15 January 2025
EMA/20601/2025
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Bluevac-3 (EMEA/V/C/006575/0000)

Vaccine common name: Bluetongue virus vaccine (inactivated)

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

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Introduction

The applicant CZ Vaccines S.A.U. submitted on 30 September 2024 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Bluevac-3, through the centralised procedure under Article 42(2)(c) of Regulation (EU) 2019/6 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 18 April 2024 as Bluevac-3 contains an active substance which has not been authorised as a veterinary medicinal product within the Union at the date of the submission of the application (Article 42(2)(c)).

At the time of submission, the applicant applied for the following indications:

Sheep

For active immunisation of sheep to reduce the viraemia, preventing mortality and to reduce clinical signs caused by the serotype 3 of the bluetongue virus.

Onset of immunity: 21 days after completion of the primary vaccination scheme.

Duration of immunity: not established.

Cattle

For active immunisation of cattle to reduce the viraemia against the serotype 3 of the bluetongue virus.

Onset of immunity: 21 days after completion of the primary vaccination scheme.

Duration of immunity: not established.

The active substance of Bluevac-3 is inactivated bluetongue virus, serotype 3, strain BTV-3/NET2023 intended to stimulate the active immunity of sheep and cattle against bluetongue virus serotype 3. The target species are cattle and sheep.

Bluevac-3 suspension for injection contains $10^{6.5}$ $CCID_{50}$ (50% cell culture infective dose equivalent to titre prior inactivation) bluetongue virus, serotype 3, strain BTV-3/NET2023 per ml and is presented in packs of one bottle containing 52, 100 or 252 ml.

The rapporteur appointed is Esther Werner and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances.

For the assessment of this procedure, an accelerated timetable was applied for by the applicant and agreed by the CVMP. In fact, the benefit of the immediate availability on the market of a veterinary medicinal product against BTV serotype 3, currently circulating in the European Union (EU), was recognised by the CVMP.

This vaccine is being used in some countries of the European Union under Article 110 of Regulation (EU) 2019/6. The manufacturing process follows the one of already authorised vaccines against bluetongue belonging to the multi-strain dossier of Bluevac BTV. The same starting materials are also well-known substances used in authorised vaccines.

On 15 January 2025, the CVMP adopted an opinion and CVMP assessment report.

On 20 February 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Bluevac-3.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF), has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

Manufacture and quality control of the active substance inactivated bluetongue virus, serotype 3, strain BTV-3/NET2023 takes place at CZ Vaccines S.A.U., Spain.

A certificate confirming compliance with the principles of GMP for the active substances is provided, issued by the Competent Authority of the Autonomous Community of Galicia in Spain. The GMP certificate is also available in EudraGMDP.

Finished product

Manufacture, quality control, primary packaging, secondary packaging and batch release of the finished product take place at CZ Vaccines S.A.U., A Relva s/n -Torneiros, O Porriño, Pontevedra, Spain.

The site has a manufacturing authorisation that was issued by the Competent Authority of Spain, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).

A GMP certificate is also provided, issued by the Competent Authority of the Autonomous Community of Galicia in Spain. The GMP certificate is also available in EudraGMDP.

Secondary packaging can also be carried out at two additional sites and Good Manufacturing Practice (GMP) certificates covering the appropriate activities were presented.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements. The GMP status of the active substances and of the finished product manufacturing sites have been established and are in line with legal requirements.

Part 2 - Quality

The vaccine benefits from the reduced data requirements intended for applications in exceptional circumstances under Article 25 of Regulation (EU) 2019/6 and the "Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021).

The applicant provided data from other bluetongue vaccines already authorised (including those from the multi-strain dossier of Bluevac BTV) to support the quality of Bluevac-3. This is considered

acceptable and this data fills some of the data gaps identified by the CVMP.

Quality documentation (physico-chemical, biological, and microbiological information)

Qualitative and quantitative composition

The finished product is presented as a suspension for injection containing inactivated Bluetongue virus of serotype 3 as active ingredient. Quil A (purified saponin) and aluminium hydroxide are added as adjuvants. The vaccine contains thiomersal as preservative.

Other excipients include phosphate-buffered saline (potassium phosphate, disodium phosphate, sodium chloride and water for injections) as described in section 2 of the SPC.

Container and closure system

Bluevac-3 is available in multi-dose presentations of high-density polyethylene (HDPE) bottles of 52, 100 or 252 ml, closed with perforable stoppers made of butyl rubber and sealed with aluminium caps. The bottles are each packed in a cardboard box as described in section 5.4 of the SPC.

The pack sizes are consistent with the dosage regimen and duration of use.

The containers and closures are identical to the ones used in the authorised bluetongue vaccines associated to the multi-strain dossier of Bluevac BTV.

Product development

Following the reported outbreaks of Bluetongue virus serotype 3 in sheep and cattle across Europe and the lack of authorised vaccines within the Union market at the time of submission, the urgent need to develop suitable products to control the disease was recognised. Thus, in these exceptional circumstances related to animal or public health, an application under Article 25 of Regulation (EU) 2019/6 is submitted. It is in fact acknowledged that the benefit of the immediate availability on the market of the veterinary medicinal product outweighs the risk inherent to the fact that certain quality, safety or efficacy documentation has not been provided.

An explanation and justification for the composition and available presentations of the vaccine has been provided.

The BTV strain used as active ingredient was isolated from a sample of sheep blood collected in The Netherlands in 2023. The RNA extracted from the sheep blood was sequenced by next generation sequencing (NGS) and identified as BTV of the serotype 3. Using this isolate and based in a seed-lot system, the Master and Working seed were prepared and characterised.

The vaccine formulation is based on the pre-inactivation titre of the strain, which is established at a concentration of $10^{6.5}$ $CCID_{50}$/ml. Thus, each batch of the vaccine is formulated with a fixed antigen input titre.

The BTV-3 strain is propagated in BHK21 cells (permanent Baby Hamster Kidney cell line). This cell line is well-known and successfully used for other authorised European vaccines. The BTV-3 is inactivated by using binary ethylene imine (BEI). Aluminium hydroxide and Quil A (purified saponin) are added as adjuvants. Furthermore, the vaccine, filled in multi-dose bottles, contains thiomersal as preservative.

The inactivating agent, the adjuvants and the preservative are well known materials used in other vaccines production.

The formulation of batches used during clinical studies is the same as that intended for marketing.

Description of the manufacturing method

The manufacturing process consists of four main steps: (1) Preparation of bluetongue serotype 3 virus, (2) Vaccine formulation and bulk preparation, (3) Preparation of finished product and (4) Labelling and boxing.

BHK-21 cells used as host system and the BTV-3 virus used as active ingredient (vaccine antigen) are handled in seed-lot systems using master and working seeds.

For mass cultivation, the vaccine virus is propagated in BHK-21 cells. After clarification, the virus is inactivated using BEI. Thereafter, the inactivated virus is purified and concentrated, and the BEI is neutralised using sodium thiosulphate. The vaccine bulk is prepared by blending the inactivated virus with the other components (e.g. aluminium hydroxide, Quil A, thiomersal) to a vaccine suspension. For preparation of the finished product, the vaccine bulk is filled into sterile bottles which are then closed with rubber stoppers and aluminium caps, labelled and stored.

Full inactivation has been demonstrated, and the inactivation step has been validated.

The production process is considered to be a standard manufacturing process. In general, the essential parts of the production process are described in comprehensible manner. Compared to the manufacturing process description for authorised bluetongue vaccines associated to the multi-strain dossier and to which the applicant refers, certain information is missing for different production steps and parameters. Generally, a more detailed description would be expected in the dossier for an application under Art. 8 of Regulation (EU) 2019/6. However, in exceptional circumstances, the description provided is considered sufficient and further clarifications and details are considered data gaps acceptable under an Art. 25 of Regulation (EU) 2019/6 authorisation.

Production and control of starting materials

Specifications of the active ingredient and starting materials are defined and the analytical methods to which the applicant refers are provided. Generally, in exceptional circumstances, sufficient information is provided with regard to the starting materials which are also used in the currently approved multi-strain dossier of Bluevac BTV.

The starting materials of biological origin comply with the 'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathies agents via human and veterinary medicinal products' (EMEA/410/01-Rev02). The overall TSE risk associated with the inactivated vaccine has been assessed and is considered negligible.

Starting materials listed in pharmacopoeias

A description of the function and certificates of analysis (CoAs) have been provided for the substances listed in pharmacopoeias. They all conform to relevant Ph. Eur. and USP monograph requirements. When relevant, Certificates of suitability and additional information in compliance with chapter 5.2.5 "Management of extraneous agents in immunological veterinary medicinal products" of the European Pharmacopeia have been provided.

These substances are well-known and used also in the already authorised multi-strain dossier of Bluevac BTV.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

All starting materials of animal origin used during the production of the vaccine, i.e. BHK-21 cell line, Bluetongue virus, serotype 3 (BTV-3), the adult and foetal bovine sera as well as the bovine serum albumin, comply with the Ph. Eur. Monograph 5.2.8 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" and the TSE Note for Guidance (EMEA/410/01 Rev.3). The master seed materials for the BTV-3 antigen are in line with the "Position Paper on the assessment of the risk of transmission of animal spongiform encephalopathy agents via master seed materials used in the production of veterinary vaccines" (EMEA/CVMP/019/01).

Valid TSE certificates of suitability for the adult bovine serum and the foetal bovine serum from the stated manufacturers are provided.

Additional information in compliance with chapter 5.2.5 "Management of extraneous agents in immunological veterinary medicinal products" of the European Pharmacopeia has been provided.

The cell line BHK-21 is known and also used in the currently approved multi-strain dossier of Bluevac BTV containing other BTV serotypes.

