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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for BTVPUR AlSap 1-8 (EMEA/V/C/002231/II/0007/G)

Common name: Bluetongue vaccine (inactivated) (multistrain: 1-2 strains out of a set of 3)

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

Rapporteur: C. Muñoz Madero

Co-rapporteur: M. Tollis

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, MERIAL (the applicant), submitted to the European Medicines Agency (the Agency) an application for a grouped type II variations for BTVPUR AlSap 1-8.

1.1.1. Scope of the variation

Variations requested		**Type**
C.II.4	Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue	II
C.II.4	Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue	II

This application is to convert the BTVPUR AlSap 1-8 dossier for sheep and cattle into a BTVPUR multi-strain dossier and to add the BTV4 to the BTVPUR multistrain dossier.

Current	**Proposed**
classical dossier BTVPUR AlSap 1-8 for sheep and cattle strains included: BTV1 BTV8	multistrain dossier BTVPUR for sheep and cattle strains included: BTV1 BTV4 BTV8

2. Scientific discussion

2.1. Assessment

An application for a grouping of two Type II variations of BTVPUR AlSap 1-8 was submitted to the European Medicines Agency:

- converting the BTVPUR AlSap 1-8 dossier in a BTVPUR multistrain dossier

- adding BTV4 into BTVPUR multistrain dossier

Justification of the proposed type II variation

The applicant justifies the proposed type II variation on the urgent need of bluetongue vaccine (BTV) in the field and the current epidemiological situation in Europe. It can be seen in the bluetongue (BT) restricted zones map submitted by the applicant there is a spread of BT virus serotype 4 (BTV4) in Croatia, Romania, Hungary, Bulgaria and Greece, together with Cyprus, Spain and zones of Italy, in which BTV4 is associated to BT virus serotype 1 (BTV1). This is the reason for the urgent need of minimising the dissemination of these serotypes to the rest of EU.

The approach of a multistrain dossier is to maintain only one dossier with a range of vaccine strains which are produced with the proper characteristics of each other but with the same relevant information for all of them. This allows selection of strain/s depending on the disease situation.

VARIATION CONVERTING THE BTVPUR ALSAP 1-8 DOSSIER INTO A BTVPUR MULTISTRAIN DOSSIER

In October 2010, the Committee for Medicinal Products for Veterinary Use (CVMP) adopted a positive opinion, recommending the granting of a marketing authorisation under exceptional circumstances for the veterinary medicinal product BTVPUR AlSap 1-8, an inactivated vaccine intended for the active immunization of sheep and cattle to prevent viraemia and to reduce clinical signs caused by BTV1 and BT virus serotype 8 (BTV8).

This dossier was authorised in line with the provisions of Article 39(7) of Regulation (EC) No. 726/2004 for an authorisation under exceptional circumstances and the recommendations of the CVMP "Guideline on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue" (EMEA/CVMP/IWP/220193/2008).

In 2010, in view of the outbreaks of BTV1 and BTV8 in Europe, there was an epidemiological risk from BTV1 and BTV8 for European sheep and cattle populations. That circumstance constituted an objective need to have authorised products available for use.

BTV1 was responsible for outbreaks in the regions of the Southern Europe (Spain, Portugal and France), whereas epidemics due to BTV8 occurred in several countries in Northern West Europe such as Belgium, Denmark, France, Germany, Luxembourg, The Netherlands, United Kingdom, Czech Republic, Switzerland, and also Austria, Italy, Spain, Sweden and Norway.

Documentation submitted

The applicant submitted a reduced dossier, with cross-references to the relevant and previous documentation to fulfill the requirements in the above mentioned legislation, supported by the fact of that these previous data includes the information regarding BTV1 and BTV8 antigens (the both active ingredients of the multistrain dossier), and this documentation has already been submitted and accepted for the registration of the BTVPUR AlSap 1-8, BTVPUR AlSap 8 and BTVPUR AlSap 1 vaccines.

In the frame of the above mentioned guideline on data requirements for multistrain dossiers for inactivated vaccines against Avian Influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD) (EMA/CVMP/IWP/1 05506/2007), the applicant fulfills the requirement according to the following sections:

QUALITY

Qualitative and quantitative particulars

The applicant has defined the maximum number of antigens that can be included in the multistrain vaccine, in two antigens as maximum.

