EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 August 2020
EMA/451510/2020
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for type II variation for Bluevac BTV8 (EMEA/V/C/000156/II/0010/G)

INN: Bluetongue virus vaccine (inactivated)

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

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Table of contents

1. Introduction

1.1. Submission of the variation application

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, CZ Veterinaria S.A. (the applicant), submitted to the European Medicines Agency (the Agency) on 6 March 2019 an application for a grouped type II variation for BLUEVAC BTV8.

1.2. Scope of the variation

Variation(s) 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. To convert the BLUEVAC BTV8 dossier for sheep and cattle in a BLUEVAC BTV multi-strain dossier.	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. To add serotype BTV4 into BLUEVAC BTV multi-strain dossier.	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. To add serotype BTV1 into BLUEVAC BTV multi-strain dossier.	II

The proposed variation is to convert the BLUEVAC BTV8 dossier into a multi-strain dossier (BLUEVAC BTV), and to add the strains BTV1 and BTV4 into the multi-strain dossier. Additionally, the applicant takes the opportunity to slightly amend the address.

1.3 Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 2, Part 3 and Part 4

1.4 Scientific advice

Not applicable.

1.5 MUMS/limited market status

Not applicable.

2. Scientific Overview

Based on the information provided by the applicant, a grouped Type II variation is submitted for three different, but related claims:

- 1. To convert the BLUEVAC BTV8 dossier for sheep and cattle in a BLUEVAC BTV multi-strain dossier and

- 2. + 3. To add the strains BTV1 and BTV4 into this BLUEVAC BTV multi-strain dossier.

With respect to the first issue (conversion of dossier), it has been considered that it is not necessary to perform any further studies or the submission of complementary documentation as:

- the vaccine BLUEVAC BTV8 was authorised in February 2011 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); along the years complementary information has been submitted (e.g. answers to list of major questions and "other concerns", annual re-assessments on 2012 till 2014, specific obligations, variations) till conversion to a full marketing authorisation in 2015.

- in the frame of the '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/105506/2007), the BLUEVAC BTV8 vaccine documentation fulfils in general the requirements of this guideline to implement the concept of a "multi-strain 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 major characteristics of the vaccine (indications, target species, scheme of vaccination, route of administration).

Based on this, relevant references to the BLUEVAC BTV8 dossier and the non-inclusion of new studies are provided and considered justified regarding the already available information on quality, safety and efficacy of this authorised vaccine.

The documentation submitted for this variation is generally acceptable to sustain the proposed conversion of the BLUEVAC BTV8 dossier in a BLUEVAC BTV multi-strain dossier. Specific information on quality concerning some control tests (e.g. antigen quantification by SLOT BLOT immunoassay, changed specification on the potency test) are adequately presented.

With respect to the second issue (addition of two strains), information is provided to add two new virus strains of BT serotypes 1 and 4 into the multi-strain dossier of BLUEVAC BTV.

The provided documentation in relation with the techniques validation for BTV1 and BTV4 and the efficacy in cattle, is acceptable to sustain the quality, safety and efficacy of this BTV1 and BTV4 serotype, as part of multi-strain dossier and considering the maximum number of one strain, with the objective of guaranteeing a faster procedure to fight the Bluetongue spreads in EU.

In order to fulfil the requirements of '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/105506/2007), and to accept these new antigens as part of the multi-strain dossier, complementary information regarding quality and new studies regarding safety and efficacy have been provided.

Based on this, different quality aspects in relation with specific control tests including validation (e.g. antigen quantification by SLOT-BLOT immunoassay, identification and potency test) have been clarified and justified. Furthermore, sufficient data from safety studies are provided.

2.1. Part 2 Quality

Qualitative and quantitative particulars

The applicant has defined the maximum number of antigens that can be included in the multi-strain vaccine; a maximum of one serotype only.

The quantity of each antigen included in BLUEVAC BTV is as follows:

	Substance Name	Quantity per mL
Active substances [1]	Inactivated Bluetongue virus: [2]	
	- serotype 8, BTV-8/Bel/2006/01	≥ 55.80 µg [3]
	- serotype 1, BTV-1/ALG/2006/01	≥ 22.60 µg
	- serotype 4, BTV-4/SPA-1/2004	≥ 2.55 µg
Excipient	Aluminium hydroxide	6 mg
	Purified saponin (Quil A)	0.05 mg
	Thiomersal	0.1 mg
	Phosphate-buffered saline (sodium chloride, disodium phosphate, potassium phosphate and water for injections	q.s. 1 ml

Container

BLUEVAC BTV is presented in boxes containing high-density polyethylene (HDPE) bottles of 52, 100 or 252 ml, closed with stoppers made of perforable butyl rubber and sealed with aluminium caps. The containers correspond with the registration of the BLUEVAC BTV8 vaccine.

