SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

Zulvac 8 Ovis, is a conventionally produced, liquid and ready-to-use, inactivated vaccine, adjuvanted with aluminium hydroxide ($Al(OH)_3$) and saponin. The vaccine is intended for the active immunisation of lambs from 1.5 months of age for the prevention of viraemia caused by bluetongue virus, serotype 8. The active substance of Zulvac 8 Ovis is the inactivated bluetongue virus (BTV) serotype 8.
The benefit of Zulvac 8 Ovis is that it induces an active immunity in lambs against bluetongue virus, serotype 8. The vaccine dose is 2 ml. The basic vaccination schedule consists of one injection given subcutaneously from a minimum of 1.5 months of age followed by a second injection given 3 weeks later. Onset of immunity is 25 days after the completion of the basic vaccination course. The duration of immunity (DoI) has not been fully established yet but interim result support one of at least 6 months. As a consequence, any revaccination scheme should be agreed by the Competent Authority or by the responsible veterinarian, taking into account the local epidemiological situation. The most common side effect is a transient increase in rectal temperature, not exceeding 1.2°C, during the 24 hours following vaccination. Vaccination may be followed in most animals by a local reaction at the injection site. These reactions take the form in most cases of a general swelling of the injection site (persisting for not more than 7 days) or of palpable nodules (subcutaneous granuloma, possibly persisting for more than 48 days).

BTV can cause intense disease outbreaks in sheep. Fever is the most usual but not invariable clinical sign. If fever occurs sheep first become pyrexic 4-10 days after infection. Acute form in sheep is usually characterised by pyrexia up to 42°, depression, emaciation, ulceration of the oral cavity, swollen and sometimes cyanotic tongue, excessive licking movements of the tongue, lameness and abortion. Infection may result in the death of sheep within approximately 8-10 days or in a long recovery period with negative impact on the animals' welfare and growth. Mortality rate in sheep could reach up to 70% in a flock. Over the last ten years, the bluetongue disease situation in the EU has considerably changed with incursions of new serotypes, particularly of serotype 8 into an area of the Community where outbreaks had not been reported before and which was not considered at risk of bluetongue. Outbreaks due to serotype 8 occurred in the Netherlands, in Belgium, Germany, Luxemburg, France and in the UK. It is considered likely that the disease will remain in Europe for the next few years creating an endemic situation.

The dossier was reviewed in line with the provisions of Article 39(7) of Regulation (EC) No 726/2004 for an authorisation under exceptional circumstances and the recommendations of the CVMP Reflection Paper on Minimum Data Requirements for an Authorisation Under Exceptional Circumstances for Vaccines for Emergency Use Against Bluetongue (EMEA/CVMP/ /IWP/105008/2007) which later into the procedure was developed into a guideline (EMEA/CVMP/IWP/220193/2008).

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2. QUALITY ASSESSMENT

COMPOSITION

Composition for dose of 2 ml is provided in the following table.

Names of ingredients		Quantity per 2 ml dose	Function	Reference to standards
Active substance	Inactivated Bluetongue virus (BTVi) serotype 8, strain BEL2006/02	RP* ≥ 1	antigen	In-house monograph
Constituents of the adjuvant				
Aluminum hydroxide		4 mg Al^{3+}	Adjuvant	Eur. Ph. monograph 1664
Saponin		0.4 mg	Adjuvant	In-house monograph
Excipient	Thiomersal	0.2 mg	Preservative	Eur. Ph. monograph 1625
Including				
Component of saline solution	Saline solution	qs 2 ml	Volume adjustment	
	Sodium chloride			Eur.Ph. mn. 193
	Potassium chloride			Eur.Ph. mn. 185
	Disodium phosphate dihydrate			Eur.Ph. mn. 602
	Potassium dihydrogen phosphate			Eur.Ph. mn. 920
	Water for injections			Eur.Ph. mn. 169

*Relative Potency by a mice potency test compared to a reference vaccine that was shown efficacious in lambs.

The blending of vaccine is based on the infection titre ($TCID_{50}$/ml) before inactivation. A batch potency test in mice suitable to discriminate between potent and sub-potent batches of the vaccine was also developed by the Applicant.

Container

The vaccine is filled in 100 ml (corresponding to 50 doses of 2 ml) and 250 ml (corresponding to 120 doses of 2 ml) capacity glass (hydrolytic type II) bottles (complying with Eur. Ph. monograph 3.2.1), closed with a butyl rubber stopper (Eur. Ph 3.2.9) and sealed with an aluminium cap. Tests of compliance with Eur. Ph were provided.

DEVELOPMENT PHARMACEUTICS

A BTV strain was isolated from the blood of an infected sheep during an outbreak of bluetongue in Belgium in 2006 and was used as the active ingredient for the production of Zulvac 8 Ovis. The production is based on virus and cell seed lot systems. Materials used for the production of both active

ingredient and final product as well as relevant manufacturing processes were either classical or conventional ones. The vaccine is filled in multi-dose bottles and for this reason thiomersal is added as preservative. The virus is grown on BHK-21 cells; thereafter, the virus harvest is titrated to determine the number of virus particles per ml capable to infect BHK-21 cells ($TCID_{50}$/ml) and is tested for sterility and identity. Consistency of production should guarantee a minimum titre in antigen yield. The virus suspension is then inactivated and tested for complete inactivation.

A series of preliminary studies was carried out in sheep using experimental batches of a monovalent proprietary vaccine containing a different BTV serotype (e.g. Zulvac 4), in order to determine the optimal quali-quantitative composition regarding adjuvants and antigen concentration. Initial immunogenicity and challenge experiments demonstrated a better performance of BTV4 vaccine antigen adjuvanted with a combination of $Al(OH)_3$ and saponin and provided some evidence for a correlation between the antigen concentration and reduction of viraemia in 2 months old vaccinated sheep. The higher the concentration of antigen, the lower was the viraemia. On the basis of these preliminary findings, some improvements in the manufacturing of the active ingredients were introduced and two concentrations of BTV4 antigen were tested for safety and immunogenicity in the presence of higher concentration of selected adjuvants and in comparison with two oily adjuvants. Challenge experiments were carried out using two different vaccine antigen concentrations and a selection of adjuvants (including $Al(OH)_3$ and saponin) in order to establish the best safety/immunogenicity ratio. Based on the results obtained from this final study, a concentration of vaccine antigen (according to pre-inactivation titre) and a quantity of 4 mg Al^{3+}/dose and 0.4 mg/dose of saponin respectively were selected. The information generated from these experiments was also taken into account for the development of the vaccine under application, as the same process is used for the manufacturing of the vaccine antigen, and the inactivation of BTV8 as for the BTV4 serotype. Also the same adjuvant(s) at the same concentration(s)/ dose were used.

Zulvac 8 Ovis is blended on the basis of the pre-inactivation viral titre of the bulk antigen.
In order to establish the concentration of active ingredient to be used in the formulation of the bulk vaccine, a specific dose-response study was designed to test the safety and immunogenicity (in 1 month old lambs) of the current vaccine at different concentrations of inactivated BTV8 antigen. A minimum antigen concentration (according to the pre-inactivation titre) was selected on the basis of this study taking into account that at this antigen concentration, 100% prevention of viraemia was achieved as well as a satisfactory level of local and systemic safety results. The vaccine is manufactured under GMP conditions, applying established manufacturing processes, using adjuvants and excipients well characterized and widely used for the production of veterinary vaccines. Control tests planned to be carried out during production and on the finished product should further guarantee a consistent quality profile of the vaccine. Regarding the Antimicrobial Preservative Efficacy (APE) the Applicant confirmed that a study is on going in order to demonstrate the efficacy of antimicrobial preservation during the product shelf life. The APE test is scheduled to cover each bottle size. In this study batches are tested for APE at different times after manufacturing.

Composition of the batches used in the clinical trials

Data were only provided from safety and efficacy trials carried out under laboratory conditions. This was acceptable based on the provisions in CVMP Reflection Paper on Minimum Data Requirements for an Authorisation Under Exceptional Circumstances for Vaccines for Emergency Use Against Bluetongue. Overall the relevance of the batches used to support the safety and efficacy studies was satisfactorily supported.

METHOD OF MANUFACTURE

A detailed flow chart of the whole manufacturing process of the vaccine was provided and considered satisfactory. The stages of the manufacturing process were described in sufficient details and all the operations stated to be conducted in conditions of sterility following established methods or sterile manipulation techniques. The process comprises 13 steps starting with the propagation of the working seed virus (WSV) and ending with the preparation of the vaccine in bulk, followed by filling and

packing of the final product. The production system and control guarantees the traceability of each component during the manufacturing process.
More specifically, the virus vaccine is obtained after a number of passages on BHK-21 cells. After harvest the culture is inactivated and the inactivant neutralized at the end of the inactivation process. The bulk vaccine is further produced after blending pre-determined amount of inactivated and neutralized vaccine antigen, thiomersal, saline solution and adjuvants. All calculations of the volumes of the different components were described in sufficient details. These components are sequentially added to obtain the final blend. Two blending processes can be alternatively used by the Applicant. In both processes the same parameters and adjustments are performed to guarantee consistent batches. The equivalence of both processes has been satisfactorily demonstrated.

The filling operation is carried out in a laminar flow cabinet (class A), in class B environment. The filling operation has been validated. Glass bottles are washed and sterilised in validated cycles. Stoppers and seals are sterilized in autoclave in validated cycles.

The packing operation is conducted following a fully automatic process according to approved procedures for the packing of products, in accordance with the specific protocol.

Manufacture of vaccine antigen

Vaccine antigen is grown in BHK-21 cells. Parallel steps are carried out in order to obtain proper amplification of both BHK-21 cells and virus inoculum for the production of the active ingredient.

