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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

**An overview of field safety data from the EU for
Bluetongue virus vaccines serotype 8
emerging from the 2008 national vaccination campaigns**

Table of contents

EXECUTIVE SUMMARY	3
1. INTRODUCTION	4
2. OVERVIEW AND DISCUSSION	4
2.1 CHARACTERISTICS OF VACCINATION CAMPAIGNS AND EPIDEMIOLOGY	4
2.1.1 <i>Details on national vaccination campaigns</i>	4
2.2 SALES AND EXPOSURE	7
2.3 REPORTING.....	8
2.4 ADVERSE EVENTS.....	8
2.4.1 <i>Abortions and other effects on pregnancy</i>	9
2.4.2 <i>Reduced quality of milk</i>	9
2.4.3 <i>Spontaneous death</i>	10
2.4.4 <i>General signs or symptoms</i>	10
2.4.5 <i>Allergic reactions</i>	10
2.4.6 <i>Injection site reactions</i>	11
2.5 HUMAN REACTION DATA	11
2.6 CLINICAL AND LABORATORY STUDIES.....	12
2.6.1 <i>Field studies performed in MS</i>	12
2.6.2 <i>Laboratory studies in target species</i>	12
2.6.3 <i>Laboratory studies in other species</i>	12
2.6.4 <i>Other quality control tests</i>	12
2.7 PHARMACOVIGILANCE DATA FOR OTHER VACCINES OF COMPARABLE COMPOSITION.....	12
2.7.1 <i>Other inactivated BTV vaccines</i>	13
2.7.2 <i>Other inactivated viral vaccines, including those intended to vaccinate cows and heifers</i> ..	13
3. SUMMARY OF DISCUSSION ON MEMBER STATE DATA	13
3.1 ADVERSE EVENT REPORTING DURING EMERGENCY MASS VACCINATION IN RUMINANTS	13
4. SUMMARY CONCLUSIONS	14
5. REFERENCES	16

EXECUTIVE SUMMARY

Bluetongue is a disease caused by the Bluetongue virus. It affects sheep and other ruminants such as cattle and has a typical clinical picture involving fever, inflammation, congestion, facial swelling, haemorrhages and ulceration of the mucous membranes. The disease is spread by certain types of biting midges and is therefore classified an insect-borne disease. The disease causes substantial economical losses.

Due to an outbreak of the disease caused by Bluetongue virus serotype 8 (BTV-8) in 2006 in Central Europe and the spreading of the disease, the European Commission has encouraged mass vaccination in affected Member States to protect susceptible animals and to prevent the spread of the disease.

In 2008, various BTV-8 vaccines have been produced by several vaccine manufacturers which have been permitted by the national competent authorities for field use in mass vaccination mainly of sheep and cattle. Vaccines used for cattle included Bovilis BTV8, BTVPUR AlSap 8, Zulvac 8 Bovis and Bluevac BTV8. Vaccines used for sheep included Bovilis BTV8, BTVPUR AlSap 8, Zulvac 8 Ovis and Bluevac BTV8.

This report reviews safety information from field use of BTV-8 vaccines during the mass vaccination campaign carried out in 2008. This information is based on adverse event reports received initially from the users of the vaccines, which was collated and supplied for review by Member States' competent authorities. The primary purpose of the review was to provide background information from the extensive use of this class of products. This information was considered helpful to CVMP when assessing the benefit risk balance of potential applications for authorisation under exceptional circumstances of inactivated Bluetongue vaccines. The data provided, and the methods of analysis applied, were not intended to analyse possible differences between the safety profiles of individual vaccines against BTV-8 and no such conclusions were drawn.

Estimates of exposure to the BTV-8 vaccines, reports of adverse events observed in animals after mass vaccination, suspected human adverse reactions following accidental self-injection and other data are discussed in light of the specific characteristics related to mass vaccinations schemes.

Overall the pharmacovigilance data provided by the Member States are consistent with a good safety record for all vaccines used during the 2008 vaccination campaign.

The main other conclusions drawn were:

- The typical adverse reactions for inactivated viral vaccines, such as local reactions and non-severe general reactions typified by pyrexia (fever) and lethargy, were reported at a very low level.
- Reported reactions included: abortions, spontaneous death and some effects on milk production associated in time with the vaccinations which are, at least in part, thought to be influenced by the special conditions of mass vaccinations.
- Taking into account the high number of vaccine doses used, the frequency of reported adverse reactions is very low (less than 1 animal affected in 10,000 treated animals).
- A direct comparison of the data for individual products is prevented by the fact that the use of products differed between Member States.
- The adverse event data are affected by the fact that mass vaccinations differ from ordinary vaccinations and the procedure is generally more stressful for the animal.
- The frequency of adverse events reporting and the pattern of reports are also affected by compensation schemes that several MS have in place to reduce financial losses for the farmers that arise due to the vaccination procedure.
- The number of reports of allergic reactions is low. However, as with any vaccine, it seems prudent to monitor for allergic reactions more closely during the next vaccination season when animals, sensitised from the basic immunisation, are boosted.