Method of manufacture

The production flow chart and description of the manufacture of BLUEVAC BTV follows the already authorised manufacturing process for BLUEVAC BTV8. It begins with the preparation of the different antigens of BTV1, BTV4 and BTV8 serotypes, the formulation and preparation of bulk vaccine, the preparation of the finished product (monovalent) and ends with the control on finished product and batch release.

The method of preparation of the active ingredients as such is identical for each antigen of BTV1,

1 Two doses of 2ml vaccine administered 21 days apart to sheep will prevent the development of viremia caused by challenge with the relevant virulent BTV strain three weeks after second dose. Viremia is measured by a validated RT-PCR method.

2 A maximum of one inactivated bluetongue virus serotype.

3 Quantity based on antigen quantification on the inactivated antigen bulk

BTV4 and BTV8 and follows the same steps as authorised for BLUEVAC BTV8. It uses a Seed Lot System with multiplication and cultivation on BHK21 cells, virus harvest, clarification by centrifugation and filtration, inactivation, purification by ultrafiltration and concentration and bottling.

However, minor adjustments identified between the authorised manufacturing process described for BLUEVAC BTV8 and for BLUEVAC BTV are justified. Furthermore, the second inactivation test has been removed taking into account that the inactivation has already been validated according to the Ph. Eur. requirements for BTV8 and consequently the second inactivation test has been omitted.

Concerning serotype BTV8 and the additional serotypes BTV1 and BTV4 each inactivation process and the test for complete inactivation are described and validated. In these cases, the inactivation kinetics and the inactivation control test guarantee the effectiveness of the process with respect to the inactivation of the infective BTV viruses.

The blending is described for each antigen, which is the component of the vaccine. The fixed amount of each BTV antigen has been established in dose-response efficacy studies.

The maximum pre-inactivation virus titres of 10^6.5 cell culture infectious dose 50% ($CCID_{50}$) (BTV4, BTV8) or 10^6.4 $CCID_{50}$ (BTV1) are fixed orientated on the already authorised vaccine BLUEVAC BTV8. The formulation of all batches used in the safety studies follow the pattern of this established production process.

With respect to the vaccine ingredients other than the antigens, they are added in the same quantities whatever the antigen as it is reflected in the method of production of the BLUEVAC BTV8 dossier.

In order to evaluate the reliability and robustness of the manufacturing process, a summary of critical process parameters from consecutive batches of each of the antigens and vaccine batches are provided. All batches were produced and tested according to the manufacturing process described. The tests results are within limits of acceptance thus confirming consistency of the production process in the context of the multi-strain dossier.

Control of starting materials - **Active substances, excipients and other starting materials**

The same starting materials used to prepare the three BTV serotypes (BTV1, BTV4 and BTV8) and the vaccine BLUEVAC BTV are the same as for the already authorised vaccine BLUEVAC BTV8. The existing quality standards currently approved for these materials used in the production of BLUEVAC BTV8 will be maintained. In addition, also the same starting materials of biological origin as those already authorised for BLUEVAC BTV8 are used without any changes, deletions or additions (except BTV1 and BTV4 seed materials).

Concerning the additional serotypes BTV1 and BTV4 to be included in the dossier, a summary on the origin, history and testing of the virus is presented. The MSV/WSV controls are the same as follows: test for exclusion of bacteria and fungi (sterility), test for exclusion of mycoplasma, test for exclusions of extraneous viruses and identity. In this regard, validations for relevant quality control tests applicable to these strains are presented. Additional information, assurances and data show that these strains are acceptable for inclusion in the vaccine.

Control tests during the production

All the tests are the same in view of the three BTV serotypes (BTV1, BTV4 and BTV8) and follow the same control tests during manufacturing process as those already authorised for BLUEVAC BTV8.

