clinical signs were observed in vaccinated or control animals, thus, the applicant proved the safety of the administration of 10 doses of the vaccine virus. The serological profile showed that no humoral response was developed in the control animals, which demonstrated that it does not spread from vaccinated to non-vaccinated animals, whereas the vaccinated animals developed ELISA antibodies against BRSV. No virus shedding was detected from the nares of vaccinated and control animals. Therefore, no viral spread occurs from vaccinated to control animals.

Examination of reproductive performance
The examination of reproductive performance was evaluated by the applicant under field conditions.
No adverse effects were observed during the observation periods either in lactating or in pregnant cows.

Examination of immunological functions
No specific studies on the immunological functions have been performed, since no immunosupression effect would be foreseen from this vaccine.

Interactions
No interactions with other products are known; consequently, the SPC includes the precaution „Do not mix with any other veterinary medicinal product”.

Residues

The applicant did not perform a specific trial to evaluate this aspect since the vaccine contains only two ingredients likely to leave residues (the aluminium hydroxide gel fluid and the thimerosal). However those components are included in Annex II of the Commission Regulation (EEC) no. 2377/90 26th Juny 1990, for which it is established the community procedure of establishment of the Maxim Residue Limits for veterinary medicines in the food of animal origin. Based on this information, no withdrawal period is proposed.

Field trial no. 1

This trial was carried out to study the safety of the vaccine when administered to lactating and pregnant cows and to assess the level of antibodies conferred to the offspring of vaccinated cows.

40 Friesian cows were divided in 4 groups according to their production stage: lactation (A), 3rd month of gestation (B), 5th month of gestation (C) and 7thmonth of gestation (D). All cows were vaccinated with 3 ml of HIPRABOVIS-4 by intramuscular route and revaccinated 21 days later. All groups were observed during the trial to check that no adverse reaction (local or general) was present after vaccination and to detect any abortion in pregnant cows, malformation or teratogenic effects on the foetus.
Milk production of Group A was monitored to confirm that HIPRABOVIS-4 had no negative influence on that parameter, when compared to with milk production before vaccination.
The animals from groups B, C and D were observed until calving and the reproductive parameters were recorded (abortion, mummification, malformation of foetus, etc...).
Blood samples were taken from new-born calves and sera were tested.

Results

Milk production was not affected by vaccination with HIPRABOVIS-4. Cows calved at the expected days. All calves were born healthy. Neither teratogenic effects nor malformations were observed in new-born calves. No adverse effects attributed to the vaccination were observed during the observation periods neither in lactating nor in pregnant cows. Satisfactory serological results against IBR, BVD, PI3 and BRS viruses were showed by the new-born calves of the group D.

Ecotoxicity

The applicant fully demonstrated that the live component of the vaccine does not revert to virulence and it is no shed. None of the components of the formulation is known to cause environmental problems. The method of administration is injection, which does not allow the direct dispersion of the product into the environment. Therefore, it is concluded that the vaccine does not pose risk for the environment.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements. These studies show that this vaccine prevents bovine viral diarrhoea (BVD) in adult cattle and prevents Parainfluenza 3 (PI3) virus, bovine viral diarrhoea and pneumonia by bovine respiratory syncytial virus (BRS) in calves. Eight different batches of vaccine were used for this purpose.

Laboratory trial no. 1

The trial was carried out to assess the efficacy of the vaccine in calves. The induction of specific antibodies and the protection against challenge tests by IBRV, PI3V, BVDV and BRSV were assessed.

Twenty eight (28) animals were vaccinated with one dose of HIPRABOVIS-4 by intramuscular route and 12 animals were not vaccinated and considered as controls. Twenty one (21) days later, the vaccinated calves were revaccinated with another dose. The animals were bled at different time intervals in order to assess the induction of antibodies against IBR, PI3, BVD and BRS viruses. One month after revaccination, all animals were challenged using virulent viruses (IBRV, PI3V, BVDV and BRSV). Clinical signs post-challenge were monitored.

Results

Significant differences in the seroconversion against each one of the vaccine antigens and in the appearance of the respiratory signs were observed when comparing the unvaccinated control calves with the vaccinated and revaccinated calves; thus, this study demonstrated the efficacy of the vaccine in calves.