BHK-21 cell culture
The expansion of the initial cell seed is carried out in order to obtain the amount of cells needed for production. WCS cryotubes are thawed and then inoculated in a culture flask. From these culture flasks, the required subcultures are carried out. During the cell scale up process cultures are observed periodically, and its evolution (confluence), cell morphology and cell passage are recorded. The cell passage is recorded in order to monitor that the final passage used for virus production cannot be more that 20 from the MCS.

Virus growth
A Master Seed Virus (MSV) was constituted on BHK-21 cells, and stored frozen prior to vaccine production, the working seed virus (WSV) is expanded from the MSV into BHK-21 cells and also stored frozen.
In the antigen production process, the virus vaccine will produced from the WSV by passages into BHK-21 cells. Details were provided of optimal culture time triggering a virus harvest. During the antigen production process, samples are taken for titration, sterility and identity controls. Details were provided for all the controls carried out on the final antigen.
The Applicant indicated that the virus vaccine will be maximum a passage 5 from the MSV. The current culture vessels for BTV manufacture were provided. However, depending on future market demand, larger or various sizes may be used.

Manufacture of the inactivated and neutralized vaccine antigen

Final viral suspension is inactivated with BEI. The excess of inactivating agent is neutralised with sodium thiosulphate at the end of the inactivation process. Samples are taken from the inactivated and neutralized antigen to carry out in process controls.
The titre of the antigen before inactivation and the dilution factor that represent the additions in the inactivation and neutralization processes are taken into account in order to provide an indication of the theoretical titre of the inactivated and neutralized antigen. At routine industrial production, the vaccine is formulated to contain a defined amount of non-concentrated virus culture.
Provisions in the CVMP Reflection Paper on Minimum Data Requirements for an Authorisation Under Exceptional Circumstances for Vaccines for Emergency Use Against Bluetongue-EMEA/CVMP/IWP/105008/2007 allow to consider the virus titre before inactivation as appropriate for vaccine formulation.

Manufacture of the finished product

The bulk vaccine is prepared by blending pre-determined amounts of one or a mixture of several batches of inactivated and neutralized BTV-8 antigen with thiomersal, saline solution and adjuvants. The bulk vaccine can be stored at +5.0±3.0°C until the start of the filling operation. Primary packaging elements (bottles and closures) are sterilized by validated cycles. Once filled, bottles of vaccine are submitted to secondary packaging operations which are carried out using a fully automatic process. Finished product is stored at +5.0±3.0°C. The Applicant indicated the size of the antigen ingredient /vaccine batch and that, if necessary, more than one antigen batch may be used for vaccine blending. All the antigen batches used for vaccine bulk preparation must be in compliance with the approved specifications. The last step is the secondary packaging operations. Confirmation of GMP compliance was provided for relevant manufacturer batch protocols.

Validation studies

Validation of the manufacturing process

A number of studies were presented as part of the validation of the manufacturing process.

Inactivation kinetics
Several virus inactivation kinetics studies using batches of non-standard and standard sizes were carried out as part of the validation of the manufacturing process. Studies were GLP compliant and aimed to investigate the inactivation kinetics of BTV serotype 8. Studies using a BTV serotype 4 model were also presented. According to Eur. Ph. requirements, the selected inactivating agent and the inactivation procedure shall be shown, under conditions of manufacture, to be capable to inactivate BTV8 within a time period equivalent to not more than 67% of the duration of the whole inactivation process. Based on the results of these studies the Applicant proposed a maximum pre-inactivation titre which was accepted.

Inactivation control
A GLP compliant study aiming to demonstrate the sensitivity of the inactivation control technique using serotype 8 of BTV was also provided. The limit of detection for BTV8 in the inactivation control is 0.08 $TCID_{50}$.

Conclusions: The Applicant provided evidence for the robustness of antigen production process by demonstrating the consistency in the manufacturing process and in the corresponding results obtained. Relevant data has been reported for 3 Batch Release Protocols from each manufacturing site. The above were considered satisfactory.

PRODUCTION AND CONTROL OF STARTING MATERIALS

STARTING MATERIALS LISTED IN A PHARMACOPOEIA

Starting materials of biological origin

None

Starting materials of non-biological origin

List of materials
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium edetate
Water for injections

Disodium phosphate dodecahydrate
Sodium hydrogen carbonate
Gentamicin sulphate
Aluminum hydroxide
Thiomersal
Sodium hydroxide
Sodium Thiosulphate
Disodium phosphate dehydrate
Hydrochloric acid
Phenol red

The Applicant provided evidence of compliance to all relevant Eur. Ph., and presented updated certificate of analysis (CoA) for the above substances.

STARTING MATERIALS NOT LISTED IN A PHARMACOPOEIA

Starting materials of biological origin

The following starting materials were assessed:

Starting material	Function
BHK-21 cells (clone 13)	Substrate for the replication of BTV-8
BTV serotype 8	Vaccine antigen (active ingredient)
Bovine calf serum (irradiated)	Source of protein for cell substrate
Pancreatic Digest of Casein produced from bovine milk (casein) and enzymes of porcine origin (ingredient of Glasgow MEM)	Glasgow MEM culture medium for BHK-21 cells used for manufacturing BTV8 antigen
Porcine trypsin	Used for the detachment of cells (BHK-21) from culture vessel surface
Saponin	Vaccine adjuvant
Gelatin, dextran (raw material for Microcarriers production)	Microcarriers used as support for BHK-21 cell growth

BHK-21 cells

The BHK-21 cell line is a baby hamster kidney cell line used as substrate for the production of BTV8 vaccine antigen. Once received by the Applicant from the Cell bank of Brussels, the cells underwent a series of passages in monolayer before a Master Cell Stock (MCS) was prepared. Current WCS is stated to have been prepared by performing subcultures from this MCS. MCS and WCS are stored at –196°C in liquid nitrogen. Further details of MCS and WCS were provided in specific studies. According to the Applicant's records, the BHK-21 cell line was derived from the kidneys of five unsexed, 1-day-old hamsters, in March 1961, by I. A. Macpherson and M. G. P. Stoker (Virology 16:147, 1962). Details of the cell passage history before acquisition were not available. At Fort Dodge, the BHK-21 cell line is handled in a seed lot system. Details of the production of current MCS and WSC were provided. Certificates of Analysis and EDQM certificates of the batches of bovine serum used to produce the WCS and the MCS, respectively were provided.
Evidence was provided for the absence of cytogenetic differences between Master Cell Stock –MCS- and passage 20 from MCS. The absence of extraneous agents relevant to bovine and ovine species, and to the species of origin of the cell line (hamster) was tested. According to current EU legislation, the absence of viral contamination was checked by using general (CPE and HA) and specific testing. Moreover, ovine and bovine primary cells such as foetal lamb kidney (FLK) cells and primary bovine embryo kidney cells (PBEK), and continuous cell lines such as VERO (African Green Monkey Kidney) and Madin Darby Bovine Kidney (MDBK)-these cells sensitive to viruses pathogenic to the target species and to pestiviruses were also used to detect cytopathogenic and HA viruses and bovine/ovine specific viruses after the inoculation of MCS and WCS. The results of such a testing,

carried out in order to fulfil the requirements of current EU legislation, were reported and were acceptable.

BTV8 antigen

The vaccine virus strain was isolated from the blood of an infected sheep during an outbreak of BTV in Belgium in 2006 and BTV was confirmed by RT-PCR. A flow chart showing the initial passages which the virus strain underwent after isolation was provided.
Sterility and absence of mycoplasma contamination in the MSV and WSV according to Eur. Ph. was demonstrated. MSV and WSV are stored frozen at a T° lower or equal to –70°C ± 10°C.
The Applicant provided evidence that the MSV is negative to cytopathic viruses, haemadsorbing viruses and that it is free of the following specific agents: Adenovirus, Bornavirus, FMDV, BRSV, Louping ill virus, EHDV, Akabane virus, Rabies Virus, BVDV, BLV, Brucella, Mycobacterium and *Chlamydia.* It was shown that controls on MSV and WSV were conducted according to relevant EU legislation using validated techniques. Concerning the absence of contamination by Rift Valley fever virus, Nairobi sheep disease virus and Ross River Virus the Applicant indicated that as the MSV is not derived from an isolate coming from the relevant countries/continents to these viruses they have not been performed.
Information was also provided that indicated that the BTV 8 strain used in the Zulvac 8 vaccine was isolated from the blood of a 2-year-old Belgian sheep and that before exportation, 3 sheep from the same flock were tested for scrapie, in 2005, 2006 and 2007, and were found negative at each time point testing. The negative TSE status of the farm of the sheep at the origin of the vaccine was also confirmed.

Bovine calf serum*, irradiated*

Bovine calf serum is used as component of cell culture medium. Assurance that the donor animals comply with the regulations concerning TSEs including a certificate of analysis of one batch of bovine calf serum provided by the official supplier and a corresponding EDQM certificate of suitability. Confirmation was provided of the specifications for each batch of bovine serum. Purity tests and γ-irradiation are used as complementary measures to achieve a high security level against potential contamination. Overall the principle adopted for extraneous agents testing was acceptable. The validation of the irradiation method was provided.

Pancreatic Digest of Casein produced from bovine milk (casein) and enzymes of porcine origin (ingredients of Glasgow MEM culture medium)

A CoA provided by the supplier together with details of source/origin of raw materials mentioning that this contains pancreatic digest of casein obtained from fermentation. Fermentation medium contains casein produced from bovine milk and porcine enzymes. A statement was also provided that the milk is collected from healthy animals in the same conditions as milk collected for human consumption.