Having completed the review, the EMEA recognised that the information was of potential interest to a wide range of stakeholders and therefore made the necessary arrangements for this publication.

National mass vaccinations campaigns recommence gradually as of end of December 2008.

1. INTRODUCTION

Bluetongue is a disease of sheep and other domestic and wild ruminants such as cattle, deer, goats and camelids. The disease is caused by a virus spread by certain types of biting midges (insect-borne disease). The clinical signs of Bluetongue disease (BTD) include a febrile response characterised by inflammation and congestion, facial oedema and haemorrhages, and ulceration of the mucous membranes.

In 2006 BTD was diagnosed for the first time in Central Europe when serotype 8 (BTV-8) was detected in The Netherlands. The infection rapidly spread to the neighbouring countries during the following year. The losses due to BTD were substantial. The European Commission encouraged mass vaccination in those Member States (MS) with a disease outbreak. The most efficient strategy, taking into account the current BTD situation in the EU, is considered to be the emergency mass vaccination for the purpose of the protection of all susceptible animals and for prevention of the spread of the disease.

The veterinary vaccine industry made great efforts to develop BTV-8 vaccines which became available beginning of 2008 for mass vaccination in several Member States.

In view of potential applications for centrally approved marketing authorisations for Bluetongue vaccines, the CVMP agreed during its meeting on 15-17 July 2008 that it would be useful to review any available adverse event/field safety data emerging from the use of inactivated vaccines against BTV-8 that had been made available for emergency use in several Member States. The CVMP Pharmacovigilance Working Party therefore arranged for collection of available data from Member States for a review, which was completed and reported to the CVMP meeting held on 9-11 December 2008.

This report reviews adverse events and other data and focuses specifically on field safety data that emerged from the permitted use of inactivated vaccines against BTV-8 in concerned countries. Information for the review was provided to the EMEA from Austria, Belgium, Czech Republic, Germany, Denmark, Spain, France, Italy, the Netherlands, Portugal, Sweden and the United Kingdom. Furthermore data was received from the competent authority in Switzerland. The primary purpose of the review was to provide background information from the extensive use of this class of products. This information was considered helpful to CVMP when assessing the benefit-risk balance of potential applications for authorisation under exceptional circumstances of inactivated Bluetongue vaccines. The data provided, and the methods of analysis applied, were not intended to analyse possible differences between the safety profiles of individual vaccines against BTV-8 and no such conclusions were to be drawn.

2. OVERVIEW AND DISCUSSION

2.1 *Characteristics of vaccination campaigns and epidemiology*

The veterinary vaccine industry made great efforts to develop BTV-8 campaign vaccines which became available in the beginning of 2008 for the mass vaccination encouraged by the European Commission.

2.1.1 *Details on national vaccination campaigns*

According to the national legislation all BTV-8 vaccines used were given provisional marketing authorisations (authorisations under exceptional circumstances) or other permits for use allowing their use for the mass vaccination campaign.

Tables 1 and 2 below list the vaccines intended for cattle and sheep according to the manufacturers' recommendations provided by the manufacturing companies.

All MS issued tenders and ordered the vaccine(s) centrally. Sufficient and timely availability of vaccines was a major concern which formed part of the decision process. The vaccines used in the MS

differed as listed in Tables 1 and 2. Usually the companies delivered the vaccine to one or more central locations within a MS. Thereafter the vaccines were distributed within the MS by the national veterinary services.

Switzerland also performed a mass vaccination in the whole country. The Swiss regulatory authority kindly contributed data for this survey.

2.1.1.1 *Vaccines used*

It was recommended to use only inactivated vaccines. Overall five different BTV-8 vaccines were used for the 2008 vaccination campaign in the MS and in Switzerland (Tables 1 and 2).

Most products are recommended by their manufacturers for subcutaneous use. Only for Zulvac 8 Bovis the intramuscular route is recommended.

