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This is to certify that I, Marco Antônio Rochadel, Official Public Translator, designated and installed in Office according to The Official Gazette of June 23, 1982, page 5428, have received and translated, to the best of my knowledge and belief, a document with the following contents:

Ministério da Ciência e Tecnologia

GOVERNO FEDERAL BRASIL PAÍS RICO É PAÍS SEM POBREZA

Ministry of Science and Technology – MCT
National Biosafety Technical Commission – CTNBio
Office of the Executive Secretary

comissão técnica nacional CTNBio de biossegurança

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Technical Opinion no. 3637/2013

Proceedings:	01200.004340/2012-68
Applicant:	Merial Saúde Animal Ltda.
CQB:	048/98
Próton:	43717/12
Matter:	Commercial release of GMOs – vaccine against equine influenza.
Previous extract:	3445/2012, published on 12.21.2012.
Meeting:	162nd CTNBio Regular Meeting, held on May 16, 2013.
Decision:	GRANTED.

SUMMARY. The person legally in charge of the institution requested CTNBio a technical opinion on biosafety of the vaccine commercially known as **ProteqFlu** for the activities of import, storage, transport and marketing. The product has as immunogenic agents the recombinant canarypox virus carrying the gene coding HA protein of equine influenza, strains vCP1533 and vCP2241. The vaccine is produced by Merial in Lyon, France, and the product shall be imported complete and finished. Vaccine ProtecFlu is already marketed in the European Union (passed by the European Medicines Agency) since 2003, with no relevant records of adverse effects involving the relevant GMOs. The institution's CIBio represents that the operating unit has an adequate infrastructure and competent technical personnel to safely

develop the activities sought. The result of the voting of this request was favorable to approval of the application for commercial releasing, under the terms of this Technical Opinion, counting seventeen (17) votes for, one (1) vote against and two (2) abstentions. In the context of the competences granted by Law nº 11105/05, regulated by Decree 5591/2005, CTNBio found that the product complies with the relevant rules and legislation aimed at securing biosafety of the environment, agriculture, human and animal health.

1. General Information

MERIAL SAÚDE ANIMAL LTDA, CQB nº 048/98, requested a Technical Opinion to activities of import and marketing a product derived from a genetically modified organism - Proteq Flu - recombinant vaccine against equine influenza. The product contains canary poxvirus modified by a genetic engineering process to express the gene coding protein HA of the equine influenza virus, strains vCP1533 and vCP2242, and its purpose is to actively immunize horses against equine influenza (H_3N_8).

The product is presented under the form of liquid vaccine (injectable suspension), indicated to immunization of horses aged four months and older, against equine influenza, with the purpose of reducing clinical signs and viral excretion after infection. The vaccine shall be administered as an intramuscular injection, under prescription and supervision of a veterinarian. The vaccine shall be marketed in glass vials airtight sealed with aluminum capsules and stored at temperatures ranging from 2^{o}C to 8^{o}C.

2. GMO Description

Canarypox virus, ALVAC clone, was submitted to the recombinant process in order to insert gene HA (hemagglutinin) of the Equine Influenza virus in insertion locus C5 of the virus. Donor strains of gene HA were strains A2/Ohio/03 generating the recombinant strain vCP2242, and A2Newmarket/2/93, generating the recombinant strain vCP1533. Thus, the product of the gene inserted in the receiving organism is just protein HA, which is able to induce specific

immune responses, mediating the protection against influenza infection in different species of animals. The virus fails to replicate in any other species except aviary ones, and there is no persistence in equines. Clone ALVAC is highly attenuated and is not pathogenic even to the canary, its natural host, failing, in addition, to present forms that are resistant to the environment.

The construct of recombinant strains used genetic engineering classical techniques. The construct uses Pjt004 plasmidial vectors to construct the recombinant strains vCP1533 and pJY1571 to construct the recombinant strain vCP2242. Both recombinant strains contain an expression cassette constructed by the coding region of gene HA plus an H6 promoter derived from the vaccinia virus, flanked by the right and left flanking arms of the insertion locus C5. The coding region of gene HA, strain A2Newmarket/2/93, of the equine influenza virus was obtained by RT-PCR, while virus from strain A2/Ohio/03 was chemically synthetized, incorporating the codons optimization. All phases of vector construct were monitored by the standard of fragments generated by digestion with restriction enzymes, and by DNA sequencing.

This clone is classified in Europe as Group 1 pursuant to the European Union Directive 90/219/EEC (non-pathogenic, with a safe record of use, and without risk of adverse action to the environment).

Applicant submitted information on the GMO, assessment of risk to human and animal health, assessment of environmental risk, monitoring plan and supporting documentation.

3. GMO Biosafety Analysis – Pursuant to Ruling Directive nº 5, of March 21, 2008, Annex III.

- ***GMO characteristics and genetic and phenotypic stability***

Pursuant to Ruling Directive nº 2, of November 27, 2006, recombinant organisms vCP2242 and vCP1533 are in Risk Class 1 low individual risk and low collectivity risk). Canary pox virus, clone

ALVAC is a highly attenuated virus, displaying a very restricted spectrum of hosts limited to avian species, non-pathogenic even for its natural host, the canary, failing to display forms that are resistant to the environment.