The quantity of each antigen is the same quantity included in BTVPUR AlSap 1-8. During the formulation, this quantity of each antigen is corresponding to a defined viral titre before inactivation, and appropriate antigens content as follows:

Antigen	Titre before inactivation (log_{10} $CCID_{50}$/ml)	VP2 antigen content Qdot-blot (log_{10} pixel/ml)
BTV-1	≥ 8.1	≥ 1.9
BTV-8	≥ 7.1	≥ 2.12

Method of preparation

The method of preparation of the active ingredients is the same for BTV1 and BTV8. The different steps for obtaining the vaccine comprise the blending (formulation) with PBS buffer BTV1 and BTV8 antigens, glycine buffer, aluminium hydroxide gel, purified saponin, silicon antifoam and filling.

The inactivation process and the test for complete inactivation were provided for BTV1 and BTV8 separately. In the both cases, the inactivation kinetics, the inactivation control test and the validation of the inactivation control test guaranteed the efficacy of the process with respect to the inactivation of the infective virus.

The blending is described for a maximum number of two antigens, which are the components of BTVPUR AlSap 1-8. With respect to the active ingredients, the volume of each one takes into account the concentration factor, and also that a suspension of bulk antigen containing an equivalent of a pre-defined fixed amount of volume of BTV1 and BTV8 must be supplied for 1 ml of dose.

Moreover, with respect to the rest of the ingredients other than the antigens, they are added in the same quantities whatever the number of these antigens (as it is reflected in the method of preparation of the monovalents BTVPUR AlSap 1 and BTVPUR AlSap 8 dossiers).

The fixed amount of each antigen has been established after the dose-response results in the efficacy studies performed with vaccine preparations containing varying payloads of BT antigen, and by adding an extra safety margin to the minimum protective antigen content. Depending on the studies on Part III or IV (safety or efficacy studies), batches with more or less quantity of active ingredient have been used within this margin.

The quantity of the active ingredient and the volume of a dose (adjusted with PBS) remain the same whatever the type of the vaccine (mono or bivalent).

The maximum pre-inactivation virus titre was fixed and accepted for the full registration of BTVPUR Alsap 1-8, and the formulation of all the batches used in the safety studies follow the same pattern of manufacture, as Part II of the dossier has established. Thus, the safety of the inactivation process at the upper limit is ensured.

Production and control of starting materials

All the results of the tests of all starting materials comply with the requirements of Directive 2001/82/EC and European Pharmacopoeia Monographs.

Specifications of the tests during the production define the consistency of the process.

Batch to batch consistency has been demonstrated.

The preparation of the active ingredients includes the same steps for BTV1 and BTV8. It uses a Seed Lot System with pre-amplification, culture on BHK21 cells, virus harvest, inactivation, concentration, filtration and purification by chromatography.

Both antigens have the same production flow chart, starting the process on the initial strain, the obtention of the Master Seed Virus (MSV) (different because of the intrinsic characteristics of each strain), the Working Seed Virus (WSV) (the same in the both cases) and the active ingredients.

The MSV and WSV controls are the same, as follows: bacterial and fungal sterility, mycoplasmic sterility, identity, viral purity (only on MSV) and titration/infective titre.

Control tests during the production

All the tests are the same for the both strains. Documentation regarding the validations of titration test and inactivation control test, as critical tests, was provided for the both antigens. These include infectivity before inactivation, the inactivation control test, titration and validation of protein quantification.

Control tests on the finished product

These include appearance, pH, volume, free formaldehyde, viral and antigen content, serology, aluminium hydroxide and sterility. The following tests are considered as final product testing, but are based on calculation on the active ingredient titre, or performed in the blend, just before adding the adjuvant (as this component interferes the detection of the tests):

- Viral content (titre before inactivation).

- Antigens content.

Initially, in each active ingredient, an identity test based on dot blot technique was performed, consisting in specific detection of VP protein using monoclonal antibodies. This technique was used on a routine basis for the BTV1 and BTV8 identification in each batch of the active ingredients and in the bulk of finished product.

In 2011, appropriate documentation was submitted by the applicant to replace the sheep challenge (the initial and previous method for determination the potency in the final batches of the vaccine) by antigen content assays. This technique was validated for each strain (for BTV1 and BTV8) to demonstrate specificity, linearity in the selected range and repeatability.

At the same time, a confirmatory rat serology test was implemented for release purposes. This technique was properly validated for each strain (for BTV1 and BTV8), and it was shown without any cross-reactions between the both strains.

Stability tests

Two approaches are considered as suitable for the aim:

- Stability of each strain formulated as a vaccine, which is available for supporting the stability of the multistrain vaccine: justified by the BTVPUR AlSap 1 and BTVPUR AlSap 8 authorisation data.