Starting materials of non-biological origin

For starting materials of non-biological origin, not listed in a pharmacopoeia, information regarding preparation, treatment before use, and storage condition were presented. In general, sufficient information is provided.

In-house preparation of media and solutions consisting of several components

Information regarding the qualitative and quantitative composition of all culture media and solutions, their treatment processes and their storage conditions is provided in the dossier. All components are either tested for or treated to ensure that there are no contaminants, or further assurance is given that there is no potential risk.

Control tests during the manufacturing process

During the manufacture of the antigen the following tests are carried out: sterility and purity at intermediate stages, cell count at intermediate stages, CPE observation, virus titration at intermediate stages, virus identity, inactivation control test, and determination of residual sodium thiosulphate. Test descriptions and the limits of acceptance are presented. Relevant in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing. Tests were thoroughly validated, where applicable, or the test validations were extrapolated from Bluevac BTV as the tests are the same.

Control tests on the finished product

Information concerning the control tests on the finished product (antigen batch, adjuvant mixture, vaccine bulk, finished product) is presented. The description of the methods used for the control of the finished product and the specifications are provided, and, where applicable, the test validations were extrapolated from Bluevac BTV as the tests are the same.

1) General characteristics of the finished product

Appearance, pH and the product presentation are determined either on the antigen batch, the vaccine bulk or on samples of each finished product batch. The vaccine should be a white or pinkish-white aqueous suspension that settles, leaving a clear supernatant and whitish sediment.

2) Identification of the active substance(s)

The antigen is identified by BTV-3 specific RT-qPCR performed on each inactivated antigen batch to confirm that the vaccine contains the correct serotype.

3) Batch titre or potency

The batch potency test is performed on each finished product batch. It is a challenge test conducted in sheep. The test method described is considered sufficient to control the finished product regarding potency and generally considered adequate to ensure the quality of the finished product. This control test corresponds to that included in the multi-strain dossier of Bluevac BTV vaccines containing other BTV serotypes and thus the test validation provided may be extrapolated to Bluevac-3.

The vaccine complies with the test if the vaccinated animals show a statistically significant reduction of viraemia and the controls are not protected. However, no further information nor concrete batch examples are given. Furthermore, in the batch protocols presented in the dossier for batch-to-batch consistency the viraemia results are not, as mentioned, attached to emphasise this pass criterion.

Furthermore, the applicant is strongly encouraged to re-consider the final batch testing methodology and to develop an *in vitro* potency test in line with 3Rs recommendations.

4) Identification and assay of adjuvants

The content of both adjuvant components (Quil A and aluminium hydroxide) is determined in the vaccine bulk and finished product batch. The test methods are sufficiently described and can be considered suitable for its purpose. The control tests correspond to those included in the multi-strain dossier of Bluevac BTV vaccines containing other BTV serotypes and thus the test validations may be extrapolated to Bluevac-3.

5) Identification and assay of excipient components

The thiomersal content in the vaccine bulk is determined on the vaccine bulk. The test method is sufficiently described and can be considered suitable for its purpose. The control test corresponds to that included in the multi-strain dossier of Bluevac BTV vaccines containing other BTV serotypes and thus the corresponding test validation may be extrapolated to Bluevac-3.

6) Sterility and purity tests

Sterility is tested according to Ph. Eur. Monograph 2.6.1 on the vaccine bulk and each finished product batch. The test method is sufficiently described and can be considered suitable for its purpose. The control test corresponds to that included in the multi-strain dossier of Bluevac BTV vaccines containing other BTV serotypes and thus the corresponding test validation may be extrapolated to Bluevac-3.

7) Filling volume

Filling volume is tested on each finished product (filled product batch).

Generally, for an application in exceptional circumstances, sufficient information is provided with regard to the control tests on the finished product (antigen batch, adjuvant mixture, vaccine bulk, finished product). These tests correspond in principle to those from the currently approved multi-strain dossier of Bluevac BTV and are acceptable in view of the data requirements for the given product under an Article 25 authorisation.

Batch-to-batch consistency

In-process data are presented for two consecutive BTV-3 antigen bulks. In addition, finished product data for four consecutive final product batches are provided.

The results confirm the specifications.

Stability

A study on stability of the active substance (i.e. BTV-3 antigen) on three antigen batches is initiated and will be completed. Preliminary time point results are provided. In the meantime, the antigen shelf life may be extrapolated from antigens of other BTV serotypes included in the multi-strain dossier of Bluevac BTV having been produced in a similar way. Corresponding results concerning a storage at 2–8 °C for 24 months before blending are provided. However, considering the shelf life of BTV-8 antigen (10.5 months) the stability of the BTV-3 antigen is set at 12 months. The applicant is requested to provide the data post-authorisation, as a specific obligation (SOB).

A real time study on stability of the finished product is initiated and will be completed. Preliminary results of two batches are given for the time point of batch release (day 0). The applicant is requested to provide the data post-authorisation, as a SOB. In the meantime, the shelf life of vaccine batches may be extrapolated from the multi-strain dossier of Bluevac BTV, vaccine containing other BTV serotypes but having the same composition in adjuvants and excipients. Corresponding results concerning a storage at 2–8 °C for 24 months are provided. However, considering the shelf life of formulations with BTV-1 antigen the shelf life of Bluevac-3 is set at 18 months. The applicant is requested to provide the data post-authorisation, as a specific obligation (SOB).

Information on preservative efficacy has not been submitted. Nevertheless, this may be extrapolated from the multi-strain dossier of Bluevac BTV, a vaccine containing other BTV serotypes but having the same composition and manufacturing process.

Data to support the 10 hours in-use stability after first broaching the container are not presented. However, the in-use shelf life may be extrapolated from the multi-strain dossier of Bluevac BTV. Corresponding reports are provided.

New active substance (NAS) status

The applicant requested the active substance inactivated bluetongue virus, serotype 3, strain BTV-3/NET2023 contained in Bluevac-3 to be considered a new active substance as it is novel and not hitherto authorised in a veterinary medicinal product in the European Union. Based on the review of the data provided, the CVMP considered that the active substance inactivated bluetongue virus, serotype 3, strain BTV-3/NET2023 contained in the veterinary medicinal product Bluevac-3 is not to be qualified as a new active substance considering that another vaccine which contains inactivated bluetongue virus,

serotype 3 was granted a marketing authorisation in the EU in October 2024.

Overall conclusions on quality

The assessment of the quality of Bluevac-3 is carried out according to Annex II of Regulation (EU) 2019/6 and considering the "Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021).

In general, information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The manufacturing process including appropriate in-process controls and quality controls on the finished product are described in sufficient detail to give confidence that the manufacture will yield a consistent, good quality immunological product.

The documentation concerning the steps describing the production process, process parameters and control tests (e.g. SOP), missing information is noticed compared with the manufacturing processes for other Bluevac vaccines containing other BTV serotypes and included in the multi-strain dossier to which the applicant refers. However, this is acceptable in view of the reduced data requirements for the given product under an Article 25 authorisation.

Concerning the antigen stability, the initiated study needs to be completed for antigen batches up to 27 months to fully justify the proposed shelf life. The applicant is requested to provide the data post-authorisation, as a SOB that the applicant will need to fulfil by November 2026.

Concerning vaccine stability, the real time studies for at least three batches of all presentations need to be completed up to 27 months to fully justify the proposed shelf life. The applicant is requested to provide the data post-authorisation, as a SOB.

The proposed 10-hour in-use shelf life is considered supported.

The applicant is strongly encouraged to re-consider the final batch testing methodology and to develop an *in vitro* potency test in line with 3Rs recommendations. Thus, as a recommendation, the applicant is requested to inform about progress with the *in vitro* test at the time of re-examination.

Based on the review of the data on quality, the manufacture and control of Bluevac-3 are considered acceptable in view of an Article 25 authorisation. The data provided were considered sufficient to conclude on the benefit risk balance of the product. Some specific obligations to supplement the data presented in Part 2 were identified.

Part 3 – Safety documentation (safety and residues tests)

General requirements

Bluevac-3 is a monovalent vaccine containing inactivated bluetongue virus, serotype 3, strain BTV-3/NET2023 adjuvanted with aluminium hydroxide and Quil A. The vaccine also contains thiomersal as preservative. The following excipients are present in the vaccine: phosphate-buffered saline, potassium dihydrogen phosphate, disodium phosphate anhydrous, sodium chloride and water for injections.

As per the initial suggested indications, Bluevac-3 is intended for subcutaneous immunisation of sheep and cattle from 2 months of age onwards to reduce viraemia against serotype 3 of the bluetongue virus. In sheep, the vaccine is also indicated to prevent mortality and to reduce clinical signs caused by

serotype 3 of the bluetongue virus.

Bluevac-3 is formulated with an antigen quantity of $10^{6.5}$ 50% cell culture infective dose ($CCID_{50}$) and can be given as stand-alone vaccine. The vaccine is filled in high density polyethylene (HDPE) bottles containing 52, 100 or 252 ml.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances. A full safety file in accordance with Article 8(1)(b) has not been provided. However, first data are presented from combined safety/efficacy study in lambs and calves vaccinated with two doses of the vaccine Bluevac-3. Clinical data are not provided yet and this is in line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances.

Safety documentation

The main safety-relevant SPC claims initially submitted were:

3.5 Special precautions for use

Special precautions for use in target species:

Not applicable.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Sheep:

Very common (>1 animal / 10 animals treated):	Injection site nodule[1]
Common (1 to 10 animals / 100 animals treated):	Hyperthermia[2]
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Loss of appetite Hypersensitivity reaction

[1]A painless nodule of 3.5 cm which decreases progressively over time and normally disappears within 14 days.
[2]A transient increase in rectal temperature not exceeding 1 ºC is common. It lasts not longer than 24 to 72 hours.