Concerning the additional serotypes BTV1 and BTV4, test descriptions and the limits of acceptance are presented. Test methods for in-process controls are satisfactorily validated. This includes the inactivation control test and titration.

Control tests on the finished product

All the tests are the same in view of the three BTV serotypes (BTV1, BTV4 and BTV8) and follow in general the same control tests during manufacturing process as those already authorised for BLUEVAC BTV8.

Concerning the additional serotypes BTV1 and BTV4, test descriptions and limits of acceptance are presented. The control methods are satisfactorily validated in order to confirm that the production and control processes generate consistent vaccine batches.

The following tests are carried out on the active ingredient in the antigen mixture/bulk just before adding the adjuvant (as this component interferes the detection of the test): test for pH, antigen quantification by SLOT-BLOT assay.

The following tests are performed on the adjuvant mixture/bulk just before adding the antigen: Quil A content and aluminium hydroxide content.

Based on all information and data provided, the control tests on the antigen and adjuvant bulks and the acceptance limits are considered sufficient to conclude on the consistency of the production process. Further clarification and confirmation concerning the SLOT-BLOT assay on each of the monovalent BTV antigen bulks is acceptable. Regarding the antigen quantification in BTV antigen bulks, the now established acceptance limits are comprehensible. These limits picture the minimum antigen quantity shown to have passed the potency test beside all other control tests.

The following control tests on the finished product are carried out either on the vaccine bulk or on the filled product: appearance, test for pH, thiomersal content, Quil A content, aluminium hydroxide content, sterility, filling volume, identification, potency (biological activity). Additional clarification and confirmation concerning the potency and identification on each of the monovalent BTV vaccines is provided and conclusive.

Stability tests

The specifications concerning stability of the BTV8 antigen and the finished product BLUEVAC BTV8 including in-use stability corresponds with the data already registered for this vaccine. These shelf life periods are considered acceptable in the context of the multi-strain dossier.

Stability data are submitted in order to justify the proposed shelf life of 26 months at +2 to +8 °C for the inactivated BTV4 antigen. Data of a real time stability study are submitted in order to justify the proposed shelf life of 24 months at +2 to +8 °C for the monovalent BTV4 vaccine.

Stability data are submitted in order to justify the proposed shelf life of 12 months at +2 to +8 °C for the inactivated BTV1 antigen. Data of a real time stability study are submitted in order to justify the proposed shelf life of 18 months at +2 to +8 °C for the monovalent BTV1 vaccine.

In-use stability of monovalent BTV1 vaccine and BTV4 vaccine is demonstrated, and the finished product is stable when stored 10 hours after broaching. In this regard, the efficacy of antimicrobial preservatives according to Ph. Eur. 5.1.3 has been demonstrated.

Overall conclusion on quality

In respect to quality, the applicant has submitted a dossier with reduced content, with corresponding cross-references to all the relevant and previous documentation. This previous documentation includes all information regarding the BTV8 strain (one of the active substances of the multi-strain dossier) and has already been submitted and accepted for registration of the vaccine BLUEVAC BTV8.
In order to fulfil all the requirements of Guideline EMA/CVMP/IWP/105506/2007, and to accept the BTV8 strain as part of the multi-strain dossier (by conversion of the dossier), complementary

information and data has been provided to clarify and justify certain aspects on quality modified in the light of the multi-strain dossier and the addition of further BTV strains.

In this regard, the applicant has presented detailed information on the addition of the new BTV serotypes BTV1 and BTV4 to be included in the dossier and validation studies for relevant quality control tests applicable to these strains. Additional information, assurances and data show that these strains are acceptable for inclusion in the vaccine.

For completion, the applicant is recommended to provide the following information [post authorisation]:

1. Supplementary data on stability of monovalent BTV4 vaccines filled in vials of 52 ml and stored at +2-8°C will be provided accordingly after finalisation and immediately in case of potentially out-of-specification results in the course of the study.
2. Supplementary data on stability of monovalent BTV1 vaccines filled in vials of 52 ml and stored at +2-8°C will be provided accordingly after finalisation and immediately in case of potentially out-of-specification results in the course of the study.

General note on the safety and efficacy part

Currently, only BLUEVAC BTV8 is licensed centrally, and it was decided by the applicant to convert this dossier into a multi-strain dossier and furthermore to add two BTV serotypes (BTV1 and BTV4).