Table 1. BTV-8 vaccines used in cattle, as reported by the indicated country

Vaccine	Manufacturer	AT	BE	CZ	DE	DK	ES	FR	IT	NL	PT	SE	UK	CH
Bovilis BTV8	Intervet							X		X			X	X
BTVPUR AlSap 8	Merial	X	X		X	X		X			X	X		X
Zulvac 8 Bovis	Fort Dodge Animal Health		X	X	X		X	X	X					X
Bluevac BTV8	CZ Veterinaria				X		X							

Table 2. BTV-8 vaccines used in sheep, as reported by the indicated country

Vaccine	Manufacturer	AT	BE	CZ	DE	DK	ES	FR	IT	NL	PT	SE	UK	CH
Bovilis BTV8	Intervet							X		X			X	X
BTVPUR AlSap 8	Merial	X	X		X	X		X	X		X	X		X
Zulvac 8 Ovis	Fort Dodge Animal Health			X			X							
Bluevac BTV8	CZ Veterinaria				X		X							

2.1.1.2 *Recommendations for use of the product*

Manufacturers' initial recommendations for use of the products were modified by national governmental agencies to meet the needs for a mass vaccination campaign. The most important modifications were related to

- the target species
According to the manufacturers' recommendation only sheep and cattle were listed as target species. However, as BTD may affect all ruminant species it was requested in many MS to include also mandatory vaccination of goats and, if indicated, a voluntary vaccination of other ruminants such as captive deer or zoo animals.
- the use of the vaccine during pregnancy
Due to a lack of data, influenced by the required speed of development, the manufacturers stated that no data are currently available on use during pregnancy which means that the vaccines are not recommended for such use. However, effective mass vaccinations make it necessary to include pregnant animals to achieve the necessary protection in the population. Furthermore, the risk to use inactivated vaccines during pregnancy is low according to the experience with other similar vaccines. Therefore the use of the vaccines during pregnancy was requested by national authorities.

- the duration of immunity
Due to the short time frame for the development of BTV-8 vaccines no or very limited data were available to propose a duration of immunity. Therefore the manufacturers estimated and proposed durations of immunity between six and twelve months. Some MS proposed variations to harmonise revaccination schemes, e.g. to revaccinate before the beginning of the vector season.
- the vaccination scheme for sheep
There were various proposals for the vaccination scheme in sheep. Whereas for some products a single injection was recommended by the manufacturers, others requested a basic vaccination of two injections. The same approaches were taken by the MS which requested only a single vaccination in some MS (e.g. Germany) whereas others consider a double vaccination as essential (e.g. Italy and Spain).
- the minimum vaccination age
Some MS requested variations to the manufacturers' recommendation for minimum age for vaccination.

2.1.1.3 Vaccination mandatory or voluntary?

BTD is a notifiable disease in the EU. Therefore requirements how to perform the vaccinations have been agreed between authorities at EU and MS level. In most MS the vaccination is mandatory, whereas in a few MS the vaccination is performed on a voluntary basis (see Table 3).

Table 3. An overview of mandatory or voluntary vaccination in MS and Switzerland

	AT	BE	CZ	DE	DK	ES	FR	IT	NL	SE	UK	CH
Mandatory	X	X	X	X	X	X	X*	X		X		X
Voluntary							X*		X		X	

* *BTV-8 voluntary, BTV-1 mandatory for 2008 vaccination campaign, but will become mandatory for both serotypes from winter 2008-2009.*

2.1.1.4 Vaccination performed by veterinary surgeons and /or farmers?

In most MS the vaccination against Bluetongue has to be performed by veterinary surgeons. Vaccinations may be performed, under the supervision of veterinary surgeons, by farmers in two MS (UK, DK) and specialised technicians in one MS (DK).

Table 4. Vaccination performed by veterinary surgeons or farmers

	AT	BE	CZ	DE	DK*	ES	FR	IT	NL	SE	UK	CH
veterinarian	X	X	X	X	X	X	X	X	X	X		X
farmer					X						X	

* *Veterinarians, specialized technicians or the farmers*

2.1.1.5 Compensation schemes

National regulations may exist to compensate vaccination damage during a mandatory vaccination campaign. This usually includes losses due to adverse events associated with the exposure to the vaccine (pharmacovigilance, e.g. abortion) but also damage due to the technical act of vaccination (e.g. injuries such as a broken leg or stress or trauma induced abortion), which is not or only indirectly related to pharmacovigilance.

Compensation schemes (Table 5) are likely to have a major influence on the frequency of reporting of adverse events which occur in close timely connection to the vaccination. These schemes are intended to increase the compliance of farmers by avoiding major financial losses due to fatalities and abortions.