- Stability data of BTVPUR AlSap 1-8 to define the stability of this multistrain dossier. According to the authorised data for this vaccine, the shelf life was established as follows:

Presentation	Shelf life
100 ml bottles	2 years
50 ml bottles	2 years
10 ml bottles	2 years

No additional studies to support the shelf life for the multistrain dossier were required.

In relation to the quality part, all the information included for the BTVPUR AlSap 1-8 and cross-referring here fulfils the requirements stated in the guideline for multistrain dossiers regarding the same manufacture of the strains, the same formulation, and the same blending with the same quantities of the other ingredients, the same control tests during production and on the finished product. Each active ingredient has a different specification but it remains the same as the one authorised in the BTVPUR AlSap 1-8 dossier. The proposed stability period is the same as the authorised for BTVPUR AlSap 1-8.

SAFETY

For a multistrain dossier, and in the frame of the document "Guideline on data requirements for multi-strain dossiers for inactivated vaccines against Avian Influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD)" (EMA/CVMP/IWP/1 05506/2007), complete safety studies should be provided.

In this case, a range of studies supported the safety of BTVPUR AlSap 1-8, using vaccine batches (with both strains) containing the higher than maximum amount of each antigen.

The studies have been performed in the both target species (sheep and cattle), and for the recommended route of administration (subcutaneous). The animals were at the proposed minimum age (approximately one-month old in the both species), and studies in pregnant females were included.

The applicant includes the following list of concerned studies:

- Safety assessment, in one-month old lambs, of two BTV bivalent inactivated vaccines BTV1/BTV4 and BTV1/BTV8 containing high antigen payloads

- Safety assessment of a bivalent inactivated BTV4/BTV8 vaccine containing high antigen payloads in young calves

- Safety of a bivalent BTV2/BTV4 vaccine with high antigens payload in pregnant ewes

- Safety of a bivalent BTV4/BTV8 vaccine with high antigens payload in pregnant cows

- Safety assessment of a BTV2/BTV4 bivalent vaccine formulated with a high antigen payload, following administration of repeated doses to 3-month-old sheep

No additional safety studies were considered necessary to support the safety for the multistrain dossier.

PHARMACOVIGILANCE DATA:

The applicant has provided in the documentation three periodic safety update reports (PSURs) that are the same as submitted for the renewals of the veterinary medicinal products BTVPUR AlSap 1, BTVPUR AlSap 1-8 and BTVPUR AlSap 8.

Regarding the safety part, and taking into account the documentation provided by the applicant, no additional documentation is necessary, as there is no change regarding the safety profile of the BTVPUR AlSap 1-8 vaccine, i.e. target species, the route of administration, doses and vaccination scheme.

The cross-referring information, together with the information included in the PSURs, is sufficient to comply with the requirements of the guideline for multistrain dossiers.

EFFICACY

For a multistrain dossier, and in the frame of the document "Guideline on data requirements for multi-strain dossiers for inactivated vaccines against Avian Influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD)" (EMA/CVMP/IWP/1 05506/2007), efficacy studies should be provided.

According to this guideline, efficacy should be demonstrated for each of the monostrain vaccines, and the efficacy of the multistrain vaccine will be the sum of the claims of each antigen included on it. The BTV1 and BTV8 monovalent vaccines have previously been shown efficacious, with the submission of the following studies:

BTV1 challenge

- Safety and efficacy assessment of four monovalent BTV1 and one trivalent BTV1/4/8 vaccines formulated with different payloads of industrial antigens – assessment of protection against a BTV1 challenge in sheep

- Efficacy assessment of vaccines formulated at different payloads of BTV1 antigen, in the presence or not of BTV8 antigen, administered in 2 injections to sheep – assessment of protection against a BTV1 challenge

- Safety and Efficacy of BTV1 vaccines after 2 injections in conventional calves, against a BTV1 virulent challenge

- Duration of immunity (DOI) of an inactivated BTV1 vaccine after 2 injections 21 days apart in sheep – assessment of protection against a BTV1 challenge, 12 months after the second administration

- DOI of an inactivated BTV1 vaccine administered in 2 injections, 3 weeks apart, to young cattle - assessment of protection against a BTV1 challenge 12 months after vaccination

<u>BTV8 challenge</u>

- Assessment of safety and efficacy, by vaccination and challenge in sheep, of vaccines formulated with different BTV8 antigen payloads

- Efficacy in sheep of two BTV8 inactivated vaccines containing low antigen payloads against a BTV8 challenge

- Efficacy in young calves of an inactivated BTV8 vaccine against a BTV8 challenge