Selected safety studies concerning serotype BTV8, which are provided in this conversion dossier were included to cover safety data for a possible bivalent vaccine. However, they were already evaluated during the marketing authorisation procedure for BLUEVAC BTV8. The results are discussed here solely to assess the safety of a possible bivalent vaccine.
All other safety and efficacy studies on BLUEVAC BTV8 were not included in this variation documentation as they were already assessed during the initial marketing authorisation of BLUEVAC BTV8.

BLUEVAC-4 is currently only licensed via mutual recognition (MR) procedure with Spain as reference member state (RMS) and Belgium (BE), Germany (DE), France (FR), Greece (GR), Portugal (PT), Romania (RO) and Slovenia (SI) as concerned member states (CMS).
BLUEVAC-1 is currently not licensed centrally or in any decentralised or mutual recognition procedure at all. However, some of the studies for serotype BTV1 were already included in the marketing authorisation dossier for BLUEVAC BTV8.

Therefore, all safety and efficacy studies provided on BLUEVAC-1 and BLUEVAC-4 needed to be evaluated during this variation.

The efficacy of a multi-strain dossier may be demonstrated by performing efficacy studies employing the respective monovalent vaccines. It is assumed that a combination of serotypes will be at least as efficacious as the monovalent vaccine. Therefore, the claim for efficacy for a multi-strain vaccine adds up for the respective serotypes contained in the product.

2.2. Part 3 Safety

Safety trials included in the initial variation submission:

Trials performed in **sheep:**

Trial number	Vaccine	Schedule	Age at vaccination
LA4+8-LT-RD-1	BLUEVAC 4+8	2 x 2 ml, 21 days, SC	2-2.5 months
LA4-LT-RD-42	BLUEVAC 4	2 x 2 ml, 21 days, SC	2 months
LA1-LT-RD-37	BLUEVAC 1	2 x 2 ml, 21 days, SC	2 months
LA8-LT-RD-34	BLUEVAC BTV8	Group I, III, IV, VI & VII 1 x 2 ml, SC	2 months
		Group II, V, VIII 2 x 2 ml, 22 days, SC	
LA8-LT-RD-15	BLUEVAC BTV8	1 x 4 ml (1st dose) 1 x 2ml (2nd dose) 21 days, SC	2 months
LA8-LT-RD-12	BLUEVAC BTV8	1 x 4 ml, SC	Pregnant
LA1-LT-RD-46	BLUEVAC 1	2 x 2 ml, SC	Pregnant
LA4-LT-RD-47	BLUEVAC 4	2 x 2 ml, SC	Pregnant
LA1+8-FR-RD-9	BLUEVAC 1+8	1 x 2 ml, SC	4-5 years

Trials performed in **cattle:**

Trial number	Vaccine	Schedule	Age at vaccination
BVB8-LT-RD-5	BLUEVAC BTV8	1 x 8 ml (1st dose) 1x 4 ml (2nd dose)	2 months
BVB-LT-RD-3	BLUEVAC 1	2 x 4 ml, 24 days, SC	2 months
BVB4-LT-RD-52	BLUEVAC 4	2 x 4 ml, 28days, SC	1.5 – 2 months
BVB-FT-RD-8	BLUEVAC 1	2 x 4 ml, 2 days, SC	Pregnant
BTV4-LT-RD-50	BLUEVAC 4	2 x 4 ml, 28 days, SC	Pregnant

Field trial **(sheep):**

Trial number	Vaccine	Schedule	Age at vaccination
LA1+8-FT-RD-9	BLUEVAC 1+8	Group 1: 2 x 2 ml, 21 days, SC (primovaccinated) Group 2: 1 x 2 ml, SC (re-vaccinated)	> 3 months

Additional safety trials submitted with responses to the LoQ (sheep + cattle):

Trial number	Vaccine	Schedule	Age at vaccination
LA1+4-LT-17	BLUEVAC 1+4 (Oily adjuvant)	4ml+2ml, D0+D21 SC in the neck	2.5 months
LA4+8-LT-ST-03	BLUEVAC 4+8	4ml vaccine D0+D21 + D42 SC in the neck 4ml PBS D0+D21+D42 SC in the neck	> 2 months
LA4+8-LT-RD-2	BLUEVAC 4+8	2ml vaccine D0+D21 SC in the neck 2ml vaccine D0+D21 SC in the neck 2ml PBS D0+D21 SC in the neck	2-3 months
LA1+8-LT-ST-01	BLUEVAC 1+8	4ml vaccine D0+D21 SC in the neck 4ml PBS D0+D21 SC in the neck	> 2 years
LA4+8-LT-ST-02	BLUEVAC 4+8	4ml vaccine D0+D21 SC in the neck 4ml PBS D0+D21 SC in the neck	> 2 years