Table 5. Availability of national compensation schemes in MS and Switzerland

National compensation scheme in force?	AT	BE	CZ	DE	DK	ES	FR	IT	NL	SE	UK	CH
	yes	no	yes	yes	no	yes	no	yes	no	yes	no	no

2.1.1.6 *Other specific national aspects*

In some MS in the Mediterranean area vaccination is also performed against other Bluetongue serotypes (BTV-1, -2, -4, and -16). However, data were only provided by France concerning two inactivated vaccines against BTV-1 and Spain concerning BTV-2 and BTV-4 vaccines (see 2.7).

2.2 *Sales and exposure*

All MS issued tenders and ordered the vaccine(s) centrally. Therefore detailed data exist about the total number of vaccine doses delivered to each MS. However, for most MS only an estimate is available of how many vaccine doses were used at the time of this review (data lock point 30 September 2008). Table 6 summarises the estimated number of treated animals.

Table 6. Estimated number of animals vaccinated (exposure) during the 2008 vaccination campaign, by species, as reported by MS and Switzerland

Member State	Cattle	Sheep	Goats	Others	Total
	Nr treated (double vaccination)	Nr treated (single vaccination)	Nr treated (single vaccination)	Nr treated (single vaccination)	
SE	140,000	20,000	(few)		160,000
UK	3,345,600	9,249,600	49,200	10,000 (camelids)	12,654,400
NL	2,500,000	1,200,000	100,000		3,800,000
DK	504,285	50,344	5,556		560,185
CZ	960,622	134,770 ¹	14,650 ¹		1,110,042
ES	2,278,620	4,776,021 ¹			7,054,641
BE	882,045	246,616	5,648	63 (cervids)	1,134,372
IT	2,200,000	1,330,000			3,530,000
FR					12,646,750–24,718,500 ²
DE	9,600,000	3,495,900	160,000		13,255,900
CH	1,076,106	260,328	63,455		1,399,889

¹ Double vaccination recommended in these MS

² Exact data not available, differences due to the differing vaccination scheme of cattle and sheep

Based on data until end of September / beginning of October 2008

Italics: Based on sales figures (whole vaccination campaign)

The following aspects prevent a precise estimation of exposure (number of doses used):

- Most products are licensed for cattle and sheep. However, the vaccination scheme differs because the basic vaccination for sheep mostly requires only one injection whereas the basic vaccination scheme for cattle requires two injections.
- The vaccination campaign began in April 2008 in the first countries but in some MS it was initiated much later (July/August 2008).
- In cattle a number of animals have not received the full vaccination course at the closing date for this review.
- Some animals which are on non-accessible pastures can only be vaccinated in late summer or autumn when animals are collected for purposes like stabling.

- Some differences may exist between the manufacturers' recommendations and the governmental order for use of the vaccines, e.g. sheep are vaccinated twice (according to the manufacturers' recommendations) in some MS (Spain, Czech Republic) but only once in the other MS due to governmental regulations. Similarly goats, which are not (yet) included as a target species recommended by manufacturers, had to be vaccinated according to the governmental order in most MS.
- There were exemptions from the population to be vaccinated in some MS, e.g. veal calves were excluded. On the other hand wild ruminants or zoo animals (camelids, buffalo, and deer) were vaccinated but those animals were not listed separately or those data are not yet available.

2.3 Reporting

The reporting routes of suspected adverse reactions during the emergency vaccination scheme are indicated in Table 7 below and differ from the usual routes of reporting. In some MS the majority of reports is received by the manufacturers whereas in others MS this route is not used or is very rarely used. In Italy and Germany reports are also sent via the veterinary administrative authorities which are different from the national competent authorities governing medicinal products for veterinary use.

The different ways of reporting may result in a delay in time until all reports are received by the manufacturer and the competent authority governing medicinal products for veterinary use. This clearly would result in discrepancies in figures provided by marketing authorisation holders in any safety overview reports and the current figures provided by the competent authorities governing medicinal products for veterinary use.

Table 7. Estimate of ratio (%) for primary reporting sources as indicated by MS and Switzerland

Member State	Primary reporting source					
	MAH	Veterinarians	Farmers	Veterinary administrative authorities	Other	Total
AT*						
BE	10	88	0	2	0	100
CZ	0	78	22	0	0	100
DE	1,1	88,7	0,6	9,6	0	100
DK	100	0	0	0	0	100
ES*						
FR	35	65				
IT	0	30	0	70	0	100
NL	60	40	0	0	0	100
SE		100				
UK	80,7	16,9	1,4	0	1	100
CH	1	81	16	2	0	100

* No suspected adverse reaction reports received at data lock point

2.4 Adverse events

No reports on suspected adverse reactions have been received in Austria, Spain, and Portugal at the closing date for this survey.