Cattle:

Very common (>1 animal / 10 animals treated):	Injection site nodule[1]
Rare (1 to 10 animals / 10,000 animals treated)	Hyperthermia
Very rare (< 1 animals / 10,000 animals treated, including isolated reports)	Loss of appetite Hypersensitivity reaction

[1]A painless nodule of 0.5 to 9 cm which decreases progressively over time and normally disappears within 21 days.

3.7 Use during pregnancy, lactation or lay

Pregnancy:

Can be used during pregnancy in ewes and cows.

Lactation:

No negative impact on the milk-yield using the vaccine in lactating ewes and cows is expected.

Fertility:

The safety and efficacy of the vaccine have not been established in breeding males (sheep and cattle). In this category of animals, the vaccine should be used only according to the benefit-risk assessment by the responsible veterinarian and/or National Competent Authorities on the current vaccination policies against bluetongue virus (BTV).

3.8 Interaction with other medicinal products and other forms of interaction

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case-by-case basis.

3.9 Administration routes and dosage

For subcutaneous use.

Primary vaccination

Sheep from 2 months of age:
Administer two doses of 2 ml subcutaneously 3 weeks apart.

Cattle from 2 month of age:
Administer two doses of 4 ml subcutaneously 3 weeks apart.

Revaccination

Not established.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

After the administration of a double dose, no adverse reactions other than those described in section 3.6 were observed.

5.1 Major incompatibilities

Do not mix with any other veterinary medicinal product.

Batches used in the safety studies:

All batches used in the safety studies were manufactured in accordance with part II.B of the dossier. Standard batches can be used for the safety studies (no maximum potency batch required), according to the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances (EMA/CVMP/IWP/251947/2021). Two standard batches and three "pilot batches" with a low, medium and high BTV-3 antigen titre were used in the safety studies. A total of five different batches was used in the submitted pre-clinical safety studies for Bluevac-3. The manufacturing batch protocols for the two standard batches representative for production are provided in part II.F of the dossier.

Safety studies performed:

The safety studies were carried out in the target species, cattle and sheep, at the minimum age of 2 months. In total, two pivotal and Ph. Eur. Monograph 5.2.6 compliant pre-clinical studies, one in sheep and one in cattle are provided. These pre-clinical studies were designed to include safety and efficacy data. Moreover, one additional dose-effect pre-clinical study in sheep is presented. This dose-response study did not fully comply with Ph. Eur. Monograph 5.2.6 requirements (availability of results of at least 8 treated animals is required), as only the results of 5 animals per group were available. Furthermore, a number of supporting pre-clinical studies carried out with the range of other BTV vaccines manufactured by the applicant, containing the serotypes BTV1, BTV4 and BTV8 within a monovalent or bivalent vaccine were included.

Two supportive clinical safety trials conducted with other vaccines of the Bluevac range containing the serotypes BTV1 and BTV8 (monovalent or bivalent) manufactured by the applicant, in which the safety under field conditions is supported were submitted. In addition, the final report on sperm function in sheep after the administration of Bluevac BTV1+8 is provided.

Vaccinations were performed in accordance with the proposed vaccination schedule and administration route (sheep: subcutaneous two doses application three weeks apart of 2 x 2 ml from 2 months of age; cattle: subcutaneous two doses application three weeks apart of 2 x 4 ml from 2 months of age).

According to Ph. Eur. Monograph 5.2.6, no overdose/double dose tests have been done, as Bluevac-3 is not a live vaccine.

With regards to guideline EMA/CVMP/IWP/251947/2021, the examination of reproductive and lactating performance shall be carried out due to the expected large use of this type of vaccine. Safety studies evaluating the reproductive performance in the target species carried out with other Bluevac vaccines of similar composition (excipients and adjuvants; except serotype) and similar vaccination schedule were submitted.

No specific studies on immunological functions were conducted, as all components of the vaccine are inactivated and no negative effect on the immunological functions is expected.

The vaccine Bluevac-3 is formulated with an antigen quantity of:

- BTV3 antigen $10^{6.5}$ $CCID_{50}$ per 1 ml.

The pre-clinical studies have been conducted in accordance with the GLP requirements.

The clinical trials have been conducted according to the principles of good clinical practice (GCP) and good veterinary practice (GVP).

Study reference	***Study title***
Pre-clinical safety studies	
Sheep	
	Safety, efficacy and OOI of Bluevac-3 in sheep by experimental challenge
Cattle	
	Safety, efficacy and OOI of Bluevac-3 in calves by experimental challenge
Additional pre-clinical safety study[1]	
	Dose-effect response of one single dose of Bluevac-3 in sheep by experimental challenge
Supportive pre-clinical safety studies conducted with other Bluevac vaccines (multi-strain dossier)	
	Safety Study on the administration of Bluevac 4+8 in sheep
	Final Report on Safety study of the administration of Bluevac 4+8 to sheep
	Final Report of dose effect study of Bluevac-4 in lambs
	Final report on dose effect study of Bluevac-1 in sheep
	Final Report – Dose-effect response study on the administration of Bluevac-8 in sheep
	Safety Study on the administration of an overdose and a repeated dose of Bluevac-8 in sheep
	Final Report – Bluevac-8 dose response study in sheep
	Final Report – Dose-effect response study on the administration of Bluevac-8 in sheep
	Safety and Efficacy Study of a single dose and a repeated dose of Bluevac-8 in sheep
	Safety and Efficacy Study on the administration of one single dose of Bluevac-8 to sheep
	Final Report on assessment of duration of the immunity of Bluevac-8 in sheep
	Safety Study on the administration of an overdose and a repeated dose of a bivalent vaccine against Bluetongue serotypes 1 and 4 (Bluevac 1+4) in sheep
	Safety Study on the administration of an overdose and a repeated dose of Bluevac-8 in cattle
	Safety and Efficacy Study on the administration of a single dose and a repeated dose of Bluevac-1 in cattle
	Assessment of the onset of the immunity of Bluevac-4 in cattle
	Safety and Efficacy Study of a single dose and a repeated dose of Bluevac-8 in cattle
	Safety and Efficacy Study on the administration of a single dose (2 mL) and a

	repeated dose (2 mL) of Bluevac-8 in cattle
	Safety study on the administration for Bluevac 4+8 in cattle
	Safety Study on the administration of an overdose of Bluevac-8 in pregnant ewes
	Safety study on the administration of Bluevac-1 to pregnant ewes
	Safety study on the administration of Bluevac-4 to pregnant ewes
	Final report on effect of Bluevac 1+8 administration on sperm function
	Safety and Efficacy study on the administration of a single dose and a repeated dose of Bluevac-8 in pregnant ewes
	Safety Follow-Up Report on the administration of Bluevac-1 in pregnant cows
	Safety study on the administration of Bluevac-4 to pregnant bovine females
	Safety study on the administration of Bluevac 1+8 in pregnant bovine at the third trimester of pregnancy
	Safety study on the administration of Bluevac 4+8 in pregnant bovine at the first trimester of pregnancy
Supportive clinical safety trials	
	Final report on safety in sheep of Bluevac 1+8 under field conditions
	Final report on effect of Bluevac 1+8 administration on sperm function
	Final report on safety in sheep of Bluevac 1+8 under field conditions

[1]Dose-response study was not fully Ph. Eur. Monograph 5.2.6-compliant and is therefore seen as additional study.

Pre-clinical studies

The safety of a single and a repeated dose in 2-month-old sheep and cattle was evaluated in two pivotal studies (one for each category of target animals). The design of these studies allows to evaluate both, the safety of the administration of a single dose and of a repeated dose.

Furthermore, an additional study evaluating the dose-response effect in sheep was presented. However, this study did not fully comply with the requirements of Ph. Eur. Monograph 5.2.6 (availability of results of at least 8 treated animals), as only the results of 5 animals per group are available and is therefore considered as additional study.

Moreover, the safety of Bluevac-3 is also supported by data obtained from other vaccines of the Bluevac range containing the serotypes BTV1, BTV4 and BTV8 (monovalent or bivalent) manufactured by the applicant. A tabulated overview is presented in section III.A. T

Safety of the administration of one dose

Safety in two-month-old lambs:

The safety of a single vaccination in lambs was evaluated in 16 BTV and Epizootic Haemorrhagic Disease virus (EHDV) seronegative lambs (8 vaccinated animals and 8 PBS controls) at the age of 8 weeks (±5 days) using a standard batch. Prior to vaccination, the general health status of the animals was observed and the rectal temperature recorded. Furthermore, all lambs were seronegative for BTV and EHDV. 1 x 2 ml of the vaccine and 1 x 2 ml of PBS, respectively, were administered subcutaneously into the left side of the neck.
The follow-up included individual clinical observation two hours after vaccination to 14 days post vaccination using a scoring system and clinical observation of the group daily from the day before administration until the end of the study (3 weeks post vaccination; revaccination). The rectal temperature was measured two and one day before vaccination, just before vaccination, four hours after vaccination and daily until 7 days post vaccination. Systemic reactions were recorded as soon as they occurred, and any shock symptom was monitored during the first 2 hours after each vaccination. Injection site assessment including palpation was done prior to and two and four hours after vaccination to 14 days post vaccination. An additional record was done on day 21 post vaccination using a scoring system. Postmortem macroscopic and microscopic examination of the injection sites were only conducted in case of macroscopic abnormalities.