Laboratory trial no. 2

The trial was carried out to assess the efficacy of the vaccine in cows. The induction of specific antibodies and the protection against challenge tests by IBR, PI3, BVD and BRS virulent viruses were assessed.

16 cows were vaccinated with one dose of HIPRABOVIS-4 by intramuscular route; the rest (4 cows) were not vaccinated and were considered as unvaccinated controls. 21 days later, the vaccinated cows were revaccinated with another dose. One month after revaccination, all animals were challenged using virulent viruses. The animals were bled at different time intervals in order to assess the induction of antibodies against IBR, PI3, BVD and BRS viruses. The challenge was made using each one of the virulent viruses. Clinical signs post-challenge were monitored.

Results
A slight increase in the level of antibodies can be observed after vaccination against the four antigenic viruses. After revaccination, the immunological response rose considerably and seroconversion was significantly higher in all vaccinated cows when compared to control group. Clinical symptoms after challenge were significantly more severe in control than in vaccinated animals. The vaccine demonstrated the efficacy to protect cows against a virulent IBR, PI3, BVD and BRS challenge.

Laboratory trial no. 3
The trial was carried out to evaluate the activity of the vaccine in target (cattle) and laboratory (rabbits) animals.

A total of 60 rabbits were split in 3 groups of 20 animals each. Two groups (A and B) were vaccinated with HIPRABOVIS-4 (2 ml/rabbit by intramuscular route in the tight) and one of them (B) was revaccinated 3 weeks later. A third group (group C) was maintained as control group. The animals were bled at different times.

Results
A slight increase in the level of antibodies was observed in group A. In group B, the immunological response and seroconversion against each one of the four antigens increased significantly, after the second vaccination.

From these results, and given that the vaccine batch used in this study was the same as that used in laboratory trial no. 1 in which satisfactory results of potency were obtained for the target animal, the model tested in this study based in rabbits was defined as the batch potency test for the vaccine.

Laboratory trial no. 4
The trial was carried out to study the effects of the maternal antibodies on the immunity of calves when vaccinated at different ages. The animals were compared to a seropositive unvaccinated group and to a seronegative vaccinated group.

A group of Friesian cows were chosen for this trial. A half of them was tested for antibodies against four viruses (IBR, PI3, BVD and BRSV) and was split in three groups (Group A, Group B and Group C). The other half of cows were tested to check of being seronegative to the previously mentioned viruses. They were split in two groups (Group D and Group E). All the cows were inseminated. At 15 days before calving a serological test was carried out on all of them to screen if during pregnancy any infection had occurred with any of the concerned viruses. When the calves were born the colostrum was obtained within the first 48 hours and the calves were separated from the cows. They were placed in five boxes, three of them with the calves coming from the cows with antibodies (Groups A, B and C). In other two boxes the offspring from Group D and E (seronegative cows) were placed. Groups were fed with their own mother's colostrums during 48 hours. From the third day onwards, they were fed with cow's milk. When they were 8 days old, blood samples were taken from all of them to check the antibody intakes through the colostrum. Control animals were not vaccinated (Groups A and D) and kept separated from vaccinated Groups, and also separated between them.

Results
The serological results obtained indicated that when the vaccination was performed at the minimum age and revaccination 21 days later, the humoral response obtained was satisfactory in both, calves coming from seropositive cows and those coming from seronegative ones, reaching soon high protective levels.

Laboratory trial no. 5
The trial was carried out to study the duration of the immunity conferred by the vaccine in calves, by titrating the antibody level against IBR, PI3, BVD and BRS viruses in vaccinated animals.

A group of 10 calves was used. Eight of them were vaccinated and revaccinated with HIPRABOVIS-4 and other 2 calves were not vaccinated and kept as unvaccinated control group. Periodical serological tests against IBR, PI3, BVD and BRS viruses were performed during nearly one year.

Results:
No side effects (neither local nor general) were observed in vaccinated calves. An increase in the level of antibodies after the vaccination in group A was noticed. After revaccination, the humoral response increased significantly in animals from group A when compared to controls and the antibody levels remained satisfactory as to claimed a duration of immunity of 12 months. All animals from group B remained seronegative during all the trial.

