Technical Opinion no. 1427/2008

Proceedings: 01200.002191/2007-35
Applicant: Boehringer Ingelheim do Brasil Química e Farmacêutica Ltda.
CNPJ: 60.831.658/0021-10
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Matter: Application for Opinion for Commercial Release.
Previous extract: 1091/2007. Published in the Federal Official Gazette of 07.19.2007.
Meeting: 114th CTNBio Regular Meeting, held on June 19, 2008.
Decision: GRANTED.

SUMMARY:
CTNBio, following a study of the application for import and marketing of an inactivated vaccine against Porcine Circovirosis – Ingelvac Circoflex, decided for GRANTING the request under the provisions of this Technical Opinion.
The institution, holder of CQB – Certificado de Qualidade em Biossegurança, the Biosafety Quality Certificate, no. 251/08, requested CTNBio a Technical Opinion on the Import and Commercial Release of the Inactivated Vaccine against Porcine Circovirosis – Ingelvac Circoflex. The active ingredient of this vaccine is a baculovirus derived from the PCV2 ORF2protein capsule, the sequence of which is derived from a PCV2 American strain, named struve 7-20-99, isolated from samples of liver and tonsil of two pigs that displayed clinical signs of PCVAD. The product is classified as an inactivated vaccine. Each dose of the vaccine contains inactivated swine circovirus type 2 ORF2 antigen, carbobol solution 0.5% and physiological serum. This vaccine is recommended for immunization of healthy and susceptible pigs aged three weeks or more as an aid in preventing and controlling diseases associated to porcine circovirus, including the Swine Post-weaning Multisystemic Wasting Syndrome caused by porcine circovirus 2, as an aid to reduce viremia and nasal elimination of the porcine circovirus.
The result of the voting in the plenary meeting was an unanimous approval of this request for commercial release, under the provisions of this opinion. In the light of competences granted by Law no. 11,105/05, as regulated by Decree no. 5,591/2005, CTNBio considered that the product complies with the applicable rules and legislation regarding the biosafety of the environment, agriculture, and human and animal health.

I. General Information

Porcine Circovirosis is an infectious disease of viral etiology caused by porcine circovirus type 2 (PCV 2), family Circoviridae, genus Circovirus. The infection of piglets and young pigs (five to twelve week old) may determine the behavior of a syndrome. Clinical signs include loss of weight, emaciation, tachypnea, dyspnea, jaundice or mucosa paleness, lymphadenopathy (inguinal lymphonodes) and diarrhea. PCV 2 was also isolated (1994) in newly-born pigs with congenital tremors and, in 1996, in Canada, the infection was related to the Swine Post-weaning Multisystemic Wasting Syndrome. PCV 2 antigens were already identified in association with proliferative and necrotic pneumonia, in reproductive failures and abortions in swine females and in the Porcine Dermatitis and Nephropathy Syndrome. However, this virus has also been isolated in sub-clinical cases and asymptomatic animals.
Economic losses caused by circovirosis may be significant and are mainly due to progressive thinning of infected animals, reduction in weight gain and increased food

conversion. Mixed infections (co-infection) of PCV 2 jointly with other microorganisms causing respiratory, enteric and reproductive infections are frequently reported. The weakened immunologic system of pigs infected by PCV 2, which may cause reduced immunity, is another area currently under studies

PCV was first identified in 1974, as a contaminant of PK-15 swine kidney cell cultures. This virus, currently known as PV 1 is held as non-pathogenic. The first isolation of PCV 2, which is antigenically and genetically different from PCV 1, occurred in 1996, in animals displaying Swine Post-weaning Multisystemic Wasting Syndrome. PCV1 and PCV2 are small viruses, of about 17 nm in diameter, displaying icosahedric morphology and devoid of envelope. The nucleic acid is composed by single stranded DNA, containing about 1759 negative polarity nucleotides of covalently closed circular structure.

Porcine circovirosis is currently one of the major sanitary concerns for swine farmers and professionals of the area. The reduced productivity caused by the disease causes significant economic losses to this Brazilian agribusiness industry and diminishes the competitiveness of the Brazilian pig meat in the international market due to increased production costs. Availability of an efficient immunogenic agent to reduce clinical signs and, consequently, the economic losses caused by the infection, is an aspiration of all who work in the industry.

2. GMO Description

The product Inactivated Vaccine Ingelvac Circoflex against Porcine Circovirus is a vaccine produced in baculovirus approved in the United States in 2006. The porcine circovirus PCV2 capsid gene was cloned in the baculovirus. Production was developed in lineages of insect cells derived from Spodoptera frugiperda ovaries, maintained in bovine fetal serum free culture medium, namely medium EX-cell 420. Collection is monitored at the moment when cell viability is below 10%. The supernatant part is collected and filtered through a pre-filter of 2 to 7 ?Ým and after in a filter of 0.8 to 1.0 ?Ým. In what follows, inactivation of the vaccine is conducted with BEI (binary ethylamine) (J. Clin. Microbiol. 3:209-10, 1976). The baculovirus has about 300 nm and is not retained by the filter and the virus inactivation phase, though efficient, fails to result in a purified product. The vaccine therefore comprises a circovirus PCV2 capsid protein and baculovirus DNA, resulting in an inactivated GMO.

3. Product Biosafety

Being an inactivated GMO, multiplied in a serumless medium, there is no risk of introduction in the country of an exotic microorganism. There is neither risk associated to the use in animal health of this recombinant virus as an immunogenic agent, either in pigs or other species; nor risk to public health, through infection of humans; nor to the environment; and therefore I am for the commercial release applied for. Tests conducted by the manufacturer indicated that the adjuvant (carbomer polymer, or carbopol), widely used by the pharmaceutical industry in veterinary vaccines, is considered to be safe.

Vaccine safety tests were conducted with high doses in newly-born, susceptible pigs. Application of the vaccine failed to cause toxic reactions and, according to the studies submitted, was held safe for pigs over two weeks of age.

The product offers all GMO biosafety conditions to be used as a vaccine.

4. Environment safety

One considers that the vaccine (protein from the PCV2 proteic capsid produced in insect cells) does not imply high risk to the environment.

5. CTNBio Final Opinion

Based on phytosanitary, human health and the environment risk assessment, and given

the information contained in the proceedings and the large technical and scientific bibliography, CTNBio is favorable to the granting of the request for commercial release of the Boehringer Ingelheim do Brasil Química e Farmacêutica Ltda. product named Inactivated Vaccine against Porcine Circovirosis – Ingelvac Circoflex, considering that the product is safe when used according to the technical descriptions contained in the proceedings.

6. Bibliography

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