The results show that no clinical abnormalities were observed during the 14-day observation period after vaccination. No lamb showed notable signs of disease or died to causes attributable to the vaccine. There was a minor and transient increase in rectal temperature at 4 hours post vaccination (mean increase of 0.35 °C ± 0.38). However, 3 out of 8 vaccinated animals exhibited rectal temperatures exceeding 40 °C with a maximum individual temperature increase of 0.9 °C. These three lambs returned to their physiological temperature levels within 24 hours. The injection site assessment revealed transient small swellings in 62.5% vaccinated lambs during one to nine days post primary vaccination (1-3 cm; max. size 3.5 cm at 4-5 days post vaccination (p.v.)). These swellings transformed into vaccine nodules. They were not painful and persisted up to 10 days post primary vaccination. No local reactions were observed at 11 days post first dose of the vaccine.

These results are supported by the data generated in an additional dose-response effect safety study. This study was conducted to show that the subcutaneous administration of one dose of Bluevac-3 in three different antigen quantity formulations (low, medium, high) is safe in 8-week-old (±5 days) lambs. The results revealed that all test vaccines demonstrated an acceptable safety profile in two-month-old lambs after subcutaneous administration of a single dose, regardless its quantitative BTV3 antigen composition. The results show that no clinical abnormalities were observed during the 14-day observation period after vaccination. No lamb showed notable signs of disease or died to causes attributable to the vaccine. A minor and transient temperature increase at 4 hours p.v. was observed in the GV1 (low) group (mean increase of 0.41 °C ±0.15). At 24-48 hours p.v., all vaccinated animals returned to their physiological temperature levels. There was no dose-effect response on the rectal temperature observed. Up to 80% (low), 40% (medium) and 60% (high) of the vaccinated lambs exhibited transient swellings (1-3 cm) from 7 to 13 days after the vaccination. These swellings also transformed into vaccine nodules (1-3 cm). By day 14 p.v., these lesions tended to resolve, and none were painful.

Safety in two-month-old calves:

The safety of a single vaccination in calves was evaluated in 16 BTV and EHDV seronegative calves (8 vaccinated animals and 8 PBS controls) at the age of 8 weeks (±5 days) using a standard batch. Prior to vaccination, the general health status of the animals was observed and the rectal temperature recorded.

Furthermore, all calves were seronegative for BTV and EHDV. 1 x 4 ml of the vaccine and 1 x 4 ml of PBS, respectively, were administered subcutaneously into the left side of the neck.
The follow-up included individual clinical observation two hours after vaccination to 14 days post vaccination using a scoring system and clinical observation of the group daily from the day before administration until the end of the study (3 weeks post vaccination; revaccination). The rectal temperature was measured two and one day before vaccination, just before vaccination, four hours after vaccination and daily until 7 days post vaccination. Systemic reactions were recorded as soon as they occurred, and any shock symptom was monitored during the first 2 hours after each vaccination. Injection site assessment including palpation was done prior to and two and four hours after vaccination to 14 days post vaccination. An additional record was done on day 21 post vaccination using a scoring system. Postmortem macroscopic and microscopic examination of the injection sites were only conducted in case of macroscopic abnormalities.

The results show that no clinical abnormalities were observed during the 14-day observation period after vaccination. No calf showed notable signs of disease or died to causes attributable to the vaccine. No relevant increase in rectal temperature in vaccinates were noted. However, all vaccinated calves showed increased rectal temperature values 24 hours post primary vaccination (mean increase of 0.13 °C ±0.47). Nevertheless, all vaccinated calves remained below the pyrexia limit (≥40.0 °C). The maximum individual increase in calves was 0.91 °C, which returned to normal values within 24 hours. Another vaccinated animal exhibited rectal temperatures exceeding 40 °C on days 3 and 5 p.v. and returned to physiological temperature levels after 24 hours. The injection site assessment revealed transient swellings in 88% vaccinated calves during one to six days post primary vaccination (≥ 3 cm; exact lesions sizes only available after the second dose). These swellings transformed into vaccine nodules, which peaked in 100% vaccinates during 9 to 14 days p.v. (diameter: 1-3 cm). They were not painful and persisted up to 21 days post primary vaccination and tended to resolve thereafter. No local reactions were observed in 88% of vaccinated calves at 21 days post first dose of the vaccine.

Safety of one administration of an overdose

No overdose studies are required for inactivated vaccines. Therefore, the design for the pre-clinical safety studies followed the recommended two-dose vaccination scheme.

Safety of the repeated administration of one dose

Safety in two-month-old lambs:

The safety of a repeated administration of one dose in lambs was evaluated in 16 BTV and EHDV seronegative lambs (8 vaccinated animals and 8 PBS controls) at the age of 8 weeks (±5 days) using a standard batch (see also above - Safety of the administration of one dose).

The results show that no clinical abnormalities were observed during the 14-day observation period after revaccination. No lamb showed notable signs of disease or died to causes attributable to the vaccine. There was a mild and temporary increase in rectal temperature at 4 hours post vaccination (0.05 °C ±0.25; 3 vaccinates ≥40.0 °C) and none of the vaccinated lambs showed pyrexia at 4 hours p.v. The mean temperature in vaccinated animals was statistically significantly higher than in the control lambs (mean values; Whisker: Mean±95% confidence interval). A minor temperature elevation on day 3 post vaccination was observed in 1 out of 8 vaccinated animals, which returned 5 days p.v. to normal physiological temperature levels. The maximum individual increase in this lamb was 0.9 °C 4 days after repeated dose administration but returned to normal within 48 hours. As the onset of pyrexia started on day 3 post repeated dose application, however, it was not possible to determine whether the elevated rectal temperatures are related to the vaccination process. The injection site assessment revealed

transient small swellings in 100% vaccinated lambs during 4 hours to 13 days p.v. revaccination. These swellings transformed into vaccine nodules (1-3 cm; max. size 4 cm at 9-10 days p.v.). They were not painful and persisted up to 13 to 14 days post repeated dose administration. No local reactions were observed at 21 days post-second dose of the vaccine.

Safety in two-month-old calves:

The safety of a repeated vaccination in calves was evaluated in 16 BTV and EHDV seronegative calves (8 vaccinated animals and 8 PBS controls) at the age of 8 weeks (±5 days) using a standard batch (see also above - Safety of the administration of one dose).

The results show that no clinical abnormalities were observed during the 14-day observation period after vaccination. After administering the second vaccine dose, a statistically significant but transient body temperature increase in all vaccinated animals could be observed 24 and 48 hours post vaccination (0.43 °C ±0.23, 24 hours p.v.; Whisker: Mean±95% confidence interval). However, none of the vaccinated animals showed pyrexia (≥40.0 °C). The maximum individual increase in calves was 0.78 °C, which returned within 24 hours to normal physiological temperature levels. The injection site assessment revealed transient swellings in 100% vaccinated calves three to four days after revaccination (3-9 cm). These swellings transformed into vaccine nodules, which peaked in 100% vaccinates during 6 to 8 days p.v., and gradually decreased thereafter. However, small nodules (1.4 and 2.4 cm) were still detectable in 75% of vaccinates 21 days after the revaccination event. None of the reported local reactions were painful.

Examination of reproductive performance

The Bluevac-3 vaccine is also intended for use in pregnant and lactating sheep and cattle. Considering guideline EMA/CVMP/IWP/251947/2021, the examination of reproductive and lactating performance shall be carried out due to the expected large use of this type of vaccine.

The safety of the reproductive performance in the target species was investigated in pre-clinical studies carried out using other Bluevac vaccines of similar composition (excipients and adjuvants; except serotype) and similar vaccination schedule. These data show no relevant differences with regard to the different fertility parameters between test and control groups; therefore, it can be concluded that the Bluevac-3 vaccine is safe for use during pregnancy and lactation in the target species sheep and cattle.

Examination of immunological functions

No further studies were conducted to investigate the effects of the product on immunological functions, but no adverse effects were observed in any of the safety or efficacy studies. It is therefore unlikely that this vaccine will have an adverse effect on immunological functions due to the nature of the product (inactivated vaccine).

User safety

Hazard identification and characterisation have been adequately performed in accordance with CVMP 'Guideline on user safety for immunological veterinary medicinal products' (EMEA/CVMP/IWP/54533/2006).

Bluevac-3 is an inactivated vaccine containing inactivated bluetongue virus, serotype 3, strain BTV-3/NET2023. The vaccine is adjuvanted with aluminium hydroxide and Quil A and also contains thiomersal as preservative. The following excipients are present in the vaccine: phosphate-buffered saline, potassium phosphate, disodium phosphate, sodium chloride and water for injections.

Bluetongue virus is not a zoonotic organism and does not infect humans.

The active substance is an inactivated bluetongue virus antigen and therefore not infectious. For inactivation, binary ethylenimine (BEI) is used. The inactivation of the production virus is verified for each antigen batch produced. Excess ethylenimine is neutralised by adding an excess amount of sodium thiosulfate. An in-process control is performed to check that an excess amount of sodium thiosulfate is actually added.

All excipients, thiomersal and the adjuvant components aluminium hydroxide and Quil A are considered to be safe for the user because they are either mentioned in Table 1 of the Annex to Commission Regulation 37/2010 as requiring no MRL or are considered as not falling within the scope of Regulation (EC) No 470/2009 (please see section III.B.8.). Aluminium hydroxide is well known to induce local or systemic reactions as a result of accidental injection and an appropriate warning is included in the SPC. Quil A is a saponin preparation and has been used as adjuvant for more than 30 years in veterinary vaccines. The preservative thiomersal contains mercury and the user could be exposed to a maximum quantity of 200 µg mercury and 12 mg of aluminium in one dose for cattle of 4 ml as worst-case scenario.

The vaccine is administered subcutaneously commonly using an automatic syringe. The vaccine bottle is inserted into the automatic syringe, and the animals are subsequently vaccinated.