Laboratory trial no. 6
The trial was carried out to study the minimum vaccine dose to protect the calves against IBR, BVD, PI3 and BRS viruses.

One group of calves was vaccinated with one dose of HIPRABOVIS-4 and 4 other groups were vaccinated by intramuscular route with different dilutions of the same dose. The sera obtained were tested against IBR, PI3, BVD and BRSV.

Results
The results showed that while half of a dose induced the minimum protective antibody levels, one dose induced satisfactory antibody levels as to be established as the vaccine dose. Therefore, this trial proved the suitability of the recommended dose (3 ml).

Laboratory trial no. 7
The trial was carried out to study the duration of the immunity conferred by the vaccine in cows, by titrating the antibody level against IBR, PI3, BVD and BRS viruses in vaccinated animals.

Twelve cows were used. Ten cows were vaccinated with HIPRABOVIS-4 and the other 2 were kept as unvaccinated control group. Periodical serological tests against IBR, PI3, BVD and BRS viruses were performed during about a year.

Results
No side effects (neither local nor general) were observed in vaccinated cows. An increase in the level of antibodies after the vaccination was observed in vaccinated animals. After revaccination, the immunological response increased considerably in animals from vaccinated group and the antibody levels remained satisfactory for about a year.

Field Trials

Field trial no. 1
The trial was carried out to verify the safety and efficacy of the vaccine in grazing calves in an area of high incidence of the Bovine Respiratory Syndrome.

In order to assess the safety and efficacy of the vaccine under field conditions, a farm was chosen where outbreaks of Bovine Respiratory Syndrome had been detected in the past. Two outbreaks of Bovine Respiratory Syndrome were observed during the trial.
At Day 0, once arrived to the farm, the calves were split randomly in two groups. One group with 20 calves (Group A) was vaccinated with one dose (3ml/calf) of HIPRABOVIS-4 leaving Group B with 20 calves as control animals. The two groups of calves were housed in two separate units. Parameters as post-vaccination clinical signs up to 21 days post-vaccination and mean body weight the first day of the trial were recorded. Three weeks later, a second dose was applied to the animals of Group A. The parameters post-vaccination clinical signs up to 21 days post-revaccination, mean body weight at the end of the trial (Day 95), feed Conversion Rates calculated at the end of the trial (Day 95), clinical signs related to the Bovine Respiratory Syndrome and number of losses were monitored and recorded, when observed.

Results
No post-vaccination clinical signs were observed at vaccination or at revaccination (from 0 to 42 days post-onset of the trial). At 67 days after the arrival of calves to the farm, the first signs of respiratory disease appeared in almost all calves from control group and sporadically in some calves from vaccinated group.
A more severe outbreak with signs of respiratory disease was observed at 80 days post-starting of the trial. A few vaccinated animals were slightly affected whilst almost all unvaccinated control animals were affected severely. Three control calves remained chronically ill and other two calves died. The BRSV (Bovine Respiratory Syncytial Virus) was isolated. At the end of the trial, the mean body weight as well as the Feed Conversion Rate was considerably better in vaccinated group than in controls.
According to the results obtained from this test, HIPRABOVIS-4 protects calves against the Bovine Respiratory Syndrome caused by BRSV under field conditions and the feed conversion rate is clearly better in the vaccinated animals than in non-vaccinated.

Field trial no. 2
This trial was carried out to verify the safety and efficacy of the vaccine in calves under field conditions.

A farm with clinical records of outbreaks of Bovine Respiratory Syndrome was used in order to assess the safety and efficacy of the vaccine under field conditions. An outbreak of Bovine Respiratory Syndrome occurred during the trial.

At day 0 200 calves arrived to the farm and 21 days were elapsed before vaccination in order to get the animals adapted to the new environment. The animals were controlled and the mean body weight at the first day of the trial was recorded. At day 21 the calves were housed in groups of 25 calves each one. An additional group was kept unvaccinated (Group B). The rest of animals (175 calves) were vaccinated with one dose (3ml/calf) of HIPRABOVIS-4 (Group A). The animals were controlled and the post-vaccination clinical signs up to 21 days post-vaccination were monitored. Three weeks later all calves from Group A were revaccinated with one dose of HIPRABOVIS-4. The animals were controlled and the following parameters were recorded: post-vaccination clinical signs up to 21 days post-revaccination, mean body weight at the end of the trial, feed Conversion Rate at the end of the trial, clinical signs of Respiratory Bovine Syndrome and number of losses during the trial.