(Porcine) Trypsin

Porcine trypsin is manufactured from pancreas of swine and contains bovine milk lactose. The statement of origin should guarantee that the bovine milk is collected from healthy animals in the same conditions as milk collected for human consumption. A series of corresponding CoAs, specifications and methods of analysis were provided. The Applicant confirmed that testing is carried out on each batch of trypsin.

Saponin (purified)

Saponin is a liquid substance of vegetable origin. A CoA was provided from the supplier regarding the control of general characteristics for saponin including appearance and identity, saponin concentration (by HPLC), dry matter and haemolysing saponin content. The Applicant provided satisfactory evidence in order to demonstrate that the irradiation process is not necessary, as animal viruses could not be found in the product.

Microcarriers biological origin raw materials

Can be alternatively used in standard manufacturing. The quality of microcarriers has been defined and specification monographs for this raw material have been provided. Gelatin and dextran are raw materials used for the manufacture of microcarriers:

Gelatin (of porcine origin)

One of the raw materials used for the manufacture is gelatine, which is processed from pigskin. Currently, materials from porcine origin do not carry any risk of transmitting TSE, according to the Note for Guidance EMEA/410/01-Rev 2.

Dextran

Dextran is also used for the manufacture of the microcarriers. Skimmed milk powder derived from bovine milk fitted for human consumption from USA is used for the manufacture of Dextran. Milk derivatives are excluded from the Note for Guidance EMEA/410/01-Rev 2 as long as the milk is sourced from healthy animals under the same conditions as milk considered fit for human consumption. TSE statement from the supplier was provided. The freedom from contamination with extraneous agents was demonstrated.

Starting materials of non-biological origin

Details, relevant control tests and certificates of analysis were provided for the following substances:

Starting material	Used for preparation of/ function
Bromoethylamine Hydrobromide (BEA)	BTV8 inactivating agent
Dimethyl sulfoxide (DMSO)	Cryoprotector

Bromoethylamine Hydrobromide (BEA): is prepared from raw materials (2-bromoethylamine hydrobromide and Sodium hydroxide) that are not susceptible to contamination. The solution is prepared under aseptic conditions and added to the culture in the same manner.
Dimethyl sulfoxide (DMSO): The Applicant clarified that DMSO supplied by Sigma Aldrich does not comply with Eur. Ph. Monograph 2005/0763. This was justified. However it was noted that as the amount of DMSO in the final product is negligible as a consequence of its use in the preparation of MCS and WCS, therefore any risk deriving from non compliance should be of negligible effect.

IN HOUSE PREPARATION OF MEDIA

The description of constituents (together with information on the quali-quantitative constituents, and shelf life of each preparation), the method of preparation (including sterilisation) and the basic controls carried out during preparation have been provided to support the quality of the following media: Glasgow MEM, PBS, Saline solution, Trypsin solution-cells; Trypsin 0.05% solution; EDTA 5% solution; Sodium hydrogen carbonate 7.5% solution; Phenol red solution; Sodium hydroxide 0.2N, 1N, 6N solutions; 0.1M BEI solution; 1M Sodium thiosulphate solution; Thiomersal 10% solution; saponin 1% solution; microcarrier suspension. These were all found acceptable.

SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

An assessment was conducted in order to demonstrate that the risk for transmission of TSE due to the starting materials of animal origin used in the manufacturing of this vaccine is minimal. The minimisation of risk is achieved by: a) the documented and recorded sourcing of animals (animal-derived material of known and controlled origin), b) the nature of animal tissues used in

manufacturing (low or no detectable infectivity), c) the production processes, and d) the negligible risk posed by a series of factors which would likely lower the risk if any. These factors include the high dilution of the materials used, the route of administration and the maximum number of dosage injected. A risk assessment (RA), certification of suitability and declaration of conformity were provided as appropriate, specifically, for the MCS and WCS of the BHK-21 cells; for the MSV and WSV, for the bovine calf serum; for the casein of bovine origin and the enzymes of porcine origin contained in Glasgow MEM; for the trypsin and for the microcarriers raw material's of animal origin. The Applicant also submitted certificates that stated the exclusion of the presence of any substance of animal origin in the production of saponin adjuvant. Satisfactory justifications were provided for the use of material from a GBRIII level Country (bovine serum sourced from US).

CONTROL TESTS DURING PRODUCTION

The Applicant clarified the production parameters of the active ingredient that are monitored during the process and the rationale for their choice. A detailed flow chart was provided, showing at which stage of production controls are carried out on the following intermediate products: antigen passage 1; antigen passage 2; antigen passage 3; inactivated/neutralized antigen and bulk vaccine.

Controls include the following tests:

- Antigen passage 1: Titration
- Antigen passage 2: Sterility and titration
- Antigen passage 3: Sterility, titration and identity
- Inactivated and neutralized antigen: Sterility, inactivation control, sodium thiosulphate contents
- Bulk vaccine: Sterility, absence of Aujeszky's disease virus, absence of Pestivirus, inactivation control

The above tests were described in detail and they were all found satisfactory.

CONTROL TESTS ON THE FINISHED PRODUCT

The controls on the finished products were described in sufficient details. The methods, frequency, pass criteria for the tests were acceptable.

Controls include the following tests:

- General characteristics of the finished product: Appearance, volume, pH
- Identification and assay of active substance: Identity, *in vivo* potency test in mice.

In vivo potency test:
In order to confirm that each batch of Zulvac® 8 Ovis formulated on the basis of the virus titre measured before inactivation is efficacious in the target species, the Applicant has developed an *in vivo* batch potency test in mice. The Applicant will use this test for the release of the commercial batches of Zulvac® 8 Ovis vaccine. Results from validation studies performed to support this Batch Potency Test were provided and were found satisfactory. The quantitative composition of the vaccine based on the test is expressed in relative potency (RP) with regard to a reference vaccine that was shown efficacious in lambs. The specification of a potent batch was ≥ 1 when compared to the reference vaccine.

- Identification and assay of adjuvants and excipients: aluminium hydroxide content and thiomersal content. The Applicant has also developed and validated a method for the determination of saponin. The method is going to be implemented by the Applicant at manufacturing sites.
- Sterility and purity test: sterility and absence of extraneous BTV
- Safety test in the target species

Consistency of production
Results of the control tests in three consecutive batches were provided.
The Applicant provided satisfactory data that demonstrated the consistency of production and the equivalence between all the manufacturing sites.

STABILITY

Active substance
Twelve months after its production, a BTV-8 antigen was blended to produce a vaccine. The Applicant confirmed that this vaccine batch will follow the stability program for which the protocol is already submitted to cover the 24 months shelf life. The Applicant will test the potency of this vaccine according to the mice batch potency test.

Finished product
A real-time-stability-study protocol aiming to demonstrate a 24 months shelf life of the finished product was provided**.** An interim report was submitted showing stability of one batch at 12 months and one batch at 3 month. The conducted tests showed that for 12 months the vaccine was stable. However in this study the new potency test in mice was not used. The Applicant committed to test the potency of the above batches in mice**.** As a support to the stability claim of the vaccine Zulvac 8 Ovis, the Applicant further provided the stability data obtained to date of the vaccines Zulvac 4 which show a 12-months shelf life for the finished product.

The CVMP concluded that in the absence of final stability data a maximum shelf life of 12 months can be granted based on the provisions in the CVMP Reflection Paper on Minimum Data Requirements for an Authorisation Under Exceptional Circumstances for Vaccines for Emergency Use Against Bluetongue-EMEA/CVMP/ /IWP/105008/2007.

OVERALL CONCLUSION ON QUALITY

All the data and clarification provided by the Applicant can be considered sufficient for granting a marketing authorisation under exceptional circumstances, when taking into account the benefit-risk balance for BTV serotype 8, and when considering the epidemiological situation in the EU.
In this context given that:

- a batch with minimum antigen content was shown efficacious on lambs,
- the production process allows production of consistent batches, with now a reliable batch potency test

then the CVMP has sufficient guarantees to assume that forthcoming batches will be efficacious on cattle when manufactured and released on the basis of the descriptions and specifications laid down in this file (because the forthcoming batches will be at least as good as the one used to show efficacy in the target species).

All these assurances are considered sufficient for granting a marketing authorisation under exceptional circumstances, but not for a full marketing authorisation.

3. SAFETY ASSESSMENT

INTRODUCTION AND GENERAL REQUIREMENTS

Zulvac 8 Ovis is a conventionally produced, liquid and ready-to-use, BEI inactivated vaccine, adjuvanted with aluminium hydroxide ($Al(OH)_3$) and saponin. The final batches of the vaccine are formulated in a 2 ml dose containing, an inactivated BTV 8 strain (blended at a target concentration based on the pre-inactivation titre) and a consistent amount of 4 mg of Al^{3+} and 0.4 mg of saponin. Thiomersal (0.2 mg/dose) is added as preservative, the vaccine being presented in multi-dose bottles.

Following the development of a reliable batch potency test the minimum titre is now expressed as RP* ≥ 1.
A 2 ml dose is recommended to be administered by subcutaneous route to sheep (including pregnant animals) to reduce, in emergency situations, the viraemia established in animals infected by serotype 8 strains of BTV. The basic vaccination schedule consists of one injection given from a minimum of 1.5 months of age followed by a second injection given 3 weeks later. Revaccination is recommended every 6 months.
Current European legislation, stipulates that studies should be performed to demonstrate the safety of a vaccine for target animals of the youngest age for which the vaccine is intended to be used, and, if the vaccine is intended to be used in breeding animals, examination of the reproductive performances should also be carried out. The safety of the administration of an overdose of the vaccine needs also to be investigated in animals of the target species. According to the CVMP Reflection Paper on Minimum Data Requirements for an Authorisation Under Exceptional Circumstances for Vaccines for Emergency Use Against Bluetongue-EMEA/CVMP/IWP/105008/2007) representative experimental batches or standard production batches of the vaccine can be used in safety studies. The reflection paper also allows that data generated from other vaccines of similar composition (in terms of excipients and adjuvants) in the same or a similar range of target species can be used to fulfil safety requirements. In the same document, field trials are not strictly required.