Tables 8 and 9 relate to the VeDDRA¹ terms most often reported for all concerned BTV-vaccines for cattle and sheep, respectively. Only a few adverse event reports were received for goats. In general these are in line with the clinical signs reported for sheep. As the goat is not a target species according to the manufacturers' recommendations this species is not listed.

¹ VeDDRA is an abbreviation for Veterinary Dictionary for Drug Regulatory Activities. VeDDRA terminology comprises of lists of standardised terms developed for reporting adverse events in animals or humans after exposure to a veterinary medicinal product.

Table 8. Lists of the VeDDRA High Level Terms (HLT)² mostly reported in cattle

Clinical term (VeDDRA HLT)	Comments including aspects on VeDDRA Low Level Term (LLT)
Pregnancy and parturition	Abortion, Foetal reabsorption, Intrauterine death, Perinatal mortality, Placental retention, Premature birth, Premature parturition, Return to oestrus, Stillbirth
Milk production disorders	Alteration of milk quality, Milk drop
Death	Death, Death by euthanasia, Sudden death
General signs or symptoms	Collapse NOS, Lethargy, Malaise, Pale mucous membrane, Pyrexia, Weakness
Allergic conditions	Anaphylaxis, Facial oedema, Hypersensitivity NOS, Urticaria
Bronchial and lung disorders	Congestion, Dyspnoea, Pneumonia, Tachypnoea
Musculoskeletal disorders	Lameness
Nasal cavity and sinus disorders	Nasal discharge, Nasal bleeding, Rhinitis
Injection site reactions	Injection site haemorrhage, Injection site lump

2.4.1 Abortions and other effects on pregnancy

In many MS a high number of reports involving abortions and other effects on pregnancy were noted in cattle. However, due to the very high number of vaccine doses the estimated overall incidence still is low (very rare or rare³). The data provided with this reports usually are not sufficient to assess the causality other than “O – inconclusive, insufficient information”.

Abortion as an adverse reaction does not fit to the toxicological profile of inactivated viral vaccines. This is only occasionally reported for other inactivated vaccines.

Abortions in cattle have been reported at a rate of more than 2% and rates up to 5% are still tolerated as being normal (Ahlers and Grunert, 1997). For abortions and stillbirth there is a long list of possible infectious and non-infectious reasons. Even if extensive additional laboratory investigations are performed the reason for the majority, over 60 %, of abortions has remained unknown (Norton and Campbell, 1990).

The effects of stress and trauma which may occur during mass vaccination procedures are also possible reasons to induce abortion. A comparable situation has been experienced two decades ago when Foot and Mouth Disease (FMD) vaccinations were performed in Europe. Abortions were one of the mostly reported adverse reactions (Baljer and Mayr, 1971). It is therefore assumed that most reported events are not product-related but may either be triggered by the procedure of mass vaccination or only be coincidental.

In sheep, the number of reports is comparably low. However, the vaccination campaign 2008 was performed outside the lambing season and the situation may change when vaccination is performed in winter time and early spring.

2.4.2 Reduced quality of milk

Two major complaints after vaccination of cows with BTV-8 vaccines were related to changes in milk production:

- reduction of milk production, milk drop
- increase of somatic cell counts in the milk

² VeDDRA terminology follows a hierarchy that categorises reported signs. The highest level is based on System Organ Class (SOC), followed by High Level Terms (HLT), Preferred Terms (PT) and Low Level Terms (LLT),

³ Standard definitions are used for expressing the estimated frequency of adverse events for veterinary medicinal products. “Very rare” indicates a frequency of less than 1 animal in 10,000 treated animals, including isolated reports, and “rare” more than 1 but less than 10 animals in 10,000 treated animals.

A reduction in milk production is a possible adverse event when lactating cows are vaccinated with inactivated vaccines. There have been several reports in MS during the 2008 vaccination campaign. Two factors contribute to the observations, namely the vaccine-related effect and the stressful situation associated with mass vaccination. According to literature a vaccine-related effect on milk production has been found for inactivated vaccines in some rare cases (Musser and Anderson, 1996; Bergeron and Elsener, 2008; Scott et al. 2001). One study is of special interest because the vaccine under test included the adjuvant composition aluminium hydroxide and QuilA (Bosch et al. 1997). The effect in this study was significant but not substantial (about 1.4 litres decrease per cow). A large number of other studies found no significant effects. It should also be kept in mind that stressful situations during mass vaccination (e.g. weather conditions, trauma, and fear or anxiety) could have a much more severe impact on milk quality.