Results
No post-vaccination clinical signs were observed neither when animals were vaccinated nor revaccinated from 21 to 63 days after the beginning of the trial.
A severe outbreak of respiratory disease occurred at 83 days post-onset of the trial. Almost all unvaccinated control animals were affected showing severe clinical signs of respiratory disease, and three out of 25 control animal died and several of the rest remained chronically ill. Vaccinated animals were also affected but the clinical signs observed were largely milder than control animals, and no losses were recorded.
The mean body weight at the end of the trial as well as the Feed Conversion Rate were clearly better in group A (vaccinated) than in group B (controls). From the samples analysed, IBRV was diagnosed.

From the obtained results it can be concluded the efficacy of HIPRABOVIS-4 since it protects calves against an outbreak of Bovine Respiratory Syndrome.

Field trial no. 3
This trial was carried out to verify the safety and efficacy of the vaccine in calves under field conditions.
A farm that had suffered outbreaks of Bovine Respiratory Syndrome was used in order to assess the safety and efficacy of the vaccine under field conditions. An outbreak of Bovine Respiratory Syndrome was observed during the trial.

At day 0, on arrival to the farm, the 60 calves were split in 2 groups of 45 and 15 calves, randomly. The group containing the 45 calves (Group A), was vaccinated with one dose (3ml/calf) of HIPRABOVIS-4. The 15 calves of Group B were not vaccinated (controls). The animals were controlled for the post-vaccination clinical signs up to 21 days post-vaccination and the mean body weight the first day of the trial (Day 0). Three weeks later, a second dose was applied intramuscularly in the neck muscles to the same animals of Group A. The animals were controlled for the following parameters: post-vaccination clinical signs up to 21 days post-revaccination, mean body weight at the end of the trial (Day 300 post-starting of the trial), feed Conversion Rates calculated at the end of the trial (Day 300 post-starting of the trial) and clinical respiratory signs and number of losses during the trial.

Results
No post-vaccination clinical signs were observed in vaccination or in revaccination (from 0 to 42 days post-onset of the trial). A mild clinical respiratory process occurred 53 days after the beginning of the trial. Only 2 vaccinated animals were affected showing mild clinical signs which were regarded as non-significant. Regarding control animals, most of them were affected by a respiratory process.
The serology performed in paired samples (at 14 days interval) showed a marked increase in the antibody levels against Parainfluenza-3 virus (PI3). Taking into account the profile of the clinical signs observed and the serology, the process was diagnosed as an outbreak of Parainfluenza-3.
At the end of the trial, the mean body weights as well as the Feed Conversion Rate was similar between vaccinated and controls. Differences were considered non-significant.
From the obtained results it can be concluded that HIPRABOVIS-4 is an effective vaccine since it protects calves against the Bovine Respiratory Syndrome caused by PI3 virus under field conditions.

Conclusions on Efficacy:

The applicant has tested HIPRABOVIS-4 under laboratory conditions for the assessment of the protection against challenge tests by IBR, PI3, BVD and BRS virulent viruses in calves and in cows as well as for the induction of specific antibodies.
The efficacy has been demonstrated in the face of maternally derived antibodies. The maternally derived antibodies did not interfere when the vaccine was administered in calves of the minimal recommended age for vaccination.
The efficacy of the vaccine (duration of protection) has been satisfactorily demonstrated by serology for 12 months.

The safety and efficacy has been additionally demonstrated by means of three field trials. These trials were performed in these farms that had suffered outbreaks of Bovine Respiratory Syndrome. Outbreak of respiratory signs was observed during these trials.
In these field trials, no post-vaccination clinical signs were observed. A few vaccinated calves showed mild respiratory signs but the clinical signs were clearly more severe in unvaccinated animals.

Therefore, the applicant has demonstrated the efficacy of the vaccine under laboratory and field conditions.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Summary of change (Application number)	Approval date
Addition of 25-dose presentation. ES/V/XXXX/WS/027	10/08/2022