ASSESSMENT OF THE EFFICACY OF BLUE TONGUE VACCINES: SYVA’S EXPERIENCE

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From 2006, Laboratorios Syva has developed and sold inactivated bluetongue vaccines including virus from serotypes 4, 1 and 8. Vaccines were granted national temporary marketing authorizations and were sold mainly in Spain, France and Portugal.

Immunogenicity of the vaccines was assessed by vaccination and challenge trials, where the primary efficacy criteria was the prevention of viraemia after challenge. Virus neutralising antibodies induced by vaccination, and prevention of clinical signs and lesions after challenge were the secondary criteria. Long lasting viraemia, demonstrated by RT-PCR, was constant in all challenged control animals, sheep or cattle, and with either virus serotype, showing a common and homogeneous pattern. Virus neutralising antibody response induced by vaccination was characterized by a high individual variability in titre. The most remarkable feature was that protection was achieved in all the animals developing neutralizing antibodies, regardless the titre. Development of clinical symptoms and lesions after challenge was not consistent in non-immunised control animals.

Regarding the batch potency test, three approaches have been used. (i) development of virus neutralising antibodies in sheep, (ii) comparison of antigen content in vaccine batches through serology (ELISA) in laboratory animal models and (iii) direct quantification of antigen in the final product.
CZ Veterinaria, S.A., located in North Western Spain, is a biotech company specialised in vaccines manufacturing. Its long tradition in the veterinary field started in 1937 with the production of antisera to protect livestock.

Bluetongue disease serotype 4 appeared in the Iberian Peninsula in 2004 and 2005, followed by an outbreak of bluetongue serotype 1 in July 2007. Both serotypes spread to different areas of Spain and Portugal fast. The need of an effective tool to control the disease, urgently raised by the Spanish Health authorities, involved CZ Veterinaria, S.A. in the development and production of a range of vaccines against the disease. First was BLUEVAC 4, an inactivated vaccine against serotype 4, intended for ovine and bovine.

All BLUEVAC vaccines (serotypes 1, 4 and 8) were tested for safety according to the specific requirements of the European laws. Their administration to target species was safe, it did not have negative impact on males nor pregnant/lactating animals, and no negative impact on immune response was reported.

To study immunogenicity, efficacy-controlled laboratory studies involved sheep and cattle challenged with specific virulent serotypes. An important induction of humoral response, anti-VP7 antibodies and serum neutralisation was observed. The response was strong enough to control the presence of viraemia in vaccinated and challenged animals as assayed by RT-qPCR, and to reduce the clinical signs associated with the disease. One year after the administration of the vaccines, similar results were observed.

Low interference of MDAs was observed in the efficacy showed by vaccinated and challenged animals.

A challenge batch potency test in sheep was developed to release BLUEVAC production. An alternative method in mice is being assessed to replace this test.
THE EXPERIENCE WITH BTV VACCINATION IN SPAIN

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The Bluetongue (BT) vaccination programme started in Spain after the first notification of the disease in 2000 (BTV-2 in Balearic Island, with attenuated vaccine) and ended being fully successful when the region was declared BTV-2 free in December 2002.

Afterwards, due to the spread of new BTV serotypes (BTV-4 in 2004, BTV-1 in 2007 and BTV-8 in 2008), massive vaccination campaigns against the BTV circulating in every restricted area were carried out mainly with inactivated vaccines. The animals subjected to vaccination were all cattle and sheep population over 3 months old.

This vaccination campaign was compulsory for all the farmers and under the strict control of the competent authority. The vaccination coverage during the last years has been higher than 80% of the animals leading to the dramatic decrease in the number of BT outbreaks. A more flexible vaccination policy has been performed since August 2011 when the compulsory vaccination model was switched for a voluntary one.

Furthermore, the control and eradication programme in Spain has been also based on the serological and virological surveillance (sentinel animals), clinical and entomological surveillance programmes, as well as the control of animal movements in accordance with the conditions set out in Regulation 1266/2007.