There are several complaints from farmers about an increase in milk cell counts in cows after vaccination in some MS. However, an increase in cell counts in the summer months is a usual seasonal effect (Dobranic et al. 2008). This may be influenced in individual cases by the emergency vaccination. However, data on a population level from Germany did not show an increase in cell counts during the vaccination period in comparison to recent years (Cussler, unpublished data).

In sheep, the vaccination campaign 2008 was performed late, out of the lambing season. It cannot be excluded that the situation may change when the next vaccination campaign is performed in late winter time or in early spring.

2.4.3 *Spontaneous death*

In many MS a considerable number of reports about spontaneous death after vaccination were reported in cattle and sheep. However, due to the very high number of vaccine doses the overall incidence still is low (very rare). Spontaneous death includes the possibility of anaphylactic or anaphylactoid fatal shock reactions after vaccination. However, there are also many other reasons for spontaneous death completely unrelated to vaccination (Watson et al. 2008). Therefore, a *post mortem* examination (autopsy) is essential. According to Watson et al. (2008) carcass submissions of cattle found dead had a diagnosis rate of 74%. Unless the clinical picture *ante mortem* (before death) is known or a *post mortem* report is available the data provided with most reports are usually insufficient to assess the causality.

2.4.4 *General signs or symptoms*

Systemic reactions such as lethargy, malaise (general discomfort), pyrexia (fever), and weakness are reported for both cattle and sheep. However the number of pharmacovigilance reports is comparably low and in line to other inactivated vaccines of this kind.

2.4.5 *Allergic reactions*

Some allergic reactions have to be expected with the use of this kind of biological products. According to existing literature, the reason could be the cell line used for production of the vaccines (Eyal and Mayer, 1971; Pappous and Verbelis, 1977; Bauer et al. 1970), the residual animal serum content (Pappous and Verbelis, 1977), or other product components. The kind and the frequency of the reports are low. However, the risk of allergic reaction increases with each injection and a considerable proportion of cattle only received the first injection when the data were collected. Experience with older types of FMD vaccines showed an increase of allergic reactions after the third or fourth injection of vaccine (Lorenz and Straub, 1973). It is prudent, as with any vaccine, to continue to monitor the pattern of reactions during 2009 to determine the extent to which this applies to inactivated BTV-8 vaccines.

2.4.6 Injection site reactions

Local reactions at the injection site of BTV-8 vaccines are reported for both cattle and sheep with a slightly higher incidence rate for sheep than for cattle. However the number of pharmacovigilance reports is comparably low and in line to other inactivated vaccines with the same adjuvant system.

Table 9. Lists of the VeDDRA High Level Terms (HLT) mostly reported in sheep

Clinical term (VeDDRA HLT)	Comments including aspects on VeDDRA Low Level Term (LLT)
Death	Death, Death by euthanasia, Sudden death
General signs or symptoms	Collapse NOS, Dehydration, Lethargy, Localised oedema, Malaise, Pale mucous membrane, Pyrexia, Weakness
Allergic conditions	Anaphylaxis, Facial oedema, Hypersensitivity NOS, Urticaria
Other digestive tract disorders	Diarrhoea, Scour
Pregnancy and parturition	Abortion, Stillbirth
Bronchial and lung disorders	Dyspnoea, Pneumonia, Respiratory sound, Tachypnoea
Cardiac rhythm disorders	Tachycardia
Cardiac/heart disorders aggravated	Cardiac failure
Musculoskeletal disorders	Lameness
Coordination and balance signs	Ataxia, Lateral recumbency, Recumbency
Performance disorders	Loss of condition, Weight loss
Bone and joint disorders	Joint oedema, Joint swelling
Injection site reactions	Injection site haemorrhage, Injection site lump

2.5 Human reaction data

Overall 26 reports on human adverse reactions had been received for BTV-8 vaccines by the national authorities. By far, most reports originate from the UK and France (N=22) as detailed in Table 10 below. All BTV-8 vaccines are sufficiently similar in their composition to allow for an evaluation of the reports on a general level.

Table 10. Number of human adverse reactions reported by MS and Switzerland

Member State	Number of reports
UK	13
FR	9
DE	2
CH	2
NL	1
DK	1
ES, SE, IT, AT, CZ, LUX	No reports or no data available

Most reports refer to accidental injections and describe the expected injection site reactions for inactivated and adjuvanted vaccines. Typical signs of inflammation at the injection site (pain, oedema, swelling and joint pain) were noted. The clinical signs usually resolved within 2 or 3 days mainly without supportive treatment.

In Germany the ocular exposure to a full dose of vaccine sprayed into the right eye of the veterinarian resulted in keratoconjunctivitis (dryness of the cornea and conjunctiva).