In summary, taking into account the cumulated data from all studies provided in the initial submission, it can be concluded that the administration of a bivalent vaccine comprised of two of the serotypes BTV1, BTV4 or BTV8, can be considered as safe in seronegative sheep and cattle of the youngest recommended age. However, the maximum number of antigens that can be included in the multi-strain vaccine is in any case a maximum of one serotype only.

Corresponding information and safety studies are provided concerning the addition of two new virus strains of BTV serotypes 1 and 4 into the multi-strain dossier of BLUEVAC BTV.

Safety has been demonstrated for repeated administration of a bivalent batch of BLUEVAC BTV comprised of maximum two of the serotypes BTV1, BTV4 or BTV8 in pregnant ewes, regardless of the period of pregnancy. This is valid even if the maximum number of antigens included in the multi-strain vaccine is one serotype only.

Safety was demonstrated for repeated administration of monovalent batches of BLUEVAC BTV containing one of the serotypes BTV1, BTV4 or BTV8 in pregnant bovine females, regardless of the period of pregnancy.

Two further safety studies in pregnant cattle vaccinated with the maximum antigen amount contained in a bivalent BLUEVAC BTV vaccine (BTV1+4; BTV4+8) were initiated and the currently available results were submitted.

The final report for study LA1+8-LT-ST-01 is provided. No serious adverse events were recorded during the study, slight local inflammation was observed after the second dose. No significant increase in body temperature was observed. No abortions or teratogenic effects were detected, offspring survival was 100%.

For study LA4+8-LT-ST-02 an interim report is provided. Until now, no serious adverse events were recorded during the study; slight local inflammation was observed after vaccination. No significant increase in body temperature was observed. The safety of the vaccine for pregnancy at this stage and offspring is still pending as parturition was estimated for April 2020. However, no new information on this study was provided until now.

From the results of both studies currently provided the applicant concludes that the administration of bivalent BLUEVAC BTV is safe during pregnancy in cattle, but a final conclusion on safety in pregnant cows can only be made after submission of final data from study LA4+8-LT-ST-02. However, it should be taken into account that the maximum number of antigens to be included in the multi-strain vaccine is at present one serotype only. Even though at present not relevant, the final results of study LA4+8-LT-ST-02 on safety of a bivalent vaccine administered at pregnancy are required for completion as soon as available.

The applicant provided new data and a thorough discussion concerning safety of the application of 3 doses with the maximum number of strains included in the vaccine. In a study in sheep dated 2008, animals received a double dose and a repeated dose two weeks later, which is considered as a 3-dose application. The vaccine contained an oily adjuvant instead of the standard adjuvant; however, the applicant stated this as worst case. Nonetheless, the administration of BLUEVAC 1+4 to 2 to 3 months old lambs is considered safe as no adverse events occurred.

Data from the field trial with BLUEVAC 1+8 in sheep were satisfactory and representative, as animals of different ages and categories as well as pregnant animals were vaccinated twice and revaccinated after one year with a bivalent vaccine.

For cattle, a new safety study in calves employing 3 doses of BLUEVAC 4+8 was initiated. The results from the study are now available. Some local reactions and behavioural abnormalities were observed during the study; however, none of them was severe. All reactions observed in the study are already included in the SPC. The study is considered as valid, even if the maximum number of antigens included in the multi-strain vaccine is one serotype only, and the administration of three doses of BLUEVAC 4+8, with an interval of 21 days to 2 to 3 months old calves is considered as safe.

Based on the above described data the applicant concludes, that the safety studies using monovalent or even bivalent vaccines meet the requirements and generally demonstrate safety for monovalent vaccines of BLUEVAC BTV for sheep and cattle. Respective information is on possible adverse reactions or specific precautions for use of the vaccine included in the product literature.

Furthermore, the applicant discusses the available PSUR data for different bivalent vaccines in sheep and cattle after administration of 3 doses. Even if the maximum number of antigens included in the multi-strain vaccine is one serotype only these PSUR information may be taken into consideration for the safety assessment.