The Applicant provided results from safety studies carried out in target animal species of the minimum age recommended for vaccination and in pregnant ewes, using a monovalent vaccine (serotype 4) and a bivalent vaccine (serotypes 1 and 8) containing the same amount of adjuvant(s)/excipients. All vaccines used in studies presented below were blended at maximum antigen concentration based on the titre before inactivation.

**Relative Potency by a mice potency test compared to a reference vaccine that was shown efficacious in sheep*

LABORATORY TRIALS

The local and general tolerance to vaccination was studied after each administration of the vaccine. The standard parameters used to support the safety profile of the vaccine are listed below:

- Clinical signs after vaccination
- Impact on body temperature (Tº)
- Local reactions (LR)
- Post mortem examination of injection sites
- Impact on reproductive parameters

Safety of the administration of one dose/ Safety of the repeated administration of one dose.

Efficacy and safety study of the vaccine Zulvac 8 Ovine formulated at different concentrations of BTV, serotype 8, in 1 month old lambs (Report 115-01-E-12-07)
Objective/Methodology
To evaluate the safety (and the efficacy) of the subcutaneous injection of four experimental vaccine preparations formulated with different payloads of BTV8 antigen and standard amounts of adjuvants.
Animals
One month old- lambs, randomly distributed in 4 groups (1 to 4) of vaccinates each and in 1 group (5) of controls not treated with any placebo. All animals were BTV seronegative and the seronegative status of the animals was demonstrated by means of a commercially available ELISA test for the detection of antibodies against (any) BTV serotype.
Materials: Vaccine/Placebo
Four experimental vaccines (A to D) were formulated with different payloads of BTV8 antigen starting with vaccine A which had the highest antigen load (maximum standard dose) and decreasing to D with the lowest. The amount of aluminium hydroxide Al^{3+} and saponin was the standard used per 2 ml dose. Saline solution q.s. to 2ml and 0.2 mg of thiomersal were also added as component of the final 2ml dose of the vaccine. Each vaccine preparation was allocated to an appropriate group.

Observation scheme and post-vaccination follow-up (limited to safety)
After each vaccination, and for 14 days thereafter, animals were monitored for relevant systemic reactions. In particular, induction of anaphylactic shock was monitored during the first 24 hours after vaccination. Rectal temperature was also measured in the 36 lambs of groups 1/A, 2/B and 5, on the day before each administration of vaccine, four hours after each administration of vaccine, and then daily for the 2 days following each administration of vaccine. Injection sites were carefully inspected
Results (limited to safety)
Systemic reactions were not reported in any of the vaccinated and revaccinated animals. There was a statistically significant increase of rectal temperature between groups of animals receiving the 1st administration of the vaccine and placebo (average 0.7°C). Local reactions appeared after 1st administration either in the form of a limited or generalized swelling in 33% and 75% of lambs belonging to groups 1/A and 2/B, respectively. On average, first appearance of lesions occurred within 8 days from vaccination. Local reactions in most cases disappeared by day 25-43 after 1st vaccination. In limited occasions lesions became chronic and resulted in the majority in small granule, with exception of one case, which resulted in a diffuse swelling of the entire zone of inoculation. Following the second administration of the vaccine, 100% of animals of both 1/A and 2/B groups presented local reactions at injection site. In most cases the reaction resulted in a generalized swelling of the entire area. For 50% in group 1/A and 58% in group 2/B local reactions were still present after 23 days. In the majority of cases lesions persisted in the form of a small granule of <0.5 cm of diameter whereas in one lamb of group 2/B, chronic lesion consisted of a diffuse swelling of the entire zone of inoculation.
Conclusions:
Overall the results were considered acceptable and supportive of the conclusion that in 1 month old lambs, vaccination and revaccination with Zulvac 8 Ovis did not induce systemic reactions. A transient increase of rectal temperature was recorded 24 hours after the revaccination which disappeared within 48 hours. Local reactions observed after vaccination were common for the type of adjuvant used, such as aluminium hydroxide and saponin.

Safety of the repeated administration of 1 dose of the vaccine Zulvac 4 in one- month old lambs
The objective of the study was to verify the safety of the administration of the repeated administration of one dose of a monovalent inactivated BTV-4 vaccine (Zulvac®4) in one-month old lambs.
In this study lambs were vaccinated subcutaneously (s.c.) three times, 3 weeks apart (D0-D21-D42), with one dose (2 ml) of Zulvac®4. Animals with similar characteristics were treated with a placebo substance consisting of PBS. The animals were monitored for the appearance of anaphylactic reactions in the hours immediately after the vaccination. Recording the lambs rectal temperature was carried out the day before vaccination, the day of vaccination just before the vaccination, 4 hours after the administration of the vaccine and thereafter, for the following 4 days. Recording local reactions at the inoculation sites took place after each vaccination from the day of vaccination until local reactions had disappeared or until euthanasia (in the case of 3rd vaccination). Throughout the study the lambs' health condition was daily observed. Three weeks after the 3rd vaccination all the lambs were euthanized in order to perform a macroscopic and/or microscopic examination of the injection sites.
Results
General reactions (anaphylactic reactions or vomiting) were not induced by the vaccinations.
After the first and second vaccinations, a rectal temperature increase was not detected. Twenty-four hours after the third vaccination, a mean rectal temperature increase of 0.8ºC was detected in the vaccinated lambs in contrast with the controls; 2 days after vaccination the rectal temperature had normalized.
The administration of three repeated doses of 2 ml of the vaccine Zulvac® 4 provoked the appearance of local reactions at the site of injection: in 92% of lambs after the first vaccination, in 15% after the second vaccination, and in 62% after the third vaccination. The average duration of the local reactions was from 7 to 13 days (might be longer, since, after the third vaccination, the animals were euthanized before the local reactions produced by the vaccination had totally resolved in all the animals).
The intensity of the reactions varied from: slight in 25 to 50% of the lambs, moderate in 25-58%, intense in 17-50%. The postmortem analysis of the sites of inoculation of vaccine manifested tissular reactions at the site of injection: in 23% of the lambs after the first dose of vaccine and in 15% after the second dose, with an average volume of only 0.05 cm^3. At the site of injection of the third dose of vaccine, reactions were observed in 54% of the lambs, with an average volume of 0.12 cm^3.

The histopathologic diagnosis of the evaluated tissular reactions correspond to subcutaneous granulomas.

Conclusions:

Repeated administration of the vaccine in sheep may result in transient local reactions that may vary from slight to moderate.

Safety of the repeated administration of 1 dose of Zulvac® 1+8 Ovis vaccine in 1.5 month-old lambs.

The objective of the study was to verify the safety of the repeated administration of one dose of Zulvac® 1+8 Ovis vaccine in 1.5-month-old lambs.

In this study lambs were vaccinated subcutaneously (s.c.) three times, 3 weeks apart (D0-D21-D42), with one dose (2 ml) of Zulvac®1+8. Animals with similar characteristics were treated with a placebo substance consisting of PBS. The animals were monitored for the appearance of anaphylactic reactions in the hours immediately after the vaccination. Recording the lambs rectal temperature was carried out the day before vaccination, the day of vaccination just before the vaccination, 4 hours after the administration of the vaccine and thereafter, for the following 4 days. Recording local reactions at the inoculation sites took place after each vaccination from the day of vaccination until local reactions had disappeared or until euthanasia (in the case of 3rd vaccination). Throughout the study the lambs' health condition was daily observed. Three weeks after the 3rd vaccination all the lambs were euthanized in order to perform a macroscopic and/or microscopic examination of the injection sites.

Results

Vaccinations did not induce anaphylactic reactions.

After 1st vaccination, lambs did not present any rectal temperature increase. After 2nd vaccination, lambs presented a transient mean rectal temperature increase of 1.19ºC (compared to controls) on day 1 after the inoculation. On day 2 after vaccination, rectal temperatures were normal.

After 3rd vaccination, lambs presented a transient mean rectal temperature increase of 0.65 ºC on day 1 after the inoculation. On day 2 after vaccination, rectal temperatures were normalized.

After the administration of three repeated doses of 2 ml of the vaccine Zulvac® 1+8 Ovis, local reactions at the injection site appeared in 100% of lambs after the first and second vaccinations, and in 92% after the third vaccination. The average duration of the local reactions was 30 to 44 days, persisting afterwards as small granules of diameter ≤ 0.5 cm in the 54 - 61% of the lambs. In the 33 to 77 % of the lambs the observed local reactions were generalized diffuse swellings of the whole injection areas of 1 to 9 days of duration that evolved into nodules of gradually decreasing diameter from ≥2 to 0.5 cm of diameter. In the 23 to 67% of the lambs the reactions were nodules of ≥2 cm in diameter that gradually decreased to nodules of smaller diameter, <2 to 0.5 cm. At the post-mortem examination tissue reactions at the injection sites were observed: in 100% of the lambs after the first dose with an average volume of 0.34 cm^3 and in 85% and 92% of the lambs after the second and third doses, with an average volume of 0.6cm^3. The histopathological study showed that tissue lesions correspond to subcutaneous granulomas.

Conclusions:

The safety of the repeated administration of a single dose of Zulvac 1+8 Ovis vaccine was demonstrated in sheep of minimum age. The results showed that the administration of a repeated single dose of the vaccine Zulvac® 1+8 Ovis in 6-week-old lambs, is safe since it did not induce anaphylactic reactions. The section of the SPC was updated accordingly.