A consequence of the implementation of the BT control and eradication programme is the absence of BTV-8 circulation since 2010 (Spain is BTV-8 free since January 2013) and the limited circulation of BTV-1 and BTV-4 during the last seasons.
Multi-strain dossier concept: impact on drafting potential Ph. Eur. monograph(s) on Bluetongue vaccines

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The multi-strain concept was introduced into the Community legislation to take into account the potential antigen variability with regard to avian Influenza, Foot-and-mouth disease and Bluetongue: given all the possible combinations of antigens within each of these diseases, the scientific requirements as normally required for classical vaccines (as per Directive 2001/82/EC amended by Directive 2009/9/EC) needed to be reconsidered accordingly. This presentation focuses on the specific requirements and extrapolations accepted when the multi-strain concept is followed.

A complete overview can be found in the corresponding guideline EMA/CVMP/IWP/105506/2007 – “guideline on data requirements for multi-strain dossiers for inactivated vaccines against avian influenza (AI), Bluetongue (BT) and Foot-and-mouth disease (FMD)”, available on the European Medicines Agency (EMA) website http://www.ema.europa.eu/ema/
Vaccination against bluetongue in Southern Europe (2000-2006): a challenging experience

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Following the incursion of bluetongue virus (BTV) into European Mediterranean countries in 1998, vaccination was used in an effort to minimize direct economic losses to animal production, reduce virus circulation and allow safe movements of animals from endemic areas. Four monovalent modified-live virus vaccines (MLV) were imported from South Africa and subsequently used extensively in both cattle and sheep. MLVs were found to be immunogenic and capable of generating strong protective immunity in vaccinated ruminants. However adverse side-effects including signs of clinical bluetongue, reduced milk production, abortion and malformation were principally evident in sheep. Viraemia of sufficient titre to infect Culicoides insects was also observed transiently in MLV-vaccinated ruminants, and natural transmission of MLV strains has been confirmed. In conclusion, both experimental and field experiences proved that MLVs are immunogenic and capable of protecting and preventing viraemia in vaccinated animals after challenge or infection. Following several years of vaccination campaigns, several Member States concluded that MLV vaccines, when used correctly, were relatively safe and successful.
IMMUNOGENICITY, BATCH POTENCY TEST AND SAFETY OF BTV VACCINES

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In this presentation I would like to explain the views of our company regarding potency test in final batch. The batch potency test is an immunogenicity assay based on a challenge against each BTV serotypes that compose the vaccine. But this test is not carried out for routine testing of all batch of vaccine. Instead an alternative batch potency test is carried out: a Seroneutralisation assay. This model implies minimal suffering of the animals involved in the trial. Animals are not challenged; merely they are vaccinated and bled. This assay measures directly an immune response in the target animal. The method is capable to ensure that released batch will produce the desired immunological response: neutralising antibodies in the target animal. The presence of type-specific neutralising antibodies is indicative of protective immunity to BTV. This assay has already been used for other inactivated vaccines (according pharmacopoeia; OIE, CFR guidelines).

I will look at the key issue of safety assays in the minimum age, in pregnant sheep and in lactating sheep. The tests have been performed for monavalent and bivalent vaccines. Only local reaction has been seen after the administration. In addition, a field safety study has been realised, with no adverse reaction detected.
ZOETIS feedback regarding potential BTV monograph

