22 May 2024
EMA/257593/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Bluevac BTV (EMEA/V/C/000156/VRA/0012/G)

Vaccine common name: Bluetongue virus vaccine (inactivated) (multistrain: 1 strain out of a set of 3)

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

Rapporteur: Esther Werner

Co-rapporteur: Fulvio Marsilio

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

Table of contents

1. Introduction

1.1. Submission of the variation application

In accordance with Article 64 of Regulation (EU) 2019/6, the marketing authorisation holder, CZ Vaccines S.A.U. (the applicant), submitted to the European Medicines Agency (the Agency) on 3 November 2023 an application for a group of variations requiring assessment for Bluevac BTV.

1.2. Scope of the variation

Variation(s) requested	
F.II.d.2.a	F.II.d.2.a - Change in test procedure for the finished product - Substantial change to, or replacement of, a biological/ immunological/ immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol
G.I.13	G.I.13 - Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine based on a multi-strain dossier.

To change the multi-strain dossier to allow up to two different inactivated bluetongue virus serotypes in the final product (bivalent vaccine) and to replace the current quantification method as a consequence.
To include the use of the current *in vivo* challenge potency and serum neutralisation tests for the bivalent vaccines.

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 and Part 3.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

A group of variations requiring assessment was submitted for different, but related points:

-1. To change the multi-strain dossier to allow up to two different inactivated bluetongue virus serotypes in the final product (bivalent vaccine)

-2. To replace the current quantification method (SLOT-BLOT method) by a specific ELISA method

-3. To introduce the current (*in vivo*) potency and identification tests for bivalent vaccines.

For the first point (change of the multi-strain dossier), it is considered not necessary to perform any further study or to submit any additional documentation to demonstrate that up to two different inactivated bluetongue virus serotypes in the final product are safe and efficacious. Supporting data were already assessed during the procedure EMEA/V/C/000156/II/0010/G. Nonetheless, the final report of a safety study concerning the use of a bivalent vaccine in pregnant cattle is provided and the results presented are considered satisfactory.

As a second point, the applicant proposes to replace the quantification test, currently performed by SLOT-BLOT immunoassay, with a specific quantitative double antibody sandwich ELISA.

The proposed ELISA method is claimed to specifically recognise the respective VP2 antigens of the different BTV serotypes possibly included in batches of monovalent or bivalent Bluevac BTV (BTV1, BTV4 or BTV8), and therefore allowing to differentiate between BTV serotypes in bivalent BTV vaccines.

Data on the validation of the test method itself, independent from its use for testing Bluevac BTV, are provided.

The fitness for purpose of the proposed ELISA test for routine antigen quantification, as an in-process test to support consistency of production, in monovalent or bivalent production batches of Bluevac BTV for each serotype, is considered demonstrated.

The parameters analysed in the studies were sensitivity, specificity, repeatability, intermediate precision, linearity, range and robustness (ruggedness), for testing of routine antigen batches of Bluevac BTV monovalent or bivalent vaccines. The parameters are generally considered suitable and the results comply with the acceptance criteria as indicated before the study start. Complete raw data and their relevant statistical analyses are provided. As an in-process control, to support consistency of production, the ELISA is considered satisfactory validated for its purpose to quantify antigen in monovalent and bivalent antigen batches of Bluevac BTV containing BTV1, BTV4 and BTV8.

The applicant proposes to perform the antigen quantification by ELISA at the stage of mono- or bivalent antigen bulk sand before final blending/formulation, as it was done with the formerly applied SLOT-BLOT method. This proposal is accepted as an in-process control to support consistency of production considering that it is supported by satisfactory validation data. The fitness for purpose of the ELISA for testing antigen quantity in mono- or bivalent antigen bulks of Bluevac BTV is therefore demonstrated.

Currently the potency of the vaccine is determined on the monovalent finished product, i.e. on the filled vaccine, by an *in vivo* potency test in sheep. For bivalent vaccines, a potency test is now proposed based on the same potency test as for monovalent vaccines. However, considering the 3Rs principle, as well as the European directives and regulations on animal welfare, the replacement of this *in vivo* method for potency testing with an adequately validated *in vitro* test and any effort in this regard concerning the development of an *in vitro* potency test is strongly encouraged.

In summary, the fitness for purpose of the proposed ELISA test for antigen quantification is considered demonstrated.

Identity testing and determination of potency is performed on the final product, i.e. on monovalent and bivalent vaccines, by introducing the use of the *in vivo* potency test (in sheep) and the identity test (serum neutralisation test) also for bivalent vaccines.