Safety of an administration of an overdose.

Safety of the administration of an overdose of the vaccine Zulvac 4 in one- month old lambs

The objective of the study was to verify the safety of the administration of an overdose of the vaccine Zulvac® 4 Ovis in one-month-old lambs.

The lambs were vaccinated with 4 ml (2x2ml doses) of the vaccine by subcutaneous route, at the same time control lambs of the same age were inoculated by subcutaneous route with 4 ml of placebo (PBS). The animals were observed for general reactions (anaphylactic reactions, vomiting, etc.) after

the administration of vaccine or placebo. Rectal temperature was monitored from the day previous to vaccination, just before vaccination, 4 hours later and daily until 4 days after vaccination. The appearance of local reactions at the site of injection was monitored during the 14 days after vaccination or until their disappearance (e.g. until 48 days).

Results:

The administration of an overdose of the vaccine Zulvac® 4 Ovis in one-month old lambs did not induce general reactions (anaphylactic reactions). The animals did not present any rectal temperature increase. The 92% of the lambs presented local reactions at the site of vaccination with an average duration of 20 days. By day 35 after vaccination these lesions had completely disappeared. The intensity of the reactions varied from slight (8% of the animals showing reactions) to moderate (69%) up to intense (23%), lasting only 2-3 days.

Conclusions:

Anaphylactic reactions or vomiting were not induced by the administration of a double dose of the tested vaccine. No increase of rectal temperature was detected in the animals after vaccination.

The administration of a double dose of the vaccine may result in the appearance of transient (average duration 20 days) local reactions in vaccinated lambs. The intensity of the reactions may vary from slight (8% of the animals showing reactions) to moderate (69%) up to intense (23%), lasting only 2-3 days.

Safety study of the administration of an overdose of the vaccine Zulvac® 1+8 Ovis in 6-week-old lambs.

The objective of the study was to verify the safety of the administration of an overdose of the vaccine Zulvac® 1+8 Ovis in 6-week-old lambs.

The lambs were vaccinated with 4 ml (2x2ml doses) of the vaccine by subcutaneous route, at the same time control lambs of the same age were inoculated by subcutaneous route with 4 ml of placebo (PBS). The animals were observed for general reactions (anaphylactic reactions.) after the administrations of vaccine or placebo. Rectal temperature was monitored from the day previous to vaccination, just before vaccination, 4 hours later and daily until 4 days after vaccination. The appearance of local reactions at the site of injection was monitored during the 14 days after vaccination or until their disappearance (e.g. until 35 days).

Results:

The administration of an overdose of the vaccine Zulvac® 1+8 Ovis in 6-week-old lambs did not induce general reactions (anaphylactic reactions, vomiting). The animals did not present any rectal temperature increase. The 85% of the lambs presented local reactions at the site of vaccination of 12 to 48 days of duration. The observed local reactions varied between nodular swellings of 1 to ≥2 cm in diameter in the 45% of the lambs to generalized diffuse swellings of 2 to 9 days of duration of the whole area of injection in the 55% of the lambs. In the 45% of the lambs the reactions persisted after day 48 p.v. as small nodules of diameter ≤0.5 cm to <2 cm.

Conclusions:

The safety of double dose administration of Zulvac 1+8 Ovis vaccine was demonstrated in sheep of minimum age.

Examination of reproductive performance

1) Safety study of the administration of an overdose of the vaccine Zulvac 4 in pregnant ewes

The objective of the study was to verify the safety of the administration of an overdose of the vaccine Zulvac 4 in ewes at different phases of gestation.

Ewes were allocated into two groups, according to their stage of gestation (determined by ultrasound diagnosis): G1-ewes in the first stage of gestation (between 1.5 and G2-2.5 months of gestation) and ewes in the second stage of gestation (between 2.5 and 4.5 months of gestation). In each group ewes were randomly distributed into two treatment groups: vaccinated (V1 and V2) and control (C1 and C2).

On D0 each ewe of groups V1 and V2 was subcutaneously injected with a double (2 x 2 ml) dose of Zulvac 4. Controls were inoculated under the same experimental conditions with 4 ml of the selected placebo.

Daily observation of ewes was carried out. Special attention was paid to the induction of anaphylactic reactions during the first hours immediately after vaccination and to systemic reactions such as vomiting. Rectal temperature was also measured on the day before administration of vaccine, on the day of vaccination, 4 hours after administration of vaccine, and then daily for the 4 days following administration of vaccine. Injection sites were individually inspected to detect any local reactions induced by vaccine or placebo. Examination took place from the day of vaccination until 35 days post vaccination.
Anomalies of reproductive parameters (e.g. incidents from vaccination such as reabsorption in ewes in the 1st stage of gestation, or abortion, stillbirths and lambs born weak) were recorded throughout the study until all ewes had given birth. Blood samples were collected before vaccination (D<0), in order to confirm the seronegative status of animals against BTV4, and 15 days after vaccination.

Results

No systemic reactions were reported in any of the vaccinates. No statistical significant difference in the mean increase of rectal temperature between vaccinated and control animals was recorded at any time point day after the administration of the double dose of the tested vaccine. Local reactions at the site of injection were recorded in 100% of vaccinated ewes. Starting one day after vaccination, local reactions appeared at the injection site and by D10 following vaccination all vaccinates were affected. On average, lesions persisted for 16 days. By day 35 after vaccination lesions had completely disappeared almost in all vaccinates. Exception to this was the case of one animal in each of the vaccinated groups, where a small hard granule was still present on D55 after vaccination. This reaction resulted in a chronic lesion. In general, lesions varied from a small granule or oedema at the site of injection which evolved into a nodule returned to a small granule, until it disappeared. The intensity of the reactions varied from moderate to intense (generalized swelling of the area of inoculation) in 52% and 48% of vaccinated animals respectively. In total 39 % ewes were found not to be pregnant. Although an assessment was provided to explain the reasons for the significant rate of non pregnancy, it was considered by the CVMP that it impacted the outcome of the study regarding the 1st phase of gestation.
Non conclusive results were obtained from the study of reproductive alterations induced by vaccination of ewes during the first phase of gestation. 73% of vaccinated animals were found not to be pregnant at ultrasound monitoring carried out at different time points throughout the observation period until parturition. 30% of controls in the same experimental conditions were found not to be pregnant. None of the vaccinated animals experienced abortion whereas one control aborted one foetus completely formed on D8 after inoculation of placebo. The Applicant completed an assessment of the non pregnancy status of the ewes (e.g. to completely exclude potential episodes of reabsorptions of foetuses) and demonstrated that no significant difference existed between the number of non pregnant ewes recorded in groups V1 and C1 (not accurate ultrasound diagnosis, detected and undetected reabsorptions and/or abortions).
More homogeneous and better interpretable results were obtained when examining the reproductive performance of animals vaccinated during the 2nd phase of gestation. 20% and 30% ewes in group V2 and C2 were not pregnant when inoculated with the corresponding test preparation; 70% of the animals in each group reached parturition without major differences in terms of numbers of live births, and health conditions of lambs; only one animal of group V2 experienced an episode of abortion which occurred 36 days after vaccination and resulted in the expulsion of a foetus completed formed and oedematous.
All ewes were seronegative to BTV when the study initiated. No appreciable increase of SN antibodies was recorded 15 days after vaccination in almost any of the test animals.

Conclusions:

No anaphylactic reactions or vomiting were induced by the administration of a double dose of the tested vaccine. No increase of rectal temperature is detected in the animals after vaccination.
The administration of a double dose of the vaccine may result in the appearance of transient (average duration 16 days) local reactions in 100% of pregnant ewes. In 10% of vaccinated animals local reaction may result in a chronic lesion. The intensity of the reactions varied from moderate (nodular swelling 1-4 cm in diameter) to intense (generalized swelling of the area of inoculation) respectively in 52% and 48% of vaccinated animals. However the above conclusions are compromised by the low rate of pregnancy in the 1st phase of gestation.
The Applicant completed an assessment of the non pregnancy status of the ewes (e.g. to completely exclude potential episodes of reabsorptions of foetuses) and demonstrated that no significant

difference existed between the number of non pregnant ewes recorded in groups V1 and C1 (not accurate ultrasound diagnosis, detected and undetected reabsorptions and/or abortions).

2) Study of the safety of the administration of an overdose of the vaccine Zulvac 4 to ewes in the 2nd phase of gestation

The objective of the study was to verify the safety of the administration of an overdose of the vaccine Zulvac 4 in ewes at 2nd phase of gestation.

At the start of the study, pregnant ewes, reported to be in their 2nd phase of gestation were distributed in two treatment groups indicated as V (vaccinates) and C (controls). A good health status was a criterion for inclusion, as well as seronegative status of ewes against BTV serotype 4.

On D0 each ewe of group V was subcutaneously injected in the right axillary area with a double (2x2ml) dose of the vaccine under test. Simultaneously, all controls were inoculated under the same experimental conditions with 4 ml of the selected placebo.

Daily observation of ewes was carried out. Special attention was paid to the induction of anaphylactic reactions during the hours immediately after vaccination, and to systemic reactions such as vomiting. In order to avoid additional stress associated with handling of animals that could potentially influence the outcome of the study, rectal temperature was not measured, nor injection sites were inspected. Anomalies of reproductive parameters (e.g. incidents from vaccination such as reabsorption or abortion, stillbirths and lambs born weak) were recorded throughout the study until all ewes had given birth. Blood samples were collected before vaccination (D<0), in order to confirm the seronegative status of animals.