- DOI of BTVPUR ALSAP 8, assessment of protection in cattle against a BTV8 challenge, 12 months after vaccination

- DOI of an inactivated BTV8 vaccine administered to sheep in one to 2 injections – protection conferred by the vaccine against virulent BTV8 challenges performed 6 or 12 months after vaccination

<u>Other referred documentation related to efficacy</u>

- BT virus (BT virus RNA) quantification by PCR automated method

- Validation of control technique method to detect and quantify BT virus in blood based on a real-time one step RT-PCR technique

- Validation of the robotized control technique - method for detection and quantification BT virus in blood using a real-time one step RT-PCR technique

- qRT-PCR efficacy results based on the positive response threshold at 95%

- Production of a BTV8 challenge stock by inoculation to sheep

- Production of a BTV1 challenge stock on sheep

- Document efficacy study, report on the efficacy tests performed inactivated for the BT virus

- Decrease of BTV2 maternally derived antibodies (MDA) in lambs from vaccinated ewes

- Decrease of BTV4 MDA in lambs from vaccinated ewes

In all the cases, the efficacy of the vaccine was supported with absence of viraemia data in the challenged and vaccinated animals with each of the two component of the vaccine (first claim: to prevent viraemia). Moreover, it was also demonstrated the reduction of the clinical signs in vaccinated animals compared to control groups, which is the second claim for the fulfillment of the efficacy, according section 4.2 of the SPC.

In most of the submitted studies (except one batch) the used batches had the minimum amount of antigen necessary to justify the efficacy of the vaccine against the correspondent challenge, according the legal requirements.

The results of these studies justified the efficacy of each strain for the target species (sheep and cattle), for the recommended route of administration (subcutaneous) and with the proposed schedule of administration of two administrations separately 3-4 weeks.

According to the performed challenge in these studies in each case, the onset of immunity (OOI) was stated as 3 weeks after the primary vaccination course for the both strains and in the both target species.

The DOI also was supported in these studies. First of all, to obtain the exceptional authorisation a commitment was made in order to support the DOI at the following annual reassessments, and in 2013 the DOI was established as 1 year for the both strains and for the both target species.

With respect to the interference of maternally derived antibodies, no specific studies was performed, but it was stated that appropriate warnings were included in the SPC, regarding the need of vaccination from 2.5 months of age to young animals born to immune sheep and cattle, and according to studies with BVT 2-4 vaccine applicable to this serotypes and relevant bibliography.

VARIATION ADDING BTV4 INTO BTVPUR MULTISTRAIN DOSSIER

Documentation submitted

In the frame work of the "Guideline on data requirements for multistrain dossiers for inactivated vaccines against Avian Influenza (Al), Bluetongue (BT) and Foot-and-Mouth disease (FMD)" (EMA/CVMP/IWP/1 05506/2007), the applicant proposed to add the BTV4 serotype to multistrain dossier using the available information from the BTVPUR AlSap 2-4 dossier, authorised under exceptional circumstances according the recommendations of the CVMP "Guideline on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue" (EMEA/CVMP/IWP/220193/2008).

It is important to take into account that this authorised bivalent vaccine (BTVPUR AlSap 2-4) is only intended for sheep, while the proposal multistrain dossier would intend the using in the both target species, sheep and cattle.

Additionally, the applicant included cross-references to the documentation of the BTVPUR AlSap 1-8 dossier, registered for the both species, sheep and cattle, to support the Part III for safety of this BTV4 addition.

New information regarding BTV4, in Part II for quality (validation of new implemented batch potency testing) and in Part IV for efficacy in cattle was presented.

QUALITY

The applicant has defined the maximum number of antigens that can be included in the final vaccine formulation, as two.

With respect the BTV4 and its inclusion into the multistrain vaccine dossier, the history of the original strain and the method of preparation of the antigen were provided during the BTVPUR AlSap 2-4 registration procedure.

All the control testing during the production of the active ingredient has been performed on a final new batch of BTV4 vaccine appropriately formulated with a batch of active ingredient fulfilling formulation quality requirements of infectious titre before the inactivation antigen quantity. This new batch was tested and demonstrated as efficacious in cattle.

The method of preparation of the active ingredient was described. All the information, regarding to the seed purity testing, inactivation kinetic and titration is valid for this addition and no studies are necessary.

The blending of the multistrain vaccine is standardised, and the volume of each active ingredient is based on the inactivated harvest concentration factor.