Data are provided for BLUEVAC 1+4 and BLUEVAC 1+8 in sheep and for BLUEVAC 1+8 in cattle. Additionally, data from simultaneous administration of monovalent BLUEVAC 1 and BLUEVAC 4 vaccines are provided.
More than 23 million animals were vaccinated with bivalent vaccines and no safety events occurred.
More than 9 million animals received simultaneous BTV1 and BTV4 vaccinations.
From these data, the applicant concludes that vaccination with bivalent BLUEVAC BTV vaccines in sheep and cattle in the field is safe. This is relevant for monovalent vaccines, too.

The requirements for the safety studies for sheep and cattle are considered fulfilled.

Overall conclusion on safety

In the frame of the '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/105506/2007), the BLUEVAC BTV8 vaccine documentation fulfils the safety requirements of this guideline to implement the concept of a "multi-strain 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 major characteristics of the vaccine (indications/claims, target species, scheme of vaccination, route of administration).

Corresponding information and studies are provided concerning the addition of two new virus strains of BTV serotypes 1 and 4 into the multi-strain dossier of BLUEVAC BTV.

Safety studies have been carried out using vaccine batches manufactured with the maximum number of strains (n=1, monovalent) as well as bivalent vaccine batches. In addition, safety data have also been generated in the most sensitive category of the target species using the recommended route of administration. In summary, safety of BLUEVAC BTV has generally been demonstrated in the target species cattle and sheep.

Safety was demonstrated for repeated administration of monovalent batches of BLUEVAC BTV containing one of the serotypes BTV1, BTV4 or BTV8 in pregnant bovine females, regardless of the period of pregnancy.

Nonetheless, even though at present not relevant the final results from the ongoing study LA4+8-LT-ST-02 concerning the use of a bivalent vaccine in pregnant cattle are required for completion.

The respective safety parameters regarding possible adverse reactions, special precautions for vaccine use and the use during pregnancy and lactation demonstrated in both target species are adequately indicated in the product literature.

2.3. Part 4 Efficacy

Laboratory tests on onset and duration of immunity were carried out in sheep and cattle.
Furthermore, the influence of maternally derived antibodies was evaluated for BLUEVAC-1 in sheep.

Additionally, one field trial in sheep employing BLUEVAC BTV 1+4 was performed in Spain.

Trials performed in **sheep:**

Trial number	Vaccine	Schedule	Age at vaccination
LA4-LT-RD-42	BLUEVAC-4	2 x 2 ml, 21 days, SC	2 months
LA4-LT-RD-54	BLUEVAC-4	1 x 2 ml, SC	2 months
LA1-LT-RD-37	BLUEVAC-1	2 x 2 ml, 21 days, SC	2 months
LA1-LT-RD-52	BLUEVAC-1	1 x 2 ml, SC	2.5 months
LA-LT-RD-8	BLUEVAC-1 BLUEVAC 1+4	2 x 2 ml, 21 days, SC	3 months
LA-LT-RD-9	BLUEVAC 1+4	2 x 2 ml, 21 days, SC	2-2.5 months
LA4-LT-RD-49	BLUEVAC -4	2 x 2 ml, 21 days, SC	2-3 months
LA4-LT-RD-50	BLUEVAC -4	1 x 2 ml, SC	2 months
LA1-LT-RD-41	BLUEVAC -1	2 x 2 ml, 21 days, SC	2-3 months
LA1-LT-RD-44	BLUEVAC -1	2 x 2 ml, 21 days, SC	2-3 months
LA1-LT-RD-51	BLUEVAC -1	1 x 2 ml, SC	2.5 months
LA1-LT-RD-40	BLUEVAC -1	2 x 2 ml, 21 days, SC	2.5 months

Trials performed in **cattle:**

Trial number	Vaccine	Schedule	Age at vaccination
BVB4-LT-RD-52	BLUEVAC -4	2 x 4 ml, 28 days, SC	1.5-2 months
BVB-LT-RD-3	BLUEVAC -1	2 x 4 ml, 24 days, SC	2 months
BTV4-LT-RD-48	BLUEVAC -4	2 x 4 ml, 28 days, SC	1.5-2 months
BVB1-LT-RD-53	BLUEVAC -1	2 x 4 ml, 21 days, SC	2-3 months