Results

No systemic reactions were reported in any of the pregnant vaccinates in the 2nd phase of gestation.

The administration of an overdose of the vaccine did not affect major reproductive parameters. 95% of vaccinated ewes reached parturition whereas the remaining one 5% was diagnosed not to be pregnant. 80% of control ewes reached parturition whereas 10% were diagnosed not to be pregnant, and the remaining one was found dead 7 days after the inoculation of placebo without showing any macroscopic lesions. All ewes were seronegative to BTV when the study was initiated.

Conclusions:

No anaphylactic reactions or vomiting were induced by the administration of a double dose of the tested vaccine. Reproductive parameters of animals vaccinated while in a late phase of gestation were not affected. However with the exclusion of three animals which were clearly vaccinated during the first phase of gestation, remaining ewes were vaccinated in the late/terminal phase of gestation (e.g., 2 ewes were vaccinated the day before parturition; 3 ewes, 2 days before; 2 ewes, 3 days before, etc).

The Applicant outlined that in this study, all the vaccinated ewes that reached parturition (95%) presented healthy lambs; just 5% was detected to be not pregnant. On the other hand, in the control group 10% did not reach parturition.

3) Study of the safety of the administration of an overdose of the vaccine Zulvac 4 to ewes in the 1st phase of gestation

The objective of the study was to verify the safety of the administration of an overdose of the vaccine Zulvac 4 in ewes at 1st phase of gestation.

At the start of the study pregnant ewes in their 1st phase of gestation from a minimum of 42 days to a maximum of 80 days of gestation were distributed in two treatment groups indicated as V (vaccinated) and C (controls)

A good health was a criterion for inclusion, as well as seronegative status of ewes against BTV serotype 4. The seronegative status of the animals was demonstrated by means of an ELISA test for the detection of antibodies against any BTV serotypes. Selection of the animals was further based upon ultrasound diagnosis done 12 days before vaccination and on the day of vaccination.

On D0 each vaccinate was subcutaneously injected with a double (2x2ml) dose of the vaccine under test. Controls were inoculated under the same experimental conditions with 4 ml of placebo.

Daily observation of ewes was carried. Special attention was paid to the induction of anaphylactic reactions during the first hours immediately after vaccination and to relevant systemic reactions. In order to avoid additional stress associated with handling of animals, potentially influencing the outcome of the study, rectal temperature was not measured, nor injection sites were inspected. The

animals' reproductive parameters were recorded at the moment of parturition. Ultrasound diagnosis was carried out 4, 42, 95 and 147 days post vaccination to monitor the status of gestation and to record anomalies of reproductive parameters such as reabsorption or abortion. Blood samples were collected before vaccination (D<0), in order to confirm the seronegative status of animals against BTV4.

Results

No systemic reactions were reported in any of the pregnant l vaccinates in the 1^{ls} phase of gestation. In total, 14.28% pregnant ewes died during the study. Two animals died manifesting clinical signs of enterotoxaemia. One animal and the foetus died as consequence of a prolapse of the uterus at parturition. The administration of an overdose of the vaccine did not affect major reproductive parameters. 28% among vaccinated ewes and 17.88% of control ewes were diagnosed not to be pregnant. Abortion did not occur in any ewe enrolled in the study. Finally, 72% and 71% ewes respectively in group V and C reached parturition giving birth to healthy lambs. A slightly higher number of lambs were delivered by controls compared to vaccinated ewes (1.3 vs 1.1). All ewes were seronegative to BTV when the study was initiated.

Conclusion:

Anaphylactic reactions or vomiting were not induced by the administration of a double dose of the tested vaccine. Reproductive parameters of animals vaccinated while in the 1^{st} phase of gestation were not affected

4) Study of the safety of the administration of an overdose of the Zulvac® 1+8 Ovis vaccine to pregnant ewes.

The objective of the study was to verify the safety of the administration of an overdose of the vaccine Zulvac®1+8 Ovis to crossbred pregnant ewes, at different phases of gestation.

Ewes at different stage of gestation were selected for the study and appropriately allocated to 3 vaccinated (V1, V2, V3) and 3 control (C1, C2, C3) groups in order to have a consistent number of ewes at different stage of gestation in both groups. Some of the pregnant ewes were vaccinated by subcutaneous route with 4 ml of Zulvac® 1+8 Ovis, and some pregnant ewes were inoculated with 4 ml of PBS-placebo (control ewes). The appearance of anaphylactic reactions was evaluated after the administration of vaccine or placebo. In the study, rectal temperatures and local reactions at the site of injection were not recorded, in order to avoid the possible reproductive problems associated with the handling of the animals.

Results

The vaccine did not induce anaphylactic shock in ewes at different stage of gestation.

The administration of an overdose of vaccine did not affect the reproductive parameters of ewes (reaching parturition, abortions, number of lambs born alive healthy and number of lambs born weak or stillborn).

Conclusions:

The safety of double dose administration of Zulvac 1+8 Ovis vaccine was demonstrated in ewes at different stages of pregnancy.

5) Safety study of the administration of an overdose of Zulvac® 1+8 Ovis vaccine in pregnant ewes at second phase of gestation.

The objective of the study was to verify the safety of the administration of an overdose of the vaccine Zulvac® 1+8 Ovis in pregnant ewes at second phase of gestation (at approximately 3-5 months of gestation).

Ewes were distributed into two groups:

- Group 1 vaccinates (V1) and controls (C1)
- Group 2: vaccinates (V2) and controls (C2)

Ewes from groups V1 and V2 were vaccinated by subcutaneous route with 4 ml of Zulvac® 1+8 Ovis and ewes from groups C1 and C2 were inoculated with 4 ml of PBS placebo. General reactions after the vaccine administration were evaluated (anaphylactic reactions, vomiting, etc.). In group 1, rectal temperature was monitored just before the vaccination, 4 hours later, and daily until 4 days after vaccination. In this group, the appearance of local reactions at the site of injection was also monitored during the 63 days after vaccination. Reproductive parameters were monitored throughout the study until all the pregnant ewes gave birth. During the study, all the reproductive incidents were recorded.

For each ewe, the date of parturition, number of born lambs and their health conditions were monitored.

Results

The vaccine did not induce general reactions, anaphylactic shock or vomiting in the pregnant ewes under test. The ewes presented a slight and transient mean rectal temperature increase of 0.6ºC (compared to the mean temperature of the control group) on day 1 after the inoculation.

After the administration of 4 ml of the vaccine Zulvac® 1+8 Ovis, 83% of the ewes presented local reactions at the site of injection. The observed local reactions varied between nodular swellings of 1 to ≥ 2 cm in diameter in the 20% of the ewes to generalized diffuse swellings of 3 to 10 days of duration of the whole area of injection in the 80% of the ewes. In the 40% of the ewes the reactions persisted after day 63 post vaccination as small nodules of diameter ≤ 0.5 cm.

The administration of an overdose of vaccine did not affect the reproductive parameters of ewes at a late phase of gestation as compared to control ewes.

Conclusion:

The safety of double dose administration of Zulvac 1+8 Ovis vaccine was demonstrated in ewes at late stage of pregnancy.

Examination of immunological functions

No specific study was carried out in this respect as no negative influence on the immune response is expected due to the vaccination. There is no evidence to support an impairment of the immune system due to the vaccination.

Special requirements for live vaccines

Not applicable

Study of residues

The Applicant has provided acceptable justifications for omitting specific studies on residues. The vaccine contains adjuvants, excipients and preservatives with well known properties and characteristics.

Interactions

Interaction with other veterinary medicinal products has not been investigated.

A recommendation for not mixing the vaccine with other IVMPs has been included in SPC.

FIELD STUDIES

Data from field studies were not provided. In light of the requirements of the CVMP Reflection Paper on Minimum Data Requirements for an Authorisation Under Exceptional Circumstances for Vaccines for Emergency Use Against Bluetongue. (EMEA/CVMP/ /IWP/105008/2007) on field studies this approach was acceptable. The Applicant provided bibliographical references from safety field studies conducted in Germany - (J Gethmann, *et al,* Comparative safety of three inactivated BTV-8 vaccines in sheep and cattle under field conditions, Vaccine, 2009) - using Zulvac® 8 Ovis vaccine. These studies demonstrated the safety of the vaccine regarding local reactions at the injection site, general reactions, reproductive parameters (abortions, normal birth, teratogenic effects, etc.) and milk production. The above bibliographical reference was noted by CVMP.

ENVIRONMENTAL RISK ASSESSMENT (ECOTOXICITY/USER SAFETY)

A Phase I assessment of risk was performed according to EMEA/CVMP/074/95. The final product contains no components which may exert a toxic effect and there are no pharmacologically active components included in this vaccine. Phase 1 assessment provided evidence that there would be no potential risk for the global environment.

No negative impact on public health or on the environment can be identified in light of the nature of the vaccine, in particular of the antigen (inactivated) and adjuvant(s) (appearing to be pharmacologically inert substances). Additionally, no special concern is posed by the final product in

light of the safety of packaging, of the limited number of injections and of the maximum quantity administered to animals, of the route and of the method of administration. Consequence and level of risk are practically nil, this justifying the absence of phase 2 assessment.

RESIDUE ASSESSMENT

The Applicant has provided acceptable justifications for omitting specific studies on residues. The vaccine contains adjuvants, excipients and preservatives with well known properties and characteristics.

MRLs

The following substances are included in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Aluminium hydroxide gel	All food producing species	
(Quillaia) Saponin	All food producing species	
Thiomersal	All food producing species	For use only as preservatives in multidose vaccines at a concentration not exceeding 0.02 %
Potassium chloride	All food producing species	
Potassium dihydrogen phosphate	All food producing species	
Disodium hydrogen phosphate dodecahydrate	All food producing species	
Sodium chloride	All food producing species	

Water for injections is considered as not falling within the scope of Council Regulation (EC) 470/09.