In the UK several reports refer to general signs and symptoms including lethargy, malaise, pyrexia, jaundice, dizziness and headache. One report involved pyelonephritis (kidney infection) and pharyngitis (throat inflammation) in a patient, although product involvement was subsequently discounted after medical tests were carried out. Two reports involved sore throat after accidental self-

injection, while abdominal pain after a needlestick injury was described in a third report. It is difficult to determine the significance of these reports as the frequency with which sore throat and abdominal pain occur in the population is not known.

2.6 Clinical and laboratory studies

Most member states had no information generated by the authorities about clinical or laboratory studies (UK, NL, FR, AT, SE, DK, BE, CZ). Data provided by manufacturers did however include both laboratory and preliminary field studies that were sufficient to perform a benefit-risk assessment and to conclude on a favourable benefit-risk ratio to permit emergency use in the vaccination campaign.

2.6.1 Field studies performed in MS

A report about field studies was received from Germany. The results of the field study, performed in the German State Mecklenburg-Vorpommern under the auspices of the Friedrich-Loeffler-Institut demonstrated that the four investigated vaccines were well tolerated by cattle and sheep, and did not cause any major adverse reactions.

A similar study initiated in Switzerland (including three different products), was performed under the auspices of the Institute of Virology and Immunoprophylaxis (L. Bruckner et al. 2009). The results obtained were not different from those of the study in Germany.

2.6.2 Laboratory studies in target species

In most MS there are no studies being undertaken relating to the safety of Bluetongue vaccines. In Spain laboratory studies were carried out for three vaccines in the Laboratory of diagnoses of Algete (Madrid). The RT-PCR demonstrated elimination of virus in the blood. No further information is available on these studies.

The Italian NCA performed batch quality control tests (see under 2.6.4) which included the safety test and tests for extraneous agents (serology for Foot and Mouth Disease and pestivirus antibodies).

2.6.3 Laboratory studies in other species

None reported.

2.6.4 Other quality control tests

The Italian NCA performed batch quality control tests on sterility, inactivation, target animal safety, extraneous agents and mycoplasmas. No further information is available on these studies.

2.7 Pharmacovigilance data for other vaccines of comparable composition

The following vaccines share several similarities with inactivated BTV-8 vaccines (see Table 11):

- other inactivated BTV vaccines (similar composition, BTV serotype(s) differs)
- other inactivated viral vaccines with an alhydrogel/saponine adjuvant system
- other inactivated viral vaccines with an alhydrogel/saponine adjuvant system intended to vaccinate cows and heifers

Table 11. Overview of vaccines with a similar composition to those against Bluetongue

Vaccine	Manufacturer	Antigen(s), inactivated	Target species and category	Use during pregnancy and lactation
1. Risposal IBR-Marker inactivatum *	Pfizer	Bovine Herpesvirus type 1	cattle	Can be used during pregnancy and lactation
2. Bovilis Bovipast RSP*	Intervet	BRS-Virus, strain EV908 Parainfluenza-3-Virus <i>Mannheimia haemolytica</i> A1	Cattle from weeks of age	Proved to be safe during pregnancy and lactation
3. Bovilis Lactovac C*	Intervet	Rotavirus Coronavirus E.coli	Cows and heifers during advanced pregnancies	Can be used during pregnancy and lactation
4. Trivacton 6*	Merial	Rotavirus Coronavirus E.coli	Cattle (pregnant females)	For vaccination of pregnant cattle

* data from Summary of Product Characteristics in English (source: VMD web site)

- All vaccines include inactivated viral antigens and have the same composition of the adjuvant system (alhydrogel & saponin/QuilA) and the same kind of preservative (Thiomersal/Natriumtmerfonat).
- Vaccine 1 and 2 are used in cattle older than 2 weeks.
- Vaccine 3 and 4 are exclusively used in pregnant animals in the last trimester.

2.7.1 Other inactivated BTV vaccines

In France inactivated BTV-1 vaccines are used in some parts of the country under the same conditions as BTV-8 vaccines. The limited data available show similar pattern and incidence frequencies (“very rare”).

In Spain vaccinations are performed with serotype 4 vaccine since four years (2005-2008) and with serotype 1 vaccines since two years. Inactivated vaccines are used in cattle and, in part, in sheep whereas live vaccine is only used for sheep. More than 22 million doses of BTV-1 vaccine and nearly 10 million doses of BTV-4 vaccine have been used in cattle. Pharmacovigilance reports were very rare.

2.7.2 Other inactivated viral vaccines, including those intended to vaccinate cows and heifers

There are several inactivated viral vaccines licensed in MS for the vaccination of cattle which have the same adjuvant combination. At least two vaccines with this adjuvant system are licensed for use in pregnant cows and heifers. The pharmacovigilance data for all those vaccines document a very good safety profile.