Genetic and phenotypic stability of the two recombinant organisms was assessed after, at least, 9 passages. Mappings with restriction endonucleases were used to confirm genetic stability and immunoassays, in plates using specific monoclonal antibodies against gene HA. Results show 100% stability, both for the genotype and expression of the HA gene product.

- ***Assessment of risk to human and animal health***

Regarding ability to disseminate the vaccine organism in animals and human beings, several tests confirmed absence of replication of GMO in non-avian cells. Therefore, the GMOs have no ability to disseminate within the inoculated animal (equine) or from the inoculated animal to another non-inoculated, or from the inoculated animal to the environment, therefore promoting a large safety margin. Studies conducted with ALVAC clone in canaries revealed that the virus was no longer detected in the inoculation location from the 15^{th} day after inoculation. In humans, nor the parental strain nor the derived GMO are replicative and therefore mean no risk to human health.

- ***Environmental safety***

Regarding environmental risk, the GMOs are not involved in environmental processes (primary production, nutrient renewal, decomposition of organic matter or respiration), and therefore have a negligible effect on the quality of air, water and soil. They do not survive, being extremely labile when exposed to the environment, do not multiply and do not disseminate in water, air or soil.

4. Post-commercial Release Monitoring Plan

Complying with Brazilian rules regarding GMOs, the company presents a monitoring plan for the ProteqFlu vaccine with a term of a least 5 (five) years, encompassing the following phases:

1. Monitoring the process of importing the product: all vaccine batches to be imported shall be noticed to CIBio, who shall notify CTNBio through a yearly report including the amount of batches, vials and doses that are being imported to be sold in the Brazilian market.
2. Monitoring of the storage and distribution processes:
   - The imported product shall be stored and distributed under the current good practices for transportation of refrigerated vaccines;
   - Local disinfection to be applied with sodium hypochlorite and alcohol at 70% in case of rupture of vials;
   - In case of accident – prompt notification of the biosafety supervisor.
3. Post-sale monitoring – this monitoring shall be incorporated to the drug monitoring already in place at the company, operating as follows:
   - SAC (Consumer Service System);
   - SAC – Planitox Customer – in case related to humans;
   - Product Technical Manager;
   - Latin America RA Technician in Charge – reception and reporting to the Merial World Drug Surveillance System all suspected cases of adverse reaction, both in animals and humans;
   - Biosafety Supervisor;
   - Merial Brazil Technician in Charge – person in charge of the company actions related to the GMO;
   - Local Decision Group – acts in events of GMO unexpected action directly related to its action. Defines the likelihood of mitigating actions and follows their deployment and results, or suspension of the product marketing.

5. Final Opinion

The application for commercial release encompasses two vaccines commercially styled as ProteqFlu. The vaccine includes two GMOs as immunogenic agents: Canary poxvirus (CNPV) recombinants vCP2242 and vCP1533, where the HA (hemagglutinant) of Equine Influenza has been inserted in insertion locus C5 by homologue recombination (using flanking arms C5R and C5L). Therefore, the vaccine shall protect against equine influenza (H_3N_8). The coding gene for the hemagglutinin (HA) inserted in locus C5 of CNPV is controlled by promoter H6 (of 94bp) of the vaccinia virus. Protein HA, together with neuroaminidase (NA), is a protein of the equine influenza virus envelope. Recombinant plasmid containing HA under the control of promoter H6 inserted of locus C5 (flanked by C5R and C5L) was used to transfect fibroblast cells of chicken embryo infected by an ALVAC clone of the canary pox virus (parental organism). This way the strain of the recombinant canary pox virus was generated.

CNPV may, *in vitro*, enter human cells, however it fails to survive and does not replicate. Indeed, it is known that the virus fails to replicate in any other species, except for birds. It also fails to persist in equines. The virus, used in the vaccine (ALVAC clone) is highly attenuated, displaying a very restricted spectrum of hosts, limited to birds (yet non-pathogenic to the canary, its natural host) and fails to present environment-resistant forms. Analyses carried out with the ALVAC clone in canaries, the virus was no longer detected in the inoculation locus on the fifteenth day after inoculation. Nor the parental strain nor the derived GMO are replicative in humans and therefore fail to pose risk to human health.

Besides, this virus has already been passed by CTNBio as a vaccine organism (Proceedings 01200.000292/98-92) and has a long record of marketing in the Brazilian market (Recombitek C4/CV and Recombitek C6/CV, used in dogs, protecting them against canine distemper, parvovirus, coronavirus, parainfluenza, type 2 adenovirus and infectious hepatitis).

The technical opinion on biosafety of the genetically modified organism is based on the following points: (1) Risk classification of the genetically modified organism present in the vaccine is that of risk class 1 (low risk for individuals and low risk for the collectivity); (2) data

analyzed show that the vaccine fails to imply additional risks to human health, environment and animal farming; and (3) the post-commercial release monitoring plan is inclusive and well-structured. Therefore, we reach the conclusion that commercial release of the vaccine ProteqFlu TE, targeted to active immunization of horses against equine influenza (H_3N_8) is not a potential cause of significant degradation of the environment nor harmful to human and animal health.

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Dr. Flávio Finardi Filho

CTNBio President

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In Witness Whereof, I have hereunto set my hand and seal in this City of Brasília, Federal District, Brazil, this Friday, November 15, 2013.

Fees according to

Official Gazette of 04/15/2011

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Marco Antônio Rochadel

Public Translator