OVERALL CONCLUSIONS ON SAFETY

The provision of additional safety data demonstrated the safety of the vaccine in sheep of minimum age and results indicated the same in pregnant animals. Overall, the safety profile of Zulvac 8 Ovis vaccine was demonstrated. The potential for any adverse effects following the administration of the vaccine under the recommended conditions of use is adequately reflected in the relevant section of the SPC.

4. EFFICACY ASSESSMENT

INTRODUCTION AND GENERAL REQUIREMENTS

The vaccine is recommended for the active immunization of sheep in order to prevent viraemia established in animals infected by serotype 8 of BTV. A 2 ml dose of the vaccine is recommended to be administered by subcutaneous route to sheep (including pregnant and lactating animals). The basic vaccination schedule consists of one initial injection given from a minimum of 1.5 month of age and followed by a second injection given 3 weeks later. Onset of immunity is 25 days after the completion of the basic vaccination course. The duration of immunity (DoI) has not been fully established yet but interim result support one of at least 6 months. The absence of any investigation of the influence of maternally derived antibodies (MDA) on the vaccine's efficacy is reflected in a statement included in SPC. Field trials were not strictly required for this type of application; the Applicant provided bibliographical data related to them. A DIVA strategy has not been implemented yet.

LABORATORY TRIALS

In order to establish a correlation between antigen load (expressed in terms of virus titre before inactivation) and the vaccine efficacy, laboratory trials were carried out. Batches of experimental vaccines were formulated to contain decreasing amounts of vaccine antigen, which were tested in a dose/response study in BTV-8 free lambs of minimum age. The efficacy induced by the different concentrations of vaccine antigen was monitored against the appearance of clinical signs and viraemia following inoculation of an infectious dose of a homologous BTV 8 challenge (strain isolated from a recent outbreak of BTV-8 in Belgium). Viraemia was analyzed by BTV specific quantitative real time RT-PCR assay.

Efficacy and safety study of the vaccine Zulvac 8 Ovis formulated at different concentrations of BTV, serotype 8, in 1 month old lambs

Objective

The objective of the study was to evaluate the efficacy of four experimental vaccine preparations formulated with different payloads of BTV8 antigen and standard amounts of adjuvants.

The vaccine was administered at two doses of 2 ml, administered 3 weeks apart, in lambs of minimum age (GLP compliant study). The efficacy of the vaccines was evaluated based on their capacity to reduce or prevent viraemia after BTV-8 challenge carried out 25 days after second vaccination.

Experimental design

One month old lambs, were randomly distributed in 4 groups (1 to 4) of vaccinates in one group (5) of controls. A good health status was certainly a criterion for inclusion, as well as seronegative status of lambs against BTV (ELISA test). On D0, each lamb of group 1, 2, 3 and 4 was subcutaneously injected with a 2 ml dose of the corresponding vaccine preparation. Three weeks later (D21), these animals were revaccinated under the same conditions

Blood samples were collected for serology before each vaccination and before challenge. They were tested by SN test and ELISA, however results were not submitted.

A challenge with a virulent BTV8 was carried out 25 days after 2nd vaccination (D46). For 15 days after challenge, animals were monitored for the appearance of major clinical signs observed during BTV8 infection, including increase of rectal temperature, nasal discharge, watering, dyspnoea, coughing, lameness, prostration and mortality. Blood samples for assessing viraemia (RT-PCR-testing) were collected 3, 5, 7, 10, 13, 17, 20, 24 and 27 days after challenge. At the end of the study all animals were euthanized. Satisfactory details were provided on the origin of the challenge strain, its production, the validation of the challenge dose and of the challenge model. The Applicant explained that the focus of the developed challenge model was to inoculate an amount of virus so that all control animals become viraemic during the study.

Results

Analysis of mortality:

One control, and respectively 2 and 1 lambs from group 2 and 4 died before challenge. In group 1, five deaths were recorded. From these, 3 lambs were euthanized 24 days after challenge due to very poor general health. The death of the two remaining animals occurred respectively 9 and 14 days after challenge. Three animals of group 3 died respectively 6, 11 and 18 days after challenge. Two animals of group 4 died respectively 10 and 24 days after challenge. An assessment of the causality (clinical signs and/or necropsy finding) of the reported deaths was provided, and in each case the death of the animal was specifically not attributed or associated to the experimental BTV infection.

Clinical monitoring:

In general, no statistically significant difference was registered between vaccinated and non vaccinated lambs regarding increase of rectal temperature after challenge.

Viraemia:

From 5 days after challenge (and for the entire observation period), all controls were viraemic as BTV genome was detected in all of their blood samples. In contrast, no BTV genome was detected in test samples collected from vaccinated animals.

Validation of real time RT-PCR used: The Applicant provided data that supported the use of RT-PCR in order to define the viraemic status of animals**.** Protection was defined as constant absence of viral load detectable by real time RT-PCR (Ct value ≥36.0) in all vaccinated animals during the monitoring period of 4 weeks.

Conclusions
The analysis of RT-PCR results provided by the Applicant was consistent with current knowledge and general principles set for BTV diagnosis by reference laboratories. Taking this into account, and as no viral genome was ever detected form blood samples taken from vaccinated/challenged animals of the immunogenicity studies, it can be concluded that under the experimental conditions set by the Applicant, Zulvac 8 Ovis vaccine was able to prevent viraemia. On this basis it was concluded that the above study provided adequate evidence that primary vaccination of 1 month old lambs, with Zulvac 8 Ovis induced 100% prevention of viraemia in all vaccinated animals. Onset of immunity was 25 days after revaccination.

2) Efficacy study of Zulvac 8 Ovis vaccine in 1.5-month-old lambs
Objective
The objective of the study was to evaluate the efficacy of four experimental vaccine preparations formulated with different payloads of BTV8 antigen and standard amounts of adjuvants.
This new study was designed to support the results of the previous study and to confirm that mortality recorded in the study was not associated to the challenge with BTV-8 virus.
The vaccine was administered at two doses of 2 ml, administered 3 weeks apart, in lambs of minimum age (GLP compliant study).
The efficacy of the vaccines was evaluated based on their capacity to reduce or prevent viraemia after BTV-8 challenge carried out 25 days after second vaccination.
Experimental design
One and a half month old lambs, were randomly distributed in 4 groups (1 to 4) of vaccinates in 1 group (5) of controls. A good health status was certainly a criterion for inclusion, as well as seronegative status of lambs against BTV (ELISA test).
On D0, each lamb of group 1, 2, 3 and 4 was subcutaneously injected with a 2 ml dose of the corresponding vaccine preparation. About three weeks later (D22), these animals were revaccinated under the same conditions
Blood samples were collected for serology before each vaccination and before challenge. They were tested by SN test and ELISA, however results were not submitted.
A challenge with a virulent BTV8 was carried out 19 days after 2nd vaccination (D41). Two ml of the challenge suspension was inoculated subcutaneously. For 15 days after challenge, animals were monitored for the appearance of major clinical signs observed during BTV8 infection, including increase of rectal T°, nasal discharge, watering, dyspnoea, coughing, lameness, prostration and mortality. Blood samples for assessing viraemia (RT-PCR-testing) were collected 3, 6, 8, 10, 13, 16, 20, 23 and 27 days after challenge. At the end of the study all animals were euthanized.

Results
Clinical monitoring:
Six and eight days after challenge control lambs presented an statistical significant rectal temperature compared with the non vaccinated. No statistically significant difference was registered between vaccinated and non vaccinated lambs regarding other clinical signs.
Viraemia:
From 6 days after challenge (and for the entire observation period), all controls were viraemic as BTV genome was detected in all of their blood samples. In contrast, no BTV genome was detected in test samples collected from vaccinated animals.
Conclusions
The study provided adequate evidence the mortality recorded in the previous study was not associated to the BTV-8 challenge.
From the study results it was concluded that primary vaccination of 1.5 month old lambs, with Zulvac 8 Ovis induced 100% prevention of viraemia in all vaccinated animals.

Pre-immunogenicity study of Zulvac® 1+8 Ovis vaccine in 1.5-month-old lambs
Objective
The objective of this study was to evaluate the efficacy of four different antigen concentrations in Zulvac 1+8 Ovis vaccine, in order to establish the lowest concentration tested which is able to prevent

viraemia (the presence of viral genome in the blood by real time RT-PCR in vaccinated lambs compared to unvaccinated animals) in 100% of vaccinated lambs.

Experimental design

The lambs were randomly allocated into 5 treatment groups of animals: G1-2-3-4, each consisted of lambs vaccinated at D0 and revaccinated at D20 by subcutaneous route, with a 2 ml dose of the corresponding vaccine preparation; G5, consisted of control lambs which did not receive any type of placebo treatment. Blood sampling was carried out at established time points in order to monitor the serological response (seroneutralizing antibodies) after vaccination. Twenty-one days after second vaccination (D41), half of the animals of each vaccinated group and 3/4 of the control group were submitted to a virulent BTV 8 challenge by subcutaneous route. Blood samples were taken from all animals after challenge. Protection was defined as constant absence of viral load detectable by real time RT-PCR (Ct value ≥36.0) in all vaccinated animals during the monitoring period of 4 weeks.

Results

From a safety point of view, none of the (vaccinated) lambs manifested any systemic reactions such as anaphylactic shocks after the 1st and 2nd vaccination.