3. SUMMARY OF DISCUSSION ON MEMBER STATE DATA

3.1 Adverse event reporting during emergency mass vaccination in ruminants

All medicinal products should be used according to the instructions for use. However, the conditions of the vaccination procedure during emergency mass vaccination differ considerably from the regular vaccination of ruminants in many respects including deviation from the manufacturers’ recommendations in certain points (see Table 12). Overall, the situation of mass vaccination is very different from the normal situation of individual vaccination, e.g. of cows. The influence of the

vaccination act on the adverse events is unknown but it is considered to be substantial due to possible stress-induced reactions.

Table 12. Differences in conditions for individual vaccination and mass vaccination

Condition	Individual vaccination	Mass vaccination
Health check	It is requested as Good Veterinary Practice to perform a health check before each vaccination	Requested but difficult or impossible to perform under field conditions
Vaccine application	Animal is rested, in a calm state, and handled with care	Animals have to be brought together in large numbers and fixed which results in stress situations
Vaccination equipment	Single dose vaccination or group vaccination with needle change	Special vaccination equipment often used, needle change less often
Recommendations for use	The manufacturer's recommendations for use should be strictly followed	Instructions given by governmental authorities may deviate from the manufacturer's recommendations for use in certain points, e.g. minimal vaccination age, duration of immunity, use during pregnancy, target species
Pregnant animals	Pregnancy status usually well-known; special care can be taken when administering the vaccine	Pregnancy status often not known; vaccination procedure mostly the same as for all other animals

Emergency and mass vaccination campaigns are performed under the rules and auspices of the national veterinary authorities.

Compensation schemes which are run in several MS where BTV-8 vaccination is compulsory are intended to avoid major financial losses for farmers due to fatalities and abortions. However, these schemes also stimulate reporting of adverse events which are not reported under "normal" conditions. This applies mainly to abortions and spontaneous death reports where it is often not possible to receive a final assessment. Therefore the compensation schemes are likely to have a major influence on the frequency of reporting. For example, a very high number of abortions is registered in Germany where several federal states compensate all losses due to abortions which occur in timely relation to the vaccination and no other obvious reason (malformation, infectious disease) are noted.

In conclusion, the pharmacovigilance data collected from mass vaccinations performed under emergency decrees will be high in number (especially when compensation schemes are in place) and include a very high percentage of reports with insufficient or inconclusive information. This is due to the vaccine act and unrelated to the individual vaccines.

In this report no attempt has been made to compare the reaction rate between individual vaccines. Such a comparison was not possible both because the data were not collected with this intention and due to the existence of differences not only between the vaccines themselves but also between the way in which the vaccination campaigns were conducted.

4. SUMMARY CONCLUSIONS

To combat the BTV-8 outbreak in Central Europe and to avoid further spreading of the disease, several MS started a vaccination campaign beginning in April 2008. The pharmacovigilance data collected until end of September in the concerned MS were evaluated. At this time the vaccination campaign was still running for cattle due to the need of two vaccinations for basic immunisation.

Concerning the data available from the MS it has to be taken into consideration that some MS used one product only or predominantly whereas others used several products. This hinders a direct comparison of the pharmacovigilance data of the individual products.

Mass vaccinations under the conditions of emergency legislation vary considerably from ordinary vaccinations and the procedure is much more stressful. Several MS have compensation schemes in place to reduce financial losses for the farmers due to the procedure. However, this obviously influences the frequency of adverse events reporting and the pattern of reports. A significant number of the reports received involved abortions. Furthermore, an increased rate of spontaneous death and some effects on milk production in timely relation to the vaccinations are reported and are, at least in part, influenced by the special conditions of mass vaccinations. However, taking into account the extremely high number of vaccine doses used the frequency of adverse reactions is always “very rare”.

Overall the pharmacovigilance data provided by the MS demonstrate a good safety record for all vaccines used during the 2008 vaccination campaign.

The typical adverse reactions for inactivated viral vaccines such as local reactions and non-severe general reactions such as pyrexia (fever) and lethargy are reported on a very low level. There may be some differences in the adverse event pattern of the individual vaccines but this would require more considerations when the data for the whole vaccination campaign are available for assessment.

The number of reports on allergic reactions is low. However, it seems prudent to monitor for allergic reactions more closely during the next vaccination season when animals sensitised from the basic immunisation are boosted.

Having completed the review, the EMEA recognised that the information was of potential interest to a wide range of stakeholders and therefore made the necessary arrangements for this publication.

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