There is the potential risk that the user is exposed to the vaccine during handling of the vaccine bottle (skin contact) or as the result of accidental self-administration. The consequences of skin exposure to this inactivated vaccine are negligible. The vaccine is filled in HDPE bottles, and this container does not break easily by accident and improves therefore user safety. The common practice is to use an automatic syringe, which reduces handling time and improves user safety, and avoids accidental self-administration. In addition, vaccination is performed by trained professionals. Risks associated through the elimination of waste material are considered by the corresponding advice in the SPC.

Based on the above risk assessment, the CVMP concludes that the product does not pose an unacceptable risk to the user when used in accordance with the SPC. The main risk is derived from accidental self-injection.

The following warning is included in section 3.5 of the SPC: "In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician."

Study of residues

Bluevac-3 is an inactivated vaccine for active immunisation of sheep and cattle against bluetongue virus, serotype 3. The vaccine is adjuvanted with aluminium hydroxide and Quil A and contains thiomersal as preservative. The following excipients are present in the vaccine: phosphate-buffered saline, potassium dihydrogen phosphate, disodium phosphate anhydrous, sodium chloride and water for injections.

For inactivation of the BTV-3 virus antigen, BEI is used. Excess ethylenimine is neutralised by adding an excess amount of sodium thiosulfate. An in-process control is performed to verify that an excess amount of sodium thiosulfate is actually added. The possibilities of virus replication in the inoculated animal and distribution into tissues intended for human consumption are negligible.

All components used to manufacture the vaccine, have been considered by the CVMP as being safe for the consumer based on the fact that they either do not require a numerical maximum residue limit as set out in Commission Regulation (EU) 37/2010 or are considered as not falling within the scope of Regulation (EC) No 470/2009. None of the vaccine components is contained in a concentration that is

pharmacologically active or may be a risk to human health.

Withdrawal period

A withdrawal period is not required, and it is therefore set at zero days.

Interactions

The applicant has not provided data investigating interactions of the vaccine with any other veterinary medicinal product and therefore proposes to include a statement in Section 3.8 of the SPC that "No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case-by-case basis."

Furthermore, the applicant proposes to include a statement in Section 5.1 of the SPC that "Do not mix with any other veterinary medicinal product."

The CVMP agrees with these proposals.

Clinical studies

Two supportive clinical trials were provided to explore the safety in the target species under field conditions (sheep; sheep & cattle: German field trial). The clinical safety trials have been carried out according to the principles of Good Clinical Practice (GCP) and Good Veterinary Practice (GVP). In these two field trials the safety of other Bluevac vaccines manufactured by the applicant was thoroughly investigated under field situation. These other Bluevac vaccines present the same qualitative and quantitative composition as the intended Bluevac-3 vaccine but contain the bluetongue virus serotypes 1 and 8 within a monovalent or bivalent combination, and, therefore, could be used as data to support the safety of Bluevac-3 under field conditions. In addition, the final report on sperm function in sheep after the administration of Bluevac BTV1+8 is provided.

Note: These supportive field trials are already presented in the multi-strain dossier of Bluevac BTV containing other BTV serotypes and are already assessed.

Final report on safety in sheep of Bluevac BTV1+8 under field conditions

A sufficient number of animals were vaccinated according to the information stated in the SPC, using a standard batch manufactured in accordance with part II of the dossier. Certain adverse events occurred during this field study; the safety of a bivalent vaccine of Bluevac BTV containing the maximum amount of antigen (exceeded the maximum antigen amount in this study) in sheep under field conditions can be considered safe.

Field Trial in Germany- Final Report on the study to assess the safety of inactivated BTV-8 vaccines in cattle and sheep

A sufficient number of animals (298 cattle, 257 sheep) were vaccinated with Bluevac BTV8 according to the information stated in the SPC, using a standard batch manufactured in accordance with part II of the dossier.

Cattle:
The vaccine was well tolerated by the cattle and only a slight increase of the rectal temperatures for a short time and a few local reactions (swellings up to 2 cm diameter) were observed. These swellings

did not persist and disappeared within a few days. No reduction in milk yield was observed. No serious vaccine incidents or abortions in any of the groups were noted.

Sheep:
On both farms, the vaccine was well tolerated and no abnormalities were observed. The increases of the rectal temperatures (no significant change) and the local reactions (swelling/redness) fell within the expected range. The swellings after vaccine injection did not persist. Local vaccine reactions were observed in adult sheep less frequently than in young animals.

Overall, as no considerable number of adverse events occurred during this field study, the safety of Bluevac-3 in sheep and cattle under field conditions can be considered safe.

Final report on effect of Bluevac BTV1+8 administration on sperm function

Sperm from seven Merino rams that were vaccinated with a single dose of Bluevac BTV1+8 and 10 control animals were analysed for 59 different parameters. This study found significant changes in sperm quality in one out of 59 analysed parameters in animals which were vaccinated with Bluevac BTV1+8.
However, a conclusion on fertility was not drawn as only semen samples were analysed; nevertheless, sperm quality of function was not significantly altered, judging by the changes observed in the sperm; it is considered unlikely that fertility was impaired by the vaccination.

Overall, the above field data are derived from vaccines of similar composition (adjuvants, excipients), formulation, manufacturing and primary packaging and could therefore, be used as supportive data to support the safety of Bluevac-3 under field conditions.

A summary of pharmacovigilance data concerning Bluevac-3 from the use in a small number of EU member states (under Article 110(2)) and in the UK were provided. These data were gathered between May and November 2024 during which approximately 11.6 million doses were administrated to sheep and cattle.

In sheep, no relevant signals were detected during the reporting period.

Concerning cattle, a number of adverse events were reported and comprised both safety and lack of expected efficacy (LEE). The most commonly reported VeDDRA terms were milk drop/ milk production decrease, hyperthermia, abortion, premature parturition, and oedema. All VeDDRA terms were reported as 'very rare'. In the proposed SPC, the applicant suggests including the VeDDRA term 'milk drop/ milk production decrease' as a very rare adverse event in the ADR table for cattle, which is consistent with the incidence calculated based on the pharmacovigilance data presented (0.00281; equates 1 animal affected out of 33,943 animals treated). However, the applicant's proposal is not accepted by the CVMP, as the presented submitted pharmacovigilance documentation of field use under article 110(2) gives no causality if the suspected adverse event 'milk drop/ milk production decrease' is an effect of vaccination or is related to other causes. The applicant is requested to specifically monitor and evaluate the effects on milk production in cattle and to provide these pharmacovigilance data post-authorisation, as a specific obligation (SOB).

Considering the cumulated data from all safety studies provided in the initial submission and variations for Bluevac BTV (multi-strain dossier), it can be concluded that the administration of the monovalent BTV3 vaccine can be considered as safe in seronegative sheep and cattle of the youngest recommended age under field conditions. Moreover, current pharmacovigilance data provide reasonable reassurance that when Bluevac-3 is used in accordance with the SPC, the safety profile is similar to that of the authorised multi-strain vaccine.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) has been provided, taking into account any potential risk of the vaccine for the environment. Furthermore, it is described in detail how potential risks can be minimised.

The vaccine is an adjuvanted inactivated vaccine containing bluetongue virus, serotype 3 and excipients. Aluminium hydroxide and purified saponin (Quil A) are used as adjuvants. Thiomersal is included as preservative. Potential hazards for the environment such as incompletely inactivated antigen used for production or the spread of incompletely inactivated antigen have been considered.

Since the product is used in sheep and cattle and administered subcutaneously by professionals, direct exposure of the environment to the product is considered to be negligible. Nevertheless, any unused product or waste should be disposed of in accordance with the national requirements. As the vaccine is inactivated, excretion of any of the components or their metabolites by vaccinated animals, if this occurs at all, will only occur in very small amounts and does not pose any risk to the environment.

Based on the data provided, the ERA can stop at Phase I. Bluevac-3 is not expected to pose a risk to the environment when used according to the SPC.

Overall conclusions on the safety documentation

A full safety file in accordance with Article 8(1)(b) has not been provided. However, the safety of a single and repeated dose of Bluevac-3 in seronegative sheep and cattle of the youngest recommended age was evaluated in the dossier. No clinical data are provided yet and this is in line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances.

Safety in two-month-old lambs:

- The use of the product in two-month-old lambs is safe.
- Maximal mean group temperature increases 4 hours p.v. of 0.35 °C ±0.38 (primary dose) and 0.05 °C ±0.25 (secondary dose) with a maximum of 0.9 °C 4 hours p.v. (primary dose) and 0.9 °C 4 days p.v. (secondary dose) was commonly observed in individual lambs. Temperatures returned to normal within 24 to 72 hours.
- No clinical abnormalities attributable to the vaccine were seen.
- Injection site assessment showed very commonly local reactions in 62.5% (first dose) and 100% (secondary dose) of all vaccinated lambs. These lesions were non-painful swellings with a maximum size of 3.5 from 5 to 6 days post vaccination (first dose) and 4 cm from 9 to 10 days after secondary dose and tended to evolve into nodules. The local reactions disappeared within 11 to 14 days post vaccination.
- The above results are also supported by data obtained and presented from other vaccines of the Bluevac range containing the serotypes BTV1, BTV4 and BTV8 (monovalent or bivalent combination) manufactured by the applicant. In these other pre-clinical studies, no increase in body temperatures were observed and only transitory local reactions were observed in a few sheep.