Regarding the ingredients other than the antigens, the quantities are the same as those used in the preparation of the other antigens BTV1 and BTV8. In case of two strains (maximum number of antigens included in the multistrain vaccine), the proportion of these ingredients is the same as in case of only one strain, as well.

The control tests during the production, and performed on the BTV4 active ingredient are the following the same as for the other two antigens: infectivity, inactivation, antigens content and sterility. On the other hand, the control tests on the finished product show different specifications for BTV4: titre before inactivation (log_{10} $CCID_{50}$/ml) ≥ 7.1 and VP2 antigen content (log_{10} pixel/ml) ≥ 1.86.

With respect the stability tests, and according the guideline of multistrain dossiers (Doc. EMA/CVMP/IWP/105506/2007), two approaches are considered:

- the stability of a multistrain dossier containing different strains corresponds to the shelf-life of the formulated strain which has the shortest stability.

- the stability data of the multistrain vaccine may also be used to define the shelf-life.

There is no stability period only for BTV4 vaccine, but for BTVPUR AlSap 2-4, which is the authorised vaccine. The shelf-life in BTVPUR AlSap 2-4 was established in 18 months for all the presentations. The duration is shorter than the other with only BTV4 (a bivalent instead of monovalent). Therefore, the applicant proposed stability for the multistrain vaccine of 18 months in the case in which the multistrain vaccine would contain the BTV4 serotype, mono or bivalent. This is acceptable, as in principle, the situation would be similar in case of BTV4 + BTV2 than for BTV4 + BTV1 or BTV4 + BTV8. Nevertheless, and as stated in this guideline, real-time studies with the monovalent vaccine containing BTV4, or bivalent, using a combination of BTV4 with whatever of the other two BTV1 and BTV8 serotypes, should be performed on an ongoing basis, with the aim of extending this shelf-life up to 24 months (proposed shelf-life for BTV1 and/or BTV8 serotypes vaccines), if it can be demonstrated.

SAFETY

According to the guideline for multistrain dossiers, a complete range of safety tests mentioned in Annex I of Directive 2001/82/EC should be provided.

With respect to the addition of the BTV4 serotype, there are two important aspects that would be taken into account: the maximum number of two strains proposed by the applicant for the final product, and the target species authorised in BTVPUR AlSap 2-4 vaccine (sheep).

The applicant proposed that the studies submitted for BTVPUR AlSap 1-8 were valid for the demonstration of the safety of BTV4 serotype. This argument was accepted as these studies that previously justified the safety for the bivalent BTVPUR AlSap 1-8 vaccine, have included the BTV4 serotype on it, as can be seen in the studies described earlier (safety of BTVPUR Alsap 1-8).

All studies have been performed in both target species (sheep and cattle), and for the recommended route of administration (subcutaneous). The used animals were at the proposed minimum age (approximately one-month old in the both species), and included studies in pregnant females. Moreover, the antigen payload included in the used vaccines is above the maximum payload fixed for the antigens.

The proposal of the applicant for not including additional studies to support the safety for the multistrain dossier including BTV4 was acceptable.

PHARMACOVIGILANCE DATA:

The applicant has provided in the documentation three PSUR that are the same submitted for the renewals of the veterinary medicinal products BTVPUR AlSap 1, BTVPUR AlSap 1-8 and BTVPUR AlSap 8. Their AR was adopted by the CVMP on dates 09.07.2015 for the two first and 16.01.2014 for the last one.

EFFICACY

According to the guideline for multistrain dossiers, the efficacy tests mentioned in Annex I of Directive 2001/82/EC should be provided.

In the frame work of this guideline, the efficacy claim of the multistrain vaccine corresponds to the sum of the claims of each antigen included in the vaccine. The applicant noted that the efficacy of the BTV4 antigen has been demonstrated in the documentation of BTVPUR AlSap 2-4 vaccine (Efficacy in conventional sheep, of BTV 2-4 vaccines, formulated with different antigen payloads, against a BTV4 virulent challenge) for sheep, by the subcutaneous route and using the proposed scheme of vaccination for this antigen: one injection and annual revaccination.

The OOI was established in 3 weeks after the primary vaccination course, and the DOI was established in sheep in one year after the primary vaccination course (Annual re-assessment of BTVPUR AlSap 2-4, EMEA/V/C/000139/S/0004). The interference of maternally derived antibodies has been taken into account in young animals born to immune sheep, through vaccination from 2.5 months of age rather than 1 month of age.