The final data provided for the safety study on administration of a bivalent Bluevac BTV to pregnant cattle are satisfactory.

3. Benefit-risk assessment of the proposed change

Bluevac BTV is a suspension for injection for cattle and sheep.

It can contain one of the following inactivated bluetongue virus serotypes:

Inactivated bluetongue virus, serotype 1 (BTV-1), strain BTV-1/ALG/2006/01 ≥ 22.60 µg/ml

Inactivated bluetongue virus, serotype 4 (BTV-4), strain BTV-4/SPA-1/2004 ≥ 2.55 µg/ml

Inactivated bluetongue virus, serotype 8 (BTV-8), strain BTV8/BEL/2006/01 ≥ 55.80 µg/ml

Depending on the serotype included in the vaccine, the vaccine can provide active immunisation of sheep to prevent the viraemia caused by bluetongue virus serotype 1 or 4 or 8 and to reduce clinical signs caused by bluetongue virus serotype 8. In cattle, it is intended for active immunisation to prevent viraemia caused by bluetongue virus serotype 1 or 4 or 8.

The proposed variation is to change the multi-strain dossier to allow up to two different inactivated bluetongue virus serotypes in the final product (bivalent vaccine). Consequently, the current quantification method needs to be replaced, as it cannot distinguish between two different serotypes.
The applicant wishes to replace the current antigen quantification method (SLOT Blot) by an *in vitro* ELISA method and to introduce the use of the *in vivo* potency test (in sheep) and the identity test (serum neutralisation test) for bivalent vaccines.

3.1. Benefit assessment

Direct therapeutic benefit

Bluevac BTV is an inactivated vaccine against bluetongue virus (BTV) consisting of one virus strain out of a set of three virus strains belonging to the BTV serotypes BTV1, BTV4 and BTV8. This BTV vaccine is intended as a multi-strain product produced within the context of a multi-strain dossier.

The benefit of a multi-strain dossier is to maintain only one dossier with a range of BTV vaccine strains of different serotypes, produced based on individual characteristics of each strain, but also the same relevant information for all of them. This procedure allows the selection of the relevant BTV strain/s depending on the respective disease situation, manufacturing a specific vaccine and thus allowing the vaccination with one or two serotypes (as maximum) with only one assessment/procedure.

This approach improves vaccine availability, makes it easier to respond to the situation in the field and gives the possibility of adding other relevant 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 to secure the possibility to rapidly and frequently change the virus strains contained in the vaccines. The BTV strains included are relevant to the current epidemiological situation of bluetongue disease in the European Union (EU).

Well conducted controlled preclinical and clinical trials demonstrated that the product is safe and

efficacious.
A prevention of viremia is supported for serotypes 1, 4 and 8 in sheep and in cattle, whereas for serotype 8 a reduction of clinical signs in sheep only is supported. An onset of immunity of 21 days in sheep for all strains with duration of immunity for 1 year is supported. An onset of 28 days for serotype 1, 21 days for serotype 4 and 31 days for serotype 8 in cattle with duration of immunity for 1 year is supported.

Additional benefits

A change of the multi-strain dossier to allow up to two different inactivated bluetongue virus serotypes in the final product (bivalent vaccine) means that corresponding vaccines that contain this/these strain(s) can be quickly produced in the event of an outbreak of bluetongue disease in the EU caused by the specific BTV serotype(s). This is considered an additional benefit. Furthermore, the ability to mix different combinations of strains may increase the flexibility to react to respective emergency situations.

Quality

Information on the development, manufacture and control of the active substances and finished products has been presented in a satisfactory manner.

Safety

Safety (user, consumer, environmental, target animal) remains unaffected by this variation.

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. The final report of a safety study concerning the use of a bivalent vaccine in pregnant cattle is now provided for completion, the adverse events observed were no worse than that described in the current SPC.

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.

Risk for the user:

Risk for the user remains unaffected by the 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.

3.2. Risk management or mitigation measures

The proposed changes should not impact 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 0 days.

3.3. Evaluation of the benefit-risk balance

The benefit-risk balance remains unaffected by this variation.

4. Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Bluevac BTV can be approved since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows:

- F.II.d.2.a - Change in test procedure for the finished product - Substantial change to, or replacement of, a biological/ immunological/ immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol.

- G.I.13 - Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine based on a multi-strain dossier.

Changes are required in the following Annexes to the Union marketing authorisation.

I, IIIA and IIIB

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

Because of these variations, sections 2, 4.2, and 4.9 of the SPC are updated. The corresponding sections of the package leaflet and labelling are updated accordingly.