Safety in two-month-old calves:

- The use of the product in two-month-old calves is safe.
- Maximal mean group temperature increases 24 hours p.v. of 0.13 °C ±0.47 (primary dose) and 0.43 °C±0.23 (secondary dose) with a maximum of 0.91 °C 24 hours p.v. (primary dose) and 0.78

°C 24 hours p.v. (secondary dose) was rarely observed in individual calves. Temperatures returned to normal within 24 hours.
- No clinical abnormalities attributable to the vaccine were seen.
- Injection site assessment showed very commonly local reactions in 88% (first dose) and 100% (secondary dose) of all vaccinated calves. These lesions were non-painful swellings with a maximum size of 3-9 cm from 1 to 6 days post first dose and 3 to 6 days post-secondary dose and tended to evolve into nodules, which peaked between days 3 to 5 (first dose) and between 6 to 8 post vaccination (secondary dose). These local reactions disappeared gradually. However, 12% of primary vaccinated calves and 75% of repeated vaccinated calves showed still detectable lesions (1.4 – 2.4 cm) 21 days post vaccination.
- The above results are also supported by data obtained and presented from other vaccines of the Bluevac range containing the serotypes BTV1, BTV4 and BTV8 (monovalent or bivalent combination) manufactured by the applicant. In these other pre-clinical studies, no increase in body temperatures were observed and only transitory local reactions were observed in a few calves.

Safety in pregnant and lactating sheep and cattle:

- According to (EMA/CVMP/IWP/251947/2021), the examination of reproductive and lactating performance shall be carried out due to the expected large use of this type of vaccine
- The safety of the reproductive performance in the target species was investigated in supportive pre-clinical studies carried out using other Bluevac vaccines of similar composition (excipients and adjuvants; except serotype) and similar vaccination schedule.
- No relevant differences with regard to the different fertility parameters between test and control groups were observed in these supportive studies.
- It can be concluded that Bluevac-3 vaccine is safe for use during pregnancy and lactation in the target species sheep and cattle.

Safety after mixed use and associated non-mixed use:

- No data investigating interactions of Bluevac-3 with any other veterinary medicinal product has been submitted.
- A statement in Section 3.8 of the SPC is included advising that "No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case-by-case basis."
- Furthermore, a statement in Section 5.1 of the SPC is included: "Do not mix with any other veterinary medicinal product."

Immunological functions/user safety/residues/environmental risk assessment:

- None of the components of the vaccine is known to have an immunosuppressive effect and no negative impact on the immune system is to be expected.
- The overall risk to the user is estimated as being very low, and an adequate warning in section 3.5 of the SPC is provided.
- No withdrawal period is necessary, as the candidate product's components are either included in Table 1 of the Annex to Commission Regulation (EU) 37/2010 with a 'No MRL required' provision or are considered as not falling within the scope of Regulation (EC) No 470/2009.
- The overall risk to the environment is estimated as being effectively zero and therefore no Phase II ERA is considered to be necessary.

Bluevac-3 complies with the safety tests as described in Ph. Eur. Monograph 5.2.6 for inactivated vaccines. Animals of the youngest age were used, and the vaccine administration followed the

recommended subcutaneous route. The number of animals per study was adequate for the pre-clinical studies with 8 animals per group in the pre-clinical studies (at least 8 animals are required) and using two groups of at least 8 animals per group. However, in one additional pre-clinical dose response study in sheep, only the results of 5 animals per group were available and this is not fully Ph. Eur. Monograph 5.2.6-compliant, and the study is considered additional. None of the animals developed notable signs of disease or died from causes attributable to the vaccine. The average rectal temperature increases for all animals did not exceed 1.5 °C and, in general, no animal showed a rise in body temperature greater than 2.0 °C.

The data from supportive clinical trials conducted with other Bluevac vaccines of similar composition (adjuvants, excipients), formulation (monovalent or bivalent combination), manufacturing and primary packaging, demonstrated no considerable number of adverse events and the safety of these other Bluevac vaccines in sheep and cattle in the field has been demonstrated. Moreover, pharmacovigilance data from current use of this product under field conditions (article 110(2)) provide reasonable reassurance that the safety profile is similar to that of the authorised multi-strain vaccine, when Bluevac-3 is used in accordance with the SPC. However, as the presented submitted pharmacovigilance documentation of field use under article 110(2) gives no causality if the suspected adverse event 'milk drop/ milk production decrease' is an effect of vaccination or is related to other causes, the applicant is requested to specifically monitor and evaluate the effects on milk production in cattle and to provide these pharmacovigilance data post-authorisation, as a specific obligation (SOB).

Considering the cumulated data, it can be concluded that the administration of the monovalent Bluevac-3 vaccine can be considered also safe in seronegative sheep and cattle of the youngest recommended age under field conditions.

All findings are considered acceptable from a safety point of view and the safety in the target species sheep and cattle is supported.

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)

General requirements

Bluevac-3 is a monovalent vaccine containing inactivated bluetongue virus, serotype 3, strain BTV-3/NET2023 adjuvanted with aluminium hydroxide and Quil A. The vaccine also contains thiomersal as preservative. The following excipients are present in the vaccine: phosphate-buffered saline, potassium dihydrogen phosphate, disodium phosphate anhydrous, sodium chloride and water for injections.

The initially submitted indications were that Bluevac-3 is intended for subcutaneous immunisation of sheep and cattle from 2 months of age onwards to reduce viraemia against serotype 3 of the bluetongue virus. In sheep, the vaccine is also indicated to prevent mortality and to reduce clinical signs caused by serotype 3 of the bluetongue virus.

Bluevac-3 is formulated with an antigen quantity of $10^{6.5}$ 50% cell culture infective dose ($CCID_{50}$) and can be given as stand-alone vaccine. The vaccine is filled in HDPE bottles containing 52, 100 or 252 ml.

The dossier has been submitted in line with the requirements for submissions under Article 25 of Regulation (EU) 2019/6 – application in exceptional circumstances. A full efficacy file in accordance with Article 8(1)(b) has not been provided. However, data on dose-response and onset of immunity for the target species sheep and cattle respectively from combined safety/ efficacy study in lambs and calves

vaccinated with two doses of the vaccine Bluevac-3 are provided. No data on duration of immunity are provided yet. This is in line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances.

Challenge model

The challenge was conducted in the target species at the minimal recommended age to meet the requirements for efficacy assessment as described in Ph. Eur. 5.2.7.

Specific information regarding the development of the challenge model has not been provided but the challenge doses and administration are well explained in the challenge studies conducted in the target species and information on the characterization of the challenge strain has been included, which is considered sufficient. For both target species, the challenge was carried out using the same BTV3 virus strain as the one used in the production of the vaccine (BTV3/Neth/2023). However, given the framework of the procedure and the current epidemiological situation in the EU, this issue will not be pursued further.

Efficacy parameters and tests

The investigated efficacy parameters as chosen by the applicant were:

- Humoral response measured by ELISA (IgG)
- Viraemia measured in cycle threshold (Ct) value in blood samples after challenge
- Clinical signs scores in vaccinates and controls after challenge
- Humoral response measured by ELISA after challenge

The parameters chosen are considered appropriate for evaluating efficacy parameters.

Before and after challenge, blood samples were taken and clinical signs indicative for disease in the animals as well as body temperature were recorded.

Blood samples were tested for viraemia by RT-qPCR and for humoral immune response by ELISA. Furthermore, daily clinical scores (d.c.s.) and a summatory global clinical score (g.c.s.) for the individual days were calculated. Clinical signs were scored from 0 to 3.
Daily clinical score was added up from the clinical score, fever score and dead score.

All test methods used for the studies were satisfactorily validated to provide reliable results.

Efficacy documentation

Sheep	
Safety, efficacy and OOI of BLUEVAC-3 in sheep by experimental challenge	
Dose-effect response of one single dose of BLUEVAC-3 in sheep by experimental challenge	
Cattle	
Safety, efficacy and OOI of BLUEVAC-3 in cattle by experimental challenge	

Three pre-clinical studies were conducted to investigate the efficacy of the product. No clinical trials were provided.
Laboratory studies were well documented and carried out in target animals of the minimum age recommended for vaccination using production batches produced as described in the dossier.

Pre-clinical studies

Dose determination

Study report

In the dose-response study, twenty 8-week old lambs, seronegative for BTV were randomly allocated to 4 groups of 5 animals. Each treatment group received 2 ml of the test product with a different antigen concentration (low, medium, high) subcutaneously in the left side of the neck. The control group received 2 ml of PBS instead.

21 days after the vaccination all groups were challenged with a virulent strain of BTV3 subcutaneously in the axillar region. Before and after challenge, blood samples were taken and clinical signs indicative for disease in the animals as well as body temperature were recorded.

In summary, vaccinated lambs displayed fewer and less severe clinical signs compared to controls and the mean Ct values were higher. In the treatment group with the highest antigen concentration fewer animals showed pyrexia and the overall body temperature increase was less pronounced.
In this group, in 3/5 lambs viraemia was prevented. ELISA results also showed a dose-response effect.

From these results the applicant concluded that the highest antigen concentration tested in the study is recommended for a single dose vaccination scheme in sheep. The CVMP agrees with this conclusion.

The provided study is well designed, seronegative animals from the target species and of the youngest age to be vaccinated were used. Methods applied and scores used are satisfactory and fit for purpose. A statistical analysis of the data is provided. A dose-response effect depending on the antigen content of the vaccine was demonstrated.

In the study, animals were vaccinated only once, and the highest antigen concentration achieved the best results. However, the applicant chose the lowest antigen concentration tested and opted for a vaccination scheme of two doses 21 days apart instead of a single vaccination based on the findings of the following described study.

Onset of immunity

Study report

For the study on efficacy and onset of immunity in sheep 16 lambs seronegative for BTV and of the youngest recommended age to be vaccinated were randomly allocated to two groups of 8 animals.

Vaccinates were injected with 2ml of the test item Bluevac-3 with $10^{6.5}$ $CCID_{50}$/ml and controls were injected with 2ml PBS subcutaneously in the left side of the neck 21 days apart.

