Vedevax®: The First Recombinant Vaccine Against BVDV

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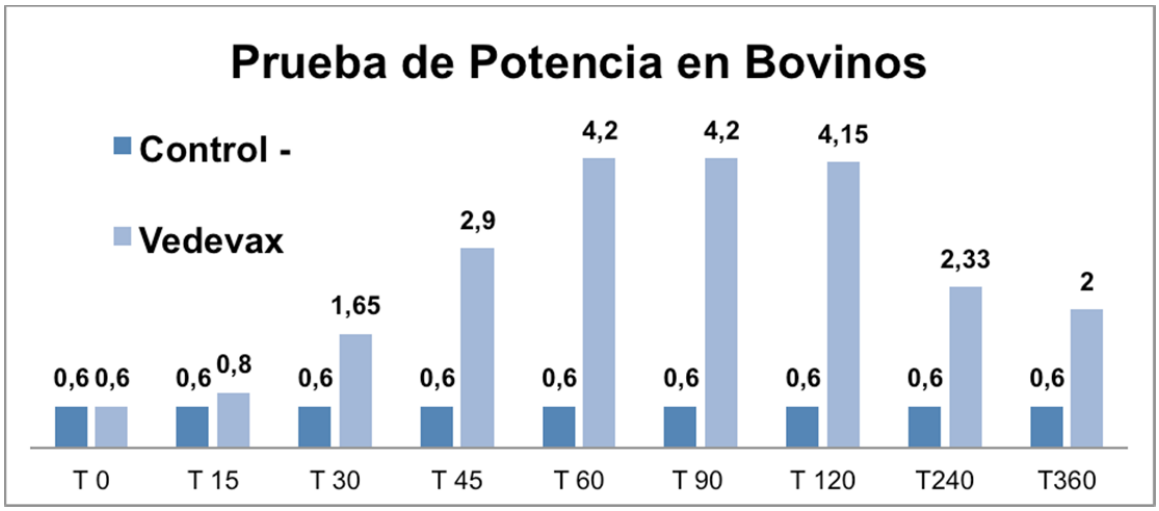
The Bovine Viral Diarrhea Virus (BVDV) is an endemic virus that causes significant economic losses in Argentina. It is a very complex virus and difficult to control, since it can cause a wide range of symptoms and has different transmission routes. Like any complex problem, the solution has to be comprehensive and include different measures, aiming at limiting the circulation of the virus in the herd. These measures can range from very simple things, such as improving fences, to complex ones, such as culling persistently-infected (PI) animals, which are the main dissemination route of the disease. One of the most important measures is the administration of vaccines that are capable of inducing protection. Vaccines have a dual function: to prevent the disease in vaccinated animals, and to lower the circulating viral load in the herd. In Argentina, the vaccines containing BVD virus are inactivated, typically combined with bacterins, and aimed at the prevention of infectious diseases linked to the respiratory or reproductive systems. The veterinarian has multiple options to choose from, as there is a wide variety of vaccines available in the local market. However, this is not necessarily an advantage, because the production of inactivated vaccines against BVDV is complicated, and the final product obtained is not always as effective as required in a diverse and complex environment, such as the Argentinian livestock industry.

Aiming at developing a vaccine superior to inactivated vaccines and capable of inducing protection against BVD, Vetanco SA established a partnership with the Institute of Virology of INTA Castelar, which had been working on this issue in collaboration with Algenex srl, a Spanish biotechnology company. The collaborative work was developed in INCUINTA, a new space of INTA for the development of technological platforms and products. The result of this interaction is Vedevax, an innovative vaccine, which production method is completely different from that of traditional vaccines. Vedevax does not use the whole inactivated virus, but only a single protein present in the external capsid of the virus, glycoprotein E2. This protein is essential for the viral replication cycle, as it participates in the virus-cell interaction. Therefore, the antibodies directed against the E2 protein are able to neutralize the viral infection, since they are capable of

blocking the entry of the virus into the cells. In addition, for the production of Vedevax, the E2 protein is fused to an antibody called APCH. This fusion allows that antibody to direct the E2 protein to the antigen-presenting cells, which are responsible for triggering the specific immune response. This mechanism that enhances the specific immune response is the main advantage of Vedevax, because it allows the use of low antigen doses, while still inducing protection against BVDV challenge. Studies conducted in our laboratory have shown that similar results are obtained either with 20 mg of E2 or with 1.5 mg of APCH-E2.

Finally, recombinant Baculovirus technology is used for the production of the vaccinal antigen. This is a different vaccine production method, which allows producing large quantities of recombinant protein at affordable costs. In addition to costs, another advantage is the replication of Baculoviruses in insect cells, which virtually eliminates the risks of cross contamination or autoimmune reactions, because, in the evolutionary scale, insect cells are very distant from mammal cells.

During the development and licensing process of Vedevax, several tests were carried out both in laboratory animals and in cattle. Vedevax far exceeded the requirements of SENASA's official test, which applies the guinea pig model for the Evaluation of Viral Vaccines (Resolution 598/12 of SENASA). The vaccinated guinea pigs presented neutralizing antibody (NA) titers higher than 2.5, exceeding by 96 % the established cut-off point. In cattle, the vaccine was tested both in calves and adult animals and, in all cases, titers higher than 3 were obtained. It should be noted that the NA titers remained higher than 2 for 12 months, which is very difficult to achieve with the traditional inactivated vaccines. Moreover, in the experiments that included challenge with infective BVD virus, all the animals vaccinated with Vedevax showed protective titers.



General considerations:

- The vaccine Vedevax is a useful tool for the control of BVDV.

- Vedevax far exceeded the cut-off point of the control test and was able to induce protection in the natural host of infection.

- Vaccination should never be used by itself, but as part of a health plan aimed at reducing the circulating viral load in the herd.

- Last, but no least, we believe that it is important to dispel the myth that "*we'll be able to control BVDV only when live vaccines are approved in Argentina*." As mentioned above, the control of BVDV requires a series of measures, including the administration of effective vaccines, whether live or inactivated.