BTVPUR AlSap 2-4 is an authorised vaccine only for sheep. For this reason, the applicant includes a new efficacy study performed in cattle of the minimum age, as follows:

Efficacy of an inactivated BTV4 vaccine formulated with administered in two injections to calves, assessed by a virulent BTV4 challenge

Objective/Methodology	To assess the protection afforded by an inactivated BTV4 vaccine administered to calves in two injections, 3 weeks apart. Efficacy was demonstrated through clinical and virological monitoring following a virulent BTV4 challenge, performed 21 days after the 2nd vaccination. A serological monitoring was performed throughout the study.
Animals	12 conventional seronegative to BT virus and healthy male calves (around 1-1.5 months old) were randomly distributed in 2 homogeneous groups (G1=Controls and G2=Vaccinates)
Materials: Vaccine	Inactivated BTV4 vaccine, with BTV4 antigen minimum payload
Administration route and vaccine scheme	Subcutaneous vaccination with 1ml dose on D0 and D21 (G2) in the left side (D0) or the right side (D21) of the neck. Group G1 without treatment.
Challenge	All animals were challenged with 3 ml of BTV4 virus by subcutaneous injection in the neck, in 3 separate sites (1 ml per site). Challenge was carried out on D42.
Post-challenge follow-up	Rectal temperature: on D42, and then daily from D43 to D70. General and body condition: general condition (good, apathy, depression, prostration, scored) and body condition (normal, thin and cachectic, scored), and other clinical signs (congestion, oedema, hypersalivation, ocular and nasal discharge), from D42 to D70. Serology: blood samples were collected on D0, D21, D42 (before challenge)

	and D70 to determine specific BTV4 antibodies by seroneutralisation tests Viraemia: blood samples were collected on the day of challenge (D42, before challenge), and D45, D49, D51, D53, D57, D60, D65 and D70 to determine viraemia by qRT-PCR
Statistical analysis	Maximal hyperthermia and rectal temperature evolution are presented. Maximal hyperthermia was calculated for each animal (between D43 and D70). Groups were compared on maximal hyperthermia (one-sided Student t test), and a score was calculated for each animal (from ≤40°C=0 up to≥41°C=3). A Daily Global Score was calculated by summing: hyperthermia+general condition+body condition+number of specific clinical signs (1 point per sign) + number of other clinical signs (1 point per sign). For each animal, a Global Clinical Score (GCS) was calculated by summing the individual DCS from D43 to D70 (one-sided Student t test). In respect with viraemia, the AUC was calculated for each challenged animal over the period. The groups were compared on the AUC parameter (one-sided Mann-Withney W test). The results of serology were described and discussed.
Results	Hyperthermia: evolution of average rectal temperature was similar between the both groups. No hyperthermia was observed in any animal. Maximal rectal temperature were reduced in G2 (mean=39ºC) as compared to G1 (mean=39.5ºC). Clinical signs: Mean DCS was constantly higher in G1 than in G2. The clinical signs principally registered were nasal discharge, cough, dyspnea and thinness; and occasionally, hypersalivation and ocular discharge. The frequency and duration of the signs in G1 were higher than in G2. The comparisons were statistically significant between the both groups. One animal was euthanized for ethical reasons for causes unrelated to BT virus. Viraemia: After challenge, all control animals were positive from D49 to D70. None of the vaccinated animals was ever detected viraemic during the full study. Comparisons on the AUC parameter were highly significant between control and vaccinated animals. Serology: All calves were BTV4 seronegative on D0 before vaccination, and the control animals remained seronegative until challenge. In G2 no seroconversion was observed after 1st vaccination, and all vaccinated animals had seroconverted 21 days after 2nd vaccination.
Conclusions	Administration of the BTV4 vaccine to calves, followed by challenge with a virulent BTV4, resulted in a: - seroconversion to BTV4, - significant clinical protection, - complete prevention of viraemia in all the vaccinated calves The efficacy of the tested vaccine was demonstrated in calves.

The applicant also indicated that the DOI of the BTV4 in cattle has been supported by studies performed with BTV1 and BTV8 antigens and studies performed with the BTVPUR AlSap 2-4 vaccine in sheep. The justification is that the results of the immediate efficacy of BTV4 in cattle are similar to the obtained results in other serotypes.

For the full authorisation of BTVPUR AlSap 1-8 vaccine, data on the DOI of 12 months after vaccination for the both BTV1 and BTV8 antigens in the two target species were submitted by the applicant in the context of the annual re-assessment dated on November 2012. Thus, the same method is needed to sustain the DOI for BTV1 and BTV8 serotypes. For that reason, laboratory studies should be performed on every target species with the BTV4 antigen.