Field trial **sheep:**

Trial number	Vaccine	Schedule	Age at vaccination
Spanish field trial	BLUEVAC 1+4	2 x 2 ml, 25 days, SC	> 2 months
	BLUEVAC -1	2 x 2 ml, 23 days, SC	> 2 months

In summary, taking into account the cumulative data from all laboratory and field efficacy studies provided, it can be concluded that batches of monovalent vaccines containing the new serotypes BTV1 or BTV4 can be considered efficacious against virulent challenge with BTV1 or BTV4 in sheep and cattle. The efficacy of a multi-strain dossier may be demonstrated by performing efficacy studies employing the respective monovalent vaccines. It is assumed that a combination of serotypes will be at least as efficacious as the monovalent vaccine. Therefore, the claim for efficacy for a multi-strain vaccine adds up for the respective serotypes contained in the product.

The applicant provided a justification on the use of the respective challenge strains BTV-4/SPA-1/2004 for testing of efficacy of BLUEVAC BTV4 and BTV-1/ALG/2006/01 for testing of efficacy of BLUEVAC BTV1. The respective challenge strains are considered suitable for the purpose and considered as representative for the epidemiological situation in Europe.

Corresponding information and dose-response studies are provided concerning the addition of two new virus strains of BTV serotypes 1 and 4 into the multi-strain dossier of BLUEVAC BTV.

The studies on onset and duration of immunity are considered valid. These studies were usually performed in seronegative animals and included unvaccinated control animals, which in all cases presented severe signs of Bluetongue disease after challenge. In some cases, they even succumbed to the disease or were humanely euthanized during the monitoring period. In general, the infection model is considered valid.

The respective efficacy parameters demonstrated for the different vaccination schemes in both target species are indicated in the product literature.
In sheep, onset of immunity (OOI) is claimed 21 days after completion of the primary vaccination scheme. Duration of immunity (DOI) is claimed as 1 year after completion of the primary vaccination scheme.

In cattle, OOI is claimed as follows for the different BTV serotypes after completion of the primary vaccination scheme: BTV1 28 days, BTV4 21 days, BTV8 31 days. DOI is claimed as 1 year completion of the primary vaccination scheme.

However, only one study on the impact of maternally derived antibodies (MDA) was provided in the initial variation submission.
This study was performed in lambs and indicated a possible impact of MDA on the BLUEVAC BTV vaccination. The possible impact of MDA on the vaccination of young animals in general, but especially concerning young calves as well as the further available data on MDA in lambs and calves has been discussed. In a MDA study in lambs assessed in the initial authorisation procedure for BLUEVAC BTV8 an influence of MDA was demonstrated. However, a MDA study in young calves was not done. Based on these findings, respective warnings and information for use of the vaccine are included in the product literature.

Overall conclusion on efficacy

In the frame of the '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/105506/2007), the BLUEVAC BTV8 vaccine documentation fulfils the efficacy requirements of this guideline to implement the concept of a "multi-strain 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 major characteristics of the vaccine (indications/claims, target species, scheme of vaccination, route of administration).

Corresponding information and studies are provided concerning the addition of two new virus strains of BT serotypes 1 and 4 into the multi-strain dossier of BLUEVAC BTV.

The efficacy of a multi-strain dossier may be demonstrated by performing efficacy studies employing the respective monovalent vaccines. It is assumed that a combination of serotypes will be at least as efficacious as the monovalent vaccine. Therefore, the claim for efficacy for a multi-strain vaccine adds up for the respective serotypes contained in the product.

Efficacy data have been provided for monovalent vaccines containing each of the additional BTV serotypes included in this multi-strain dossier; BTV-1 and BTV-4. As additional information only, efficacy data have also been generated using a bivalent vaccine containing two different BTV strains (BTV1+4).

The respective efficacy parameters regarding claims, OOI and DOI demonstrated for the different vaccination schemes in both target species are indicated in the product literature.

For sheep, OOI of 21 days after completion of the primary vaccination scheme and DOI of 1 year after completion of the primary vaccination scheme have been satisfactorily demonstrated.

For cattle, OOI is claimed for each of the different BTV serotypes after completion of the primary vaccination scheme: BTV1 28 days, BTV4 21 days, BTV8 31 days. DOI of 1year after completion of the primary vaccination scheme has been demonstrated.