21 days after the second vaccination all groups were challenged with a virulent strain of BTV3 subcutaneously in the axillar region.

Vaccinated animals showed a statistically significant reduction in viraemia (as measured by Ct values) from D4 to D14 (end of study) compared to controls. Viraemia in vaccinated animals was reduced more than 10 times compared to control animals, as calculated by the respective Ct values.

In the control group, clinical signs were overall more severe compared to vaccinates and on D14 one control animal died and another was found moribund.

Statistical comparison of daily and global clinical scores demonstrated a significant difference between controls and vaccinates with reduced disease severity in vaccinated animals.

Mean body temperatures in the control group were statistically significantly higher on D9 post infection (p.i).

After vaccination ELISA anti-VP7 antibody titre in vaccinated group increased progressively from 21 days after the first dose to 21 days after the second dose. 6/8 animals tested positive. Mean titres in vaccinated group were significantly higher than in the control group, all control animals remained negative.

Post challenge all vaccinated lambs tested positive. 6/8 control animals tested positive on D14 post challenge. Mean titre was significantly lower in the control group, which demonstrates a specific humoral immune response.

The provided study is well designed, seronegative animals from the target species and of the youngest age to be vaccinated were used. Methods applied and scores used are satisfactory and fit for purpose.

A statistical analysis of the data is provided. Results of 8 animals per group were used for evaluation as required by Ph. Eur. The study is considered valid.

In summary, the study demonstrates an onset of immunity of 21 days in sheep after two doses of Bluevac-3, 21 days apart, for reduction of viraemia, reduction of clinical signs and reduction of mortality in sheep.

Study report

For the study on efficacy and onset of immunity in cattle 16 calves seronegative for BTV and of the youngest recommended age to be vaccinated, were randomly allocated to two groups of 8 animals.

Vaccinates were injected with 4 ml of the test item Bluevac-3 with $10^{6.5}$ $CCID_{50}$/ml subcutaneously in the left side of the neck. The control group received 4 ml PBS instead.

21 days after the second vaccination all groups were challenged with a virulent strain of BTV-3 administered by intravenous route in the jugular vein. Before and after challenge, blood samples were taken and clinical signs indicative for disease in the animals as well as body temperature were recorded.

Blood samples were tested for viraemia by RT-PCR and for humoral immune response by ELISA. Furthermore, daily clinical scores (d.c.s.) and a summatory global clinical score (g.c.s.) for the individual days were calculated.

In both groups viraemia progressively increased from D2 to D7 with a peak on D7 then decreasing from D10 to D14. A statistically significant reduction for viraemia in vaccinated animals was demonstrated on D2 to D5 and D12 to D14. Viraemia in vaccinated animals was reduced nearly 10 times compared to control animals.

During the study, predominantly mild clinical signs were observed after challenge. One vaccinated calf displayed moderate respiratory signs (dyspnoea and cough) from day 7 p.i. but showed improvement after 3 days of antibiotic treatment; it was therefore concluded that this was due to a bacterial co-infection.

Due to the overall lack of clinical signs, the statistical assessment of the clinical scores showed no

significant differences in both daily clinical scores (d.c.s.) and cumulated scores (g.c.s.) between treatment groups.

In both groups, rectal temperature peaked on day 7 p.i. Several animals showed pyrexia.
Mean temperatures in vaccinated and control animals were not statistically significantly different at any time point after challenge.

Post vaccination, mean ELISA titres in vaccinates was statistically significantly higher than in control animals. All control animals remained negative up to the challenge. This demonstrates the induction of a specific immune response in vaccinated calves.

Post challenge 8/8 vaccinated animals tested positive in the ELISA.

2/7 control animals tested positive on D14 of the study. Mean titres observed in control animals were significantly lower than in vaccinates.

The provided study is well designed, seronegative animals from the target species and of the youngest age to be vaccinated were used. Methods applied and scores used are satisfactory and fit for purpose.

A statistical analysis of the data is provided. Results of 8 animals per group were used for evaluation as required by Ph. Eur. The study is considered valid.

In summary, the study demonstrates an onset of immunity of 21 days in cattle after two doses of Bluevac-3, 21 days apart, for reduction of viraemia in cattle.

Duration of immunity

No data on duration of immunity of Bluevac-3 are provided yet.
However, the applicant is requested to conduct a study on duration of immunity in sheep and cattle and to provide corresponding data as soon as available, as a specific obligation (SOB).

Maternally derived antibodies (MDA)

This is an authorisation application after Article 25 on exceptional circumstances, therefore no data on the influence of maternal antibodies on the efficacy of the vaccine is provided.

Interactions

Not applicable.

Clinical trials

No clinical trial data on efficacy for Bluevac-3 is provided. This is in line with (EMA/CVMP/IWP/251947/2021) which mentions that clinical trials are not required.

Overall conclusion on efficacy

The applicant provided three studies concerning efficacy of Bluevac-3.

One dose-response study to establish the antigen amount necessary for efficacy in the target species after one dose.

Furthermore, two studies for onset of immunity in the target species sheep and cattle respectively with a vaccine scheme of two doses three weeks apart. No studies on duration of immunity are provided. This is in line with the Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances.

For the study on efficacy and onset of immunity in sheep 16 lambs seronegative for BTV and of the youngest recommended age to be vaccinated were randomly allocated to two groups of 8 animals.

Vaccinates were injected with 2 ml of the test item Bluevac-3 with $10^{6.5}$ $CCID_{50}$/ml and controls were injected with 2 ml PBS subcutaneously in the left side of the neck 21 days apart.

21 days after the second vaccination all groups were challenged with a virulent strain of BTV3 subcutaneously in the axillar region.

Vaccinated animals showed a statistically significant reduction in viraemia (as measured by Ct values) from D4 to D14 (end of study) compared to controls. Viraemia in vaccinated animals was reduced more than 10 times compared to control animals, as calculated by the respective Ct values.

In the control group clinical signs were overall more severe compared to vaccinates and on D14 one control animal died and another was found moribund.

Statistical comparison of daily and global clinical scores demonstrated a significant difference between controls and vaccinates with reduced disease severity in vaccinated animals.

In both groups body temperature peaked on D7 p.i. with several animals showing pyrexia.
Mean body temperatures in the control group were statistically significantly higher on D9 p.i.

After vaccination ELISA anti-VP7 antibody titre in GV1 increased progressively from 21 days after the first dose to 21 days after the second dose. 6/8 animals tested positive. Mean titres in GV1 were significantly higher than in the control group, all control animals remained negative.
Post challenge all vaccinated lambs tested positive. 6/8 control animals tested positive on D14 post challenge. Mean titre was significantly lower in the control group, which demonstrates a specific humoral immune response.

From these results it can be concluded that an onset of immunity of 21 days in sheep after completing the primary vaccination course (two doses in a 21-day interval) can be established.

The provided study is well designed, seronegative animals from the target species and of the youngest age to be vaccinated were used. Methods applied and scores used are satisfactory and fit for purpose. A statistical analysis of the data is provided. Results of 8 animals per group were used for evaluation as required by Ph. Eur. The study is considered valid.

In summary, the study demonstrates an onset of immunity of 21 days in sheep after two doses of Bluevac-3, 21 days apart, for reduction of viraemia, reduction of clinical signs and reduction of mortality in sheep.

For the study on efficacy and onset of immunity in cattle 16 calves seronegative for BTV and of the youngest recommended age to be vaccinated, were randomly allocated to two groups of 8 animals. Vaccinates were injected with 4 ml of the test item Bluevac-3 with $10^{6.5}$ $CCID_{50}$/ml subcutaneously in the left side of the neck. The control group received 4 ml PBS instead.

21 days after the second vaccination all groups were challenged with a virulent strain of BTV3 administered by intravenous route in the jugular vein. Before and after challenge, blood samples were taken and clinical signs indicative for disease in the animals as well as body temperature were recorded. Blood samples were tested for viraemia by RT-PCR and for humoral immune response by ELISA.

Furthermore, daily clinical scores (d.c.s.) and a summatory global clinical score (g.c.s.) for the individual days were calculated.

In both groups viraemia progressively increased from D2 to D7 with a peak on D7 then decreasing from D10 to D14. A statistically significant reduction for viraemia in vaccinated animals was demonstrated on D2 to D5 and D12 to D14. Viraemia in vaccinated animals was reduced nearly 10 times compared to control animals.

During the study, predominantly mild clinical signs were observed after challenge. One vaccinated calf displayed moderate respiratory signs (dyspnoea and cough) from day 7 p.i. but showed improvement after 3 days of antibiotic treatment it was therefore concluded that this was due to a bacterial co-infection.

Due to the overall lack of clinical signs, the statistical assessment of the clinical scores showed no significant differences in both daily clinical scores (d.c.s.) and cumulated scores (g.c.s.) between treatment groups.

In both groups, rectal temperature peaked on day 7 p.i. Several animals showed pyrexia Mean temperatures in vaccinated and control animals were not statistically significantly different at any time point after challenge.

Post vaccination mean ELISA titres in vaccinates was statistically significantly higher than in control animals. All control animals remained negative up to the challenge. This demonstrates the induction of a specific immune response in vaccinated calves.

Post challenge 8/8 vaccinated animals tested positive in the ELISA.
2/7 control animals tested positive on D14 of the study. Mean titres observed in control animals were significantly lower than in vaccinates.

From these results it can be concluded that an onset of immunity of 21 days in cattle after completing the primary vaccination course (two doses in a 21-day interval) can be established.

The provided study is well designed, seronegative animals from the target species and of the youngest age to be vaccinated were used. Methods applied and scores used are satisfactory and fit for purpose. A statistical analysis of the data is provided. Results of 8 animals per group were used for evaluation as required by Ph. Eur. The study is considered valid.