One study to support the DOI of 12 months in cattle of BTV4 antigen is in progress, and the results are expected in January 2017.

Meanwhile, it was considered supportive of the DOI to establish the correlation in the serum neutralisation (SN) antibodies response in cattle between BTV4, BTV1 and BTV8 vaccines.

Four studies performed in sheep (with BTV1, BTV8, BTV2 and BTV4) and two studies performed in cattle (with BTV1 and BTV8), together with the similarities between the serological profiles of BTV4 and BTV1/BTV8, support the extrapolation in order to justify the DOI of 1 year for BTV4 in cattle, in compliance with the requirement of the guideline for multistrain dossier (EMA/CVMP/105506/2007) in section 6.3. Efficacy. The applicant has committed to provide the challenge results at 12 months post vaccination, as a confirmation of this conclusion.

2.2. Summary and Conclusions

With respect the first variation, the applicant has considered that it is not necessary the performance of any further studies of the submission of complementary documentation for two principal reasons:

- the BTVPUR AlSap 1-8 vaccine was authorised in December 2010 under "exceptional circumstances" (guideline on minimum data requirements for an authorisation under exceptional circumstances for vaccines for emergency use against bluetongue (EMEA/CVMP/IWP/220193/2008); moreover, along these years it has been submitted some complementary information (e.g.: answers to list of major questions, "other concerns", annual re-assessment on 2011 and 2012, specific obligations) till the full marketing authorisation in May 2013.

- in the frame work of the guideline on data requirements for multistrain dossiers for inactivated vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD) (EMA/CVMP/IWP/105506/2007), the BTVPUR AlSap 1-8 vaccine documentation also fulfills with the requirements of this guideline to implement the concept of a multistrain vaccine in order to maintain only one dossier to cover a range of vaccine strains. The conversion is performed in the same conditions of the authorised vaccine, with no change in the characteristics of this vaccine (composition, indications, target species, scheme of vaccination and route of administration).

Based on it, the applicant has provided a justification of this Type II variation proposal, the reasons for the no inclusion of new studies, and a full list with all the relevant references to the BTVPUR AlSap 1-8 dossier, regarding the available information about quality, safety and efficacy of this vaccine, to facilitate the access to that if necessary

Accordingly, the submitted documentation for this variation is acceptable to sustain the proposal conversion of BTVPUR AlSap 1-8 dossier in a BTVPUR multistrain dossier.

With respect to the second variation, the applicant has submitted the information included in the both BTVPUR AlSap 2-4 dossier (especially to sustain the Part II and Part IV), and the BTVPUR AlSap 1-8 dossier (to sustain Part III and Part IV). The BTVPUR AlSap 2-4 vaccine was given normal status in April

2014. The annual re-assessment report of this vaccine (dated on February 2014) considered that "a suitable system for quantifying active ingredient at blending stage remain as a condition of the full marketing authorisation", and for that reason the pendant quality aspects of this dossier, regarding the available method of quantify the active ingredient and the batch potency test, are now included. The BTVPUR AlSap 2-4 dossier was intended only for use in sheep, while the multistrain dossier is proposed for the both target species for the BTV1 and BTV8 serotypes, and also the BTV4 serotype.

The provided documentation, regarding the cross-references to the previous authorised dossier and the new studies in relation with the techniques validation for BTV4 and the efficacy in cattle, is acceptable to sustain the quality, safety and efficacy of this BTV4 serotype, as part of multistrain dossier and considering the maximum number of two strains, with the objective of guarantying a faster procedure to fight the BT spreads in the EU.

In order to fulfil all the requirements in the guideline on data requirements for multistrain dossiers for inactivated vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-Mouth disease (FMD) (EMA/CVMP/IWP/105506/2007), and to accept this antigen as part of this multistrain dossier, the applicant has provided the required information regarding quality aspects in relation with the formulation with BTV4.

It is considered that specific studies in relation to the DOI may be provided post-authorisation in order to demonstrate that the proposed vaccine scheme of one annual revaccination after primary vaccination for the multistrain dossier is also efficacious in the case of BTV4.

It is proposed to continue the same PSUR cycle that has been accepted for BTVPUR AlSap 1-8.

3. Benefit-risk assessment

3.1. Benefit assessment

The benefits of the multistrain dossier is the maintenance of only one dossier which covers a range of vaccine strains, and depending on the particular disease situation in the EU it is possible to select one or two needed strains in order to manufacture vaccines with strains already authorised in the appropriate formulation and manufactured in the same way, and facilitating the availability of the vaccine.