The influence of MDA on the efficacy of the vaccine has been investigated. A standard warning has been included in section 4.4 of the SPC.

3. Benefit-risk assessment of the proposed change

This product (BLUEVAC BTV8) is authorised for the active immunisation of sheep from 2.5 months of age and cattle from 2 months of age to prevent viraemia and to reduce clinical signs caused by bluetongue virus serotype 8. Each millilitre of vaccine contains Bluetongue virus inactivated, serotype 8: $10^{6.5}$ $CCID_{50}$, equivalent to titre prior to inactivation (log10).

The proposed grouped variation is to convert the BLUEVAC BTV8 dossier into a multi-strain dossier (BLUEVAC BTV), and to add the strains BTV1 and BTV4 into the multi-strain dossier.

3.1. Benefit assessment

Direct therapeutic benefit

BLUEVAC BTV is an inactivated vaccine against bluetongue virus (BTV) consisting of one virus out of a set of 3 viruses belonging to the BTV serotypes 1, 4 and 8. This BTV vaccine is intended as a multi-strain product produced within the context of a multi-strain dossier. The benefit of the multi-strain dossier is the maintenance of only one dossier, which covers a range of vaccine strains which allows to manufacture vaccines with strains already authorised in the appropriate formulation and in the same way and to mix of appropriate strains.

This approach facilitates the vaccine availability depending on the situation in the field and in response to field need and giving the possibility of adding other strains in the future. Due to the unpredictability of the virus invasion, outbreaks of disease and the different serotypes of circulating BTV there is a need for rapid and frequent change in the strains included in the vaccines. The BTV strains included are finally relevant to the current epidemiological situation of the bluetongue disease in the EU.

Well-conducted controlled laboratory trials demonstrated that the product is efficacious. A prevention

of viraemia is supported for serotypes 1, 4 and 8 (sheep, cattle) whereas for serotype 8 a reduction of clinical signs in sheep only is supported. An overall OOI of 21 days (sheep) and of 28 day for BTV1, 21 days for BTV4 and 31 days for BTV8 (cattle) for all strains with DOI for 1 year is supported.

Additional benefits

The conversion to a multi-strain product and the addition of two BTV strains to a list of three strains that may be used to manufacture the vaccine BLUEVAC BTV means that vaccines that contain one of these strains can quickly be produced in the event of an outbreak of bluetongue disease in the EU caused by the specific BTV serotype and it can be considered an additional benefit. Furthermore, this increases the flexibility to react to respective emergency situations.

3.2. Risk assessment

Quality

Information on development, manufacture and control of the active substances and finished products has been presented in a satisfactory manner. The results of tests carried out may indicate in general consistency and uniformity of important product quality characteristics, and these in turn may lead to the conclusion that the product should have in general a satisfactory and uniform performance in use.

Safety

According to the assessment and considering the same safety profile of the vaccine, no significant risks have been identified when the product is used as indicated in the SPC and under common veterinary practice conditions.

Risks for the target animal:

Risk for the target animals remains unaffected by the variations. The administration of BLUEVAC BTV in accordance with SPC recommendations is generally well tolerated. Although new studies presented were safety studies, the adverse events observed were no worse than that described in the current SPC.

Risk for the user:

Risk for the user remains unaffected by these variations when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment:

No change to the impact on the environment is envisaged. BLUEVAC BTV is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer:

Risk for the consumer remains unaffected by the variations. BLUEVAC BTV as an inactivated vaccine contains excipients and adjuvants which are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this veterinary medicinal product.

Special risks:

None.

3.3. Risk management or mitigation measures

The proposed changes should not impact on the user safety, environment safety and customer safety of the product as authorised. 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.

The withdrawal period is set at zero days.

3.4. Evaluation of the benefit-risk balance

The BLUEVAC BTV multi-strain dossier has shown to have, in general, a positive benefit-risk balance for use in sheep and cattle. The initial concerns have been clarified in order to have a final overall positive balance regarding the vaccine.

4. Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variations to the terms of the marketing authorisation for BLUEVAC BTV8 can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

- To convert the BLUEVAC BTV8 dossier into a multi-strain dossier (BLUEVAC BTV), and to add the strains BTV1 and BTV4 into the multi-strain dossier.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above-mentioned medicinal product.

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

I, II, IIIA, IIIB and A.

Please refer to the separate product information showing the tracked changes.