In summary, the study demonstrates an onset of immunity of 21 days in cattle after two doses of Bluevac-3, 21 days apart, for reduction of viraemia in cattle.

Taking into account all the data presented in the dossier, onset of immunity of 21 days in sheep after completing the primary vaccination course (two doses in a 21-day interval) for reduction of viraemia, reduction of mortality and reduction of clinical signs caused by the serotype 3 of the bluetongue virus and onset of immunity of 21 days in cattle after two doses of Bluevac-3, 21 days apart, for reduction of viraemia are considered demonstrated.

As no data on duration of immunity of Bluevac-3 are provided yet, the applicant is requested to conduct a study on duration of immunity in sheep and cattle and to provide corresponding data as soon as available, as a specific obligation (SOB).

Part 5 – Benefit-risk assessment

Introduction

Bluevac-3, suspension for injection for cattle and sheep, is an inactivated vaccine intended to stimulate the active immunity of sheep and cattle against bluetongue virus serotype 3. The active substance is inactivated bluetongue virus, serotype 3, strain BTV-3/NET2023, adjuvanted with aluminium hydroxide and Quil A. The vaccine contains $10^{6.5}$ $CCID_{50}$ (equivalent to titre prior inactivation) bluetongue virus, serotype 3, strain BTV-3/NET2023 per ml and is presented in packs of one bottle containing 52, 100 or 252 ml.

Bluevac-3 can provide active immunisation of sheep to reduce the viraemia, mortality and clinical signs caused by BTV-3. In cattle, it is intended for active immunisation to reduce viraemia caused by BTV-3.

The vaccine is foreseen for a vaccination regime of two doses subcutaneously 3 weeks apart for animals from 2 months of age: 2 ml for sheep and 4 ml for cattle.

The applicant proposed a withdrawal period of zero days.

The application was submitted under Article 25 of Regulation (EU) 2019/6 (exceptional circumstances). Reduced data requirements therefore apply and have been considered in the assessment. These reductions relate to quality, safety and efficacy.

Benefit assessment

Direct benefit

Bluevac-3 is an inactivated vaccine against bluetongue virus (BTV) belonging to BTV serotype 3.

The benefit of Bluevac-3 is the stimulation of active immunity of sheep and cattle against bluetongue virus serotype 3 and its efficacy in the proposed indication, which was investigated in three pre-clinical studies and two supportive clinical trials. However, the supportive clinical trials were conducted with other Bluevac vaccines included in the multi-strain dossier to an acceptable standard.

The onset of immunity is 3 weeks after completion of the primary vaccination scheme. The duration of protection is not established.

Additional benefits

An additional benefit is that Bluevac-3 is a monovalent vaccine that can be administered as stand-alone vaccine.

Risk assessment

The main potential risks are identified as follows:

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner for applications under Article 25 of Regulation (EU) 2019/6. However, some concerns have been identified regarding stability and specific obligations as post-authorisation measures to the marketing authorisation under exceptional circumstances are

established:

- The results of real time stability studies for the vaccine, up to 27 months, should be provided to confirm the 2-year shelf-life claim. Any out of specification detected should be communicated immediately to the European Medicines Agency.
- The results of stability studies for the active substance (BTV-3 antigen), up to 24 months, should be provided to confirm the shelf-life claim. Any out of specification detected should be communicated immediately to the European Medicines Agency.

Safety

Risks for the target animals:

Administration of Bluevac-3 in accordance with SPC recommendations is generally well tolerated.

In sheep of minimum age, a transient increase in rectal temperature and local reactions with a maximum size of 4 cm were observed. After revaccination, these swellings were detected in 100% of all vaccinated animals. The local lesions disappeared 11 to 14 days post vaccination. The vaccine can be safely used as proposed (from the age of two months subcutaneously into the neck and revaccination three weeks apart).

In calves of minimum age, a transient increase in rectal temperature and local reactions with a maximum size of 9 cm were observed. After revaccination, these swellings were detected in 100% of all vaccinated animals. The local lesions disappeared gradually but were still detectable in 12% of vaccinated animals at 21 days post primary dose, and in 75% of vaccinated animals at 21 days after the repeated dose administration. The vaccine can be safely used as proposed (from the age of two months subcutaneously into the neck and secondary dose applied three weeks apart).

The safety of the reproductive performance in both target species was investigated in several supportive pre-clinical studies carried out using other Bluevac vaccines of similar composition (excipients and adjuvants; except serotype) and similar vaccination schedule. No relevant differences with regard to the different fertility parameters between test and control groups were observed. From these supportive studies it can be concluded that Bluevac-3 vaccine is safe for use during pregnancy and lactation in the target species sheep and cattle.

No data investigating interactions of Bluevac-3 with any other veterinary medicinal product has been submitted and an adequate statement in Section 3.8 and Section 5.1 of the SPC is included.

None of the vaccine components is known to have an immunosuppressive effect, therefore, no negative impact on the immune system is to be expected.

A specific obligation as post-authorisation measure to the marketing authorisation under exceptional circumstances is established: In addition to the legal requirements applicable to reporting of adverse reactions, the applicant is required to specifically monitor and evaluate the following suspected adverse events: effects on milk production in cattle.

Risks for the user:

There is the potential risk that the user is exposed to the vaccine during handling of the vaccine bottle (skin contact) or as the result of accidental self-administration (subcutaneous administration). The consequences of skin exposure to this inactivated vaccine are negligible. Accidental self-administration may induce an immune response and lead to some inflammatory reactions. Standard advice associated with accidental self-administration is included in the SPC.

Risks for the environment:

Bluevac-3 is not expected to pose a risk to the environment when used according to the SPC

recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risk of this product relevant to the target animals, user and environment and to provide advice on how to prevent or reduce these risks.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status):

The veterinary medicinal product is subject to a veterinary prescription.

The veterinary medicinal product is authorised for use in exceptional circumstances. Therefore, the vaccine should be used in accordance with the benefit/risk assessment carried out by the responsible veterinarian.

Any person intending to manufacture, import, possess, distribute, sell, supply and use this veterinary medicinal product must first consult the relevant Member State's competent authority on the current vaccination policies, as these activities may be prohibited in a Member State on the whole or part of its territory pursuant to national legislation.

Specific obligations to complete the post-marketing authorisation measures for the marketing authorisation under exceptional circumstances are detailed in Annex II of the product information and mentioned below.

Description	**Due date**
The results of real time stability studies for the vaccine, up to 27 months, should be provided to confirm the 2-year shelf-life claim. Any out of specification detected should be communicated immediately to the European Medicines Agency.	April 2027
The results of stability studies for the active substance (BTV-3 antigen), up to 24 months, should be provided to confirm the shelf-life claim. Any out of specification detected should be communicated immediately to the European Medicines Agency.	November 2026
In addition to the legal requirements applicable to reporting of adverse reactions, the applicant is required to specifically monitor and evaluate the following suspected adverse events: effects on milk production in cattle.	September 2025
A study on duration of immunity in sheep and cattle should be conducted, and data should be provided as soon as available.	January 2027

Post-authorisation recommendation:

The applicant is strongly encouraged to re-consider the final batch testing methodology and to develop an *in vitro* potency test in line with 3Rs recommendations. The applicant is requested to inform about progress with the *in vitro* test at the time of re-examination.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indications:

"Sheep

For active immunisation of sheep to reduce the viraemia, preventing mortality and to reduce clinical signs caused by the serotype 3 of the bluetongue virus.

Onset of immunity: 21 days after completion of the primary vaccination scheme.

Duration of immunity: not established.

Cattle

For active immunisation of cattle to reduce the viraemia against the serotype 3 of the bluetongue virus.

Onset of immunity: 21 days after completion of the primary vaccination scheme.

Duration of immunity: not established yet."

The product has been shown to be efficacious for onset of immunity of 21 days in sheep after completing the primary vaccination course (two doses in a 21-day interval) for reduction of viraemia, mortality and clinical signs caused by the serotype 3 of the bluetongue virus and onset of immunity of 21 days in cattle after two doses of Bluevac-3, 21 days apart, for reduction of viraemia.

The provided information on quality, safety and efficacy of the vaccine is considered sufficient to conclude a positive benefit-risk balance under Article 25. Data gaps have been identified that do not preclude to reach a conclusion of the benefit-risk balance. Specific obligations have been established to be fulfilled post-authorisation.

As the application was submitted under Article 25, certain pivotal data on quality, safety and efficacy were not included in the dossier. The applicant presented a summary of the submitted documentation in an expert report even if formal critical expert reports are not requested for Article 25 applications. Concerning the 'benefit of the immediate availability on the market' of the vaccine, the applicant argued that there is an urgent need to make suitable BTV-3 vaccines available. This is based on the reported outbreaks of BTV-3 in sheep and cattle across Europe and the lack of authorised vaccines within the European Union to control the disease. Thus, an immediate availability of Bluevac-3 will help to solve this animal health problem.

However, the CVMP considered that the overall benefit of the availability of the veterinary medicinal product would outweigh the risk of absence of these data, also taking into consideration the risk management measures addressed above.

The product information has been reviewed, and it is considered to be satisfactory and in line with the assessment.

Conclusion

Based on the original data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Bluevac-3 is approvable since these data satisfy the requirements for an authorisation set out in the legislation in accordance with Article 25 (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned veterinary medicinal product.

In addition, based on the review of data on the quality-related properties of the active substance bluetongue virus, serotype 3, BTV-3/NET2023, inactivated, contained in the veterinary medicinal product Bluevac-3, the CVMP considers that the active substance is not to be qualified as a new active

substance considering that another vaccine which contains inactivated bluetongue virus, serotype 3 was granted a marketing authorisation in the EU in October 2024.