Dr Catrina STIRLING
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Zoetis Animal Health (formerly Pfizer Animal Health) currently have vaccines against BTV serotypes 1, 4 and 8, all of which have been developed following rapid emergency type development programs. In principle we could support the development of a monograph for BTV vaccines however it would need to be suitable to cover all current vaccines. In addition it should not result in any barriers to different expectations for new serotypes in an emergency situation. Based on our data and experience to date we would consider that a monograph with a standard safety section could be acceptable. With regards immunogenicity this would need to be based on prevention/reduction of viremia only if it were to cover all existing products and serotypes rather than any other factors such as clinical signs, an efficacy expectation is suggested. For batch potency testing the fully in vitro alternative needs to be an option, but current batch potency tests are based on a small animal model.
In August 2006 the first outbreak of Bluetongue, serotype 8, was recorded in the EU. Only 21 months later an inactivated vaccine was approved under emergency legislation and launched. In the first year of vaccination there was high political pressure to increase the speed and volume of vaccine supply. In the second year the disease control authorities were more concerned how to deal with the shelf life of the surplus of vaccine in the market left over from year 1. At the same time the regulatory pressure increased. BTV8 is now under control, the market for vaccine against BTV8 is negligible and only the regulatory issues remain.

Vaccines against BTV8 were developed under high time pressure. Experiments to validate the product in accordance with Ph. Eur. 0062 ran in parallel instead of in sequence as is normally the case. The consequence was a significant reduction in time-to-market but with a potential disadvantage that certain decisions had to be taken on the basis of relatively little information. In addition the first information about the scale of vaccine demand only became available some 6 months before the supply of the first vaccine, which changed the scale of operation and the choice for production facilities in a very late stage of the development.

MSD Animal Health established the immunogenicity by challenge in sheep and cattle. The challenge virus was grown on mammalian cells and administered by subcutaneous injection. Protection was measured by measuring clinical protection and viraemia (RT-PCR). The antigen quantification is performed with an ELISA on the virus before inactivation. The batch potency test is performed by measuring antibody titres in vaccinated chickens by virus neutralisation in comparison to a reference batch of vaccine. The test correlates with protection by challenge in both sheep and cattle.

The existing vaccines in BTV have largely been developed under emergency procedure. MSD does not recommend developing a monograph for the existing vaccines as in time scientific information might become available for more standardised approaches across the serotypes. In addition a monograph might result in compliance issues for the existing vaccines.

MSD does not recommend developing a monograph for vaccines against EU-emerging BTV serotypes as this will significantly increase the time-to-market and create hurdles for the timely approval of these vaccines and will be a significant disincentive for vaccine companies to develop emergency vaccines. Development of emergency vaccines against emerging diseases / serotypes, in the shortest time possible, is a joint responsibility of the vaccine industry, disease control authorities and the regulatory bodies.
From 1998 to 2008, eight different BTV serotypes (1, 2, 4, 6, 8, 9, 11 and 16) have spread throughout extensive portions of Europe. In 2006, BTV serotype 8 emerged unexpectedly in the North of Europe involving Belgium, France, Germany, Luxembourg and the Netherlands. In 2007, BTV-8 spread rapidly and widely throughout much of Europe, as to a lesser extent did BTV-1. In 2008, two other BTV serotypes were detected in Northern Europe: BTV-6 in the Netherlands and BTV-11 in Belgium. The European incursion of BTV has had a considerable negative economic impact, partly due to direct losses from mortality and reduced production in affected livestock but, more importantly, from the ban of ruminant trade between BTV-infected and non-infected areas. For example, outbreaks of Bluetongue disease have occurred in Spain six times, and the serotypes of BTV (Bluetongue virus) responsible were the following, in chronological order: BTV10, BTV2, BTV4, BTV1 and BTV8. Each serotype arrived in Spain by different routes and evolved in different ways. BT is an OIE notifiable disease that leads to significant economic losses not only by causing disease in animals but also by necessitating trade restrictions to contain it. Given the importance of the disease, all affected countries have established control and eradication measures, which have evolved with the availability of detection and prevention tools such as vaccines. Before 2005 only modified live virus vaccines were used in these national BTV vaccination campaigns and, except for Italy where all susceptible domestic ruminant species were vaccinated, only sheep were vaccinated. After 2005, when inactivated vaccines became available, cattle, and goats were also vaccinated. This review looks at how the disease has evolved in Europe and it focuses on the efficacy of vaccination strategy.