Direct therapeutic benefit

The direct therapeutic benefits of these BTVPUR vaccines remains unchanged for each of them: to induce immunity to prevent viraemia and to reduce clinical signs caused by BTV1 or/and BTV8 or/and BTV4, depending on each case, giving the possibility of adding another strains in the future, and select the manufacturing of one or two of them whatever the epidemiological situation of the disease in the EU.

Additional benefits

All the strains that the applicant proposes to include in BTVPUR AlSap multistrain vaccine (BTV1, BTV8 and BTV4) have been demonstrated to fulfill the requirements on quality, and safety in animals of the minimum age and during pregnancy and the efficacy in sheep and cattle.

Risk assessment

The applicant has submitted cross-references to Part III of the BTVPUR AlSap vaccines in order to assess the associated risks with the use of these vaccines. According to the assessment, and taking into account the same safety profile of the vaccine, no significant risks have been identified when the product is used as indicated in SPC and under normal veterinary practice conditions.

Nevertheless, in view of the performance of the interim study by the applicant regarding the DOI in cattle for BTV4, a recommendation regarding this issue was necessary.

For BTVPUR AlSap 1-8, and BTVPUR AlSap 8, the benefit-risk profile continues to be favorable. A recommendation was made for BTVPUR AlSap 1 and BTVPUR AlSap 1-8 by the CVMP to change in section 4.6 Adverse reactions (frequency and seriousness) of the SPC, and section 6. Adverse reactions of the labelling and package leaflet, in order to harmonise with the QRD template.

Main potential risks

For the target animals:

For sheep and cattle vaccination may be followed by a small local swelling at the injection site (at most 32 cm² in cattle and 24 cm2 in sheep) which becomes residual 35 days later (≤ 1 cm2). A transient increase in body temperature, normally not exceeding an average of 1.1°C, may occur within 24 hours after vaccination.

For the user:

For the user there is a low risk of self-injection. Appropriate warnings and advice on the SPC are included to minimize the risk.

For the environment:

The product is not expected to pose any risk to the environment when used as recommended.

For the consumer:

For the consumer there are no components which require an MRL, therefore there are no concerns over failure to observe an MRL.

Specific potential risks, according to product type and application

No further specific risks have been identified from the acceptance of the type II variation.

Risk management or mitigation measures

Appropriate warnings have been placed in the SPC to inform of the potential risks to the target animals, the user and the environment and provide advice for reducing these risks.

3.2. Evaluation of the benefit-risk balance

The BTVPUR AlSap multistrain dossier has shown to have a positive benefit-risk balance for use in sheep & cattle, with a recommendation raised in order to confirm a positive balance also in cattle, regarding the DOI of the BTV4 serotype in this target species. The results of the interim study would be provided at the end of the study to sustain the proposed period of one year of DOI in cattle for BTV4 serotype.

Since the authorisation of the monovalent or bivalent vaccines (BTVPUR AlSap 1-8, 1, 8 and 2-4) these vaccines have shown to be efficacious for the indication of preventing viraemia and of reducing clinical signs caused by the BTV1 or/and BTV8 (sheep and cattle) or/and BTV4 (sheep).

Bearing in mind the proposed two maximum strains for the multistrain dossier, the both bivalent vaccines already authorised (BTVPUR AlSap 1-8 and 2-4) have demonstrated the safety of the use of two strains together as part of this multistrain proposal.

The formulation, manufacturing, quantification and batch potency testing of the three serotypes (BTV1, BTV8 and BTV4) in the same manner, have sustained the manufacturing of different vaccines containing the involved serotype/s, according to the actual situation of the disease in the EU.

The BTVPUR authorised vaccines have demonstrated tolerance well in the target species and present a very low risk for the animals, users and the environment.

Appropriate warnings have been included in the SPC.

Conclusion on benefit-risk balance

The information provided in the dossier and in response to points raised is sufficient to confirm an overall positive benefit risk balance.

Risk management measures are not considered necessary.

The variation has no impact on the environment.

The benefit-risk balance remains unchanged.

4. Overall conclusions of the evaluation and recommendations

The CVMP considers that 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 approvable with the following recommendation:

In view of the performance of the interim study by the applicant, the results of the challenge at 12 months post vaccination in order to confirm the DOI of the BTV4 in cattle would be provided at the end of the study.

It is proposed to continue the same PSUR calendar cycle that has been accepted for BTVPUR AlSap 1-8.

4.1. Changes to the community marketing authorisation

Changes are required in the Annexes to the Community marketing authorisation.

Annexes I, IIIA, IIIB, A