Uptake of the vaccine was demonstrated 2 weeks after completion of the basic vaccination scheme. The SN titres to BTV8 declined until challenge. Control lambs remained negative at all bleeding time points. BTV8 (and BTV1) genome was not detected in any of vaccinated lambs at any time points during 27 days after challenge, whereas in all the non-vaccinated and challenged lambs, BTV8 (and BTV1) genome was detected starting from D4 post infection. No statistically significant differences regarding rectal temperatures after BTV8 (and BTV1) challenge were recorded between the vaccinated groups. There were statistically significant differences regarding rectal temperatures after BTV8 (and BTV1) challenge between the vaccinated groups and the control group on D6 and D8. Other clinical signs attributed to BTV8 (and BTV1) infection, such as nasal discharge and/or oedema, ocular discharge and/or ocular oedema, lameness and prostration, were recorded in some groups of vaccinated lambs as well as in control lambs during the observation period (other clinical signs not associated to BTV infection were also recorded).

Conclusions

From these results it was concluded that the administration of different concentrations of Zulvac 1+8 Ovis vaccine in 1.5 months old lambs was capable to prevent viraemia in the vaccinated sheep under the experimental conditions set for this study.

Efficacy study of the 2-injections of Zulvac® 1+8 Ovis vaccine in 1.5 old lambs

Objective

The objective of this study was to evaluate the efficacy of two different antigen concentrations in Zulvac 1+8 Ovis vaccine, in order to test if they were able prevent viraemia in 100% of vaccinated animals.

Experimental design

The lambs were randomly allocated into 3 treatment groups of animals. Lambs in G1 and G2 were vaccinated at D0 and revaccinated at D22 by subcutaneous route, with a 2 ml dose of the corresponding vaccine preparation. Lambs of G3 were left as unvaccinated controls, and did not receive any type of placebo treatment. After vaccination/re-vaccination, the animals were monitored for the potential occurrence of any systemic reactions associated with the administration of the vaccine. Blood sampling was carried out at established time points in order to monitor the serological response after vaccination. Three weeks after vaccination (D43), half of the animals of each vaccinated group were submitted to a virulent challenge by subcutaneous route, with a virulent suspension of BTV-8. Blood samples were taken from all animals after challenge (clinical signs were also recorded) for the evaluation of the presence of BTV genome by a real time RT-PCR technique.

Results

From a safety point of view, none of the (vaccinated) lambs manifested any systemic reactions such as anaphylactic shocks after the 1st and 2nd vaccination. The evolution of seroneutralizing antibodies against BTV8 from vaccination on D36 (2 weeks after the 2nd vaccination) and until D43, at challenge was provided. The effect of the vaccine was demonstrated 2 weeks after completion of the basic vaccination scheme as the SN titres to BTV8 increased until challenge. Control lambs remained negative at all bleeding time points. BTV8 (and BTV1) genome was not detected in any of vaccinated lambs at any time points during the 27 days after challenge, whereas in all the non vaccinated and

challenged lambs, BTV8 (and BTV1) genome was detected starting from D6 (and from D3 for BTV1) post infection. Statistically There were statistically significant differences regarding rectal temperatures between the vaccinated groups and the control group on D3, 6, 8 and 10 after challenge with BTV8 (and BTV1).

Conclusions

The efficacy of the vaccine in 2.5 month old lambs vaccinated was demonstrated.

The Influence of Maternal Antibody on the Efficacy of the Vaccine

The efficacy of the vaccine in the face of Maternally Derived Antibodies (MDA) has not been investigated. A warning it has been included in the relevant section of SPC.

Duration of Immunity

The Applicant indicated that no final data were available at present concerning the DoI, but a study is ongoing. For this study, the Applicant provided the timelines and submitted interim results. In the mean time, the absence of DoI data has been clearly reflected in relevant section of SPC.

1) Duration of immunity study of Zulvac® 8 Ovis vaccine in lambs (Interim Report)

Objective

The objective of the first part of the study was to verify if the administration of Zulvac 8 Ovis vaccine was able to prevent viraemia (no detection of viral genome by real time RT-PCR technique during 27 days post challenge) in lambs challenged 6 months post vaccination. In the second part of the study, the remaining lambs will be challenged 1-year post vaccination. Two experimental Zulvac 8 Ovis vaccine preparations formulated with different payloads of BTV8 antigen, and standard amounts of adjuvants were tested in the study.

Experimental design

Nine to ten weeks old lambs were enrolled in this study. At D0 all animals were seronegative by ELISA to any BTV serotype and no detectable viral genome was present in blood samples. The lambs were divided in 3 groups: G1 and G2, consisting of lambs vaccinated/revaccinated by subcutaneous route 3 weeks apart with 2 ml of the corresponding vaccine preparation; and G3, consisting of control lambs that did not receive any type of placebo treatment. After vaccination/re-vaccination, the animals were monitored for the potential occurrence of any systemic reactions associated with the administration of the vaccine. Blood sampling was carried out at established time points in order to monitor the serological response after vaccination. On D202, randomly selected sheep (from G1, G2and G3) were submitted to a virulent challenge with BTV8. Blood samples were taken from all animals before and after challenge for the evaluation of the presence of BTV genome by a real time RT-PCR.

Results

The evolution of seroneutralizing antibodies against BTV8 from vaccination until 6 months challenge (D202) was provided. The serological effect of the vaccine was demonstrated three weeks after completion of the basic vaccination scheme. The SN titres declined until challenge. Control lambs remained negative at all the bleeding time points. Viral genome was not detected in any of vaccinated lambs of G1 and G2 at any time points during 28 days after challenge, whereas in all the non-vaccinated and challenged lambs, viral genome was detected starting from D4 post infection. The mean Ct value of 24.67 was detected on the day of max viraemia, e.g. on D7 post infection. Exclusively on D7 after challenge, a statistically significant difference in the rectal temperature was recorded between vaccinated and control animals. There was no statistically significant difference in the clinical sign scores, recorded between vaccinated (G1 and G2) and control lambs.

Conclusions

From these results it was concluded that the administration of Zulvac 8 Ovis vaccine in 2.5 months old lambs is capable to prevent viraemia in the vaccinated sheep challenged 6 months after completion of the basic vaccination scheme.

Prevention of Transplacental Transmission

The Applicant confirmed that no data were available to date to show the efficacy of Zulvac 8 Ovis when used in pregnant animals.

Additional studies

No additional studies were reported (e.g. efficacy in other non-target ruminant species) besides the dose/response study described above.

FIELD TRIALS

Data on field trials were not provided. This was acceptable as the CVMP Reflection Paper on Minimum Data Requirements for an Authorisation Under Exceptional Circumstances for Vaccines for Emergency Use Against Bluetongue (EMEA/CVMP/ /IWP/105008/2007) stipulates that field trials may be omitted

OVERALL CONCLUSION ON EFFICACY

Satisfactory data were provided of the efficacy in the target species of vaccine preparations containing low antigen payloads and for the selection of the dose carried out in sheep of the minimum age. Interim results supported duration of immunity for 6 months.
Overall the CVMP concluded that the vaccine can be considered efficacious in the context of an authorisation of exceptional circumstances in the target species. In this respect the SPC reflects the current knowledge obtained by the submitted documentation.

5. BENEFIT- RISK BALANCE

Vaccination against BTV is a very important tool for the control of the disease and is also important for 'safe' trade in live ruminants in accordance to OIE standards and EU legislation. In recognition of the urgent need to make suitable authorised products available, the CVMP adopted a guideline regarding the minimum requirements for an authorisation under exceptional circumstances for vaccines for emergency use against BT (EMEA/CVMP/IWP/220193/2008). The benefit risk balance of the product has been based on the requirements of the above guideline and was considered favourable given the:

i) Epidemiological situation in Europe: Over the last ten years, the bluetongue situation in the EU has changed considerably with incursions of new serotypes, particularly in the last two years of serotype 8 into an area of the Community where outbreaks have never been reported before and which was not considered at risk of bluetongue. Furthermore, the onset of BTV-1 in northern Spain and south of France evolves by a spread of this serotype to the north with unknown consequences with regard to the epidemiology and pathology of a mixed infection with BTV-8. Co-infection by the two serotypes has been already notified in France. The recent observations of BTV-6 in The Netherlands and Toggenburg orbivirus in Switzerland add to the complexity of the epidemiological situation.

ii) Lack of authorised vaccines against BTV*:* In this emergency situation, the concerned European member states have given temporary authorisations to various BTV-8 vaccines but so-far only one vaccine against serotype 8 has obtained a centralised authorisation.

iii) Sufficient quality of the product:
-the production process is robust, proving consistency of the manufactured batches, and thus insuring consistency of the forthcoming batches,
- each batch will be blended at a target antigen concentration based on its pre-inactivation titre

- each batch will be released on the basis of a reliable batch potency test in transgenic mice

iv) Sufficient safety of the product
- sufficient data are available to exclude the presence of extraneous agents,
- the antigen is fully inactivated through a validated inactivation process,
- adjuvants and excipients used were already qualitatively and quantitatively used in other vaccines intended for ruminants,
- pharmacovigilance data already support safety of the vaccine under field conditions,

v) Sufficient efficacy of the product: the vaccine was shown to prevent viraemia caused by the bluetongue virus serotype 8.

No significant risks were identified when the product is used as indicated in SPC and under normal veterinary practice conditions. However the risk remains that the described benefits are based on limited information, which was submitted in the face of an emergency situation. On this basis the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that at present the overall benefit risk analysis is deemed positive and the quality, safety and efficacy of the product are sufficient to grant a community marketing authorisation under exceptional circumstances. However, the authorisation of the product will be subjected to annual re-assessment in order to recommend whether the authorisation should be continued or not. In addition, the commitments undertaken by the Applicant must be fulfilled, in order for the authorisation to revert to normal status i.e. no longer exceptional and subject to annual review.