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**CHINA ANIMAL HEALTHCARE LTD.**

中国动物保健品有限公司\*

*(Incorporated in Bermuda with limited liability)*

*(Hong Kong Stock Code: 0940)*

## **VOLUNTARY ANNOUNCEMENT**

### **AUTHORIZATION FOR INVENTION PATENT FOR NON-PATHOGENIC RECOMBINANT ATTENUATED RABIES VIRUS STRAIN AND ITS CONSTRUCTION METHOD AND APPLICATIONS**

This announcement is made by China Animal Healthcare Ltd. (“CAH” or the “Company” together with its subsidiaries, the “Group”) on a voluntary basis. The board of directors of the Company is pleased to announce that the Group has recently obtained the authorization for invention patent for “Non-pathogenic Recombinant Attenuated Rabies Virus Strain and its Construction Method and Applications (无致病性的重组减毒狂犬病毒株及其构建方法和应用) (patent number: ZL201210220784.X).

### **NON-PATHOGENIC RECOMBINANT ATTENUATED RABIES VIRUS STRAIN AND CONSTRUCTION METHOD AND ITS APPLICATIONS**

On 18 April 2014, the Group obtained the authorization for invention patent for non-pathogenic recombinant attenuated rabies virus strain and its construction method and applications (the “Rabies Virus Patent”) from the State Intellectual Property Office (“SIPO) of the People’s Republic of China (the “PRC”)(中華人民共和國知識產權局).

Rabies is a zoonotic disease caused by rabies virus which infects the central nervous system of the host. It is estimated that there are 60,000 deaths caused by rabies every year, and most of them occurring in the developing countries in Asia and Africa (approximately 56% in Asia and 44% in Africa). Currently, India has the highest rate of human rabies in the world, with about 20,000 people dying from rabies annually. About 95% of such cases were attributed to

dog bites, of which 11% was by pet dogs and the rest by stray dogs. With the second highest number of human rabies in the world and only behind India, China is also a country where rabies is highly prevalent. In 2007, the number of deaths from rabies reached 3,300 nationwide. Over 2,700 people died of rabies in 2012 and 2013. As such, rabies has been ranked as one of the top three infectious diseases in China in terms of number of death caused.

In the 1980s and 1990s, a number of countries in Europe and the United States adopted an immunization programme for host of rabies virus by using vaccines with live attenuated virus and recombinant attenuated virus. This program drastically lowered the rate of wild animal rabies, and hence indirectly reduced the risk of rabies transmission from wild animals to domestic animals and humans. This generated satisfactory social and economic benefits. There are immunization programmes for pet dogs and cats in most of the urban areas in China. However, there are many domestic dogs and cats in the rural villages spreading over an extensive area, it is difficult to conduct administration of inactivated vaccines due to a high number of injections required and a short effective period. Substantial manpower and resources are needed and the staff is also exposed to the risk of being infected.

Oral vaccine developed from live attenuated rabies virus strain has numerous advantages as it can not only provoke innate and adaptive immune reactions with fewer injections, it costs lesser and is easy to use, which will facilitate its promotion and application. World Health Organization recommends the use of live attenuated vaccines for the prevention of rabies in wild animals and stray dogs.

Prevention and treatment of rabies in China is a great challenge. Out of a huge canine population of approximately 100 million canine, only 10 to 20% of the population is immunized, and cats are barely immunized. There is also much to be done in the prevention and treatment of rabies in wild animals. Animal rabies is the source of human rabies, and the key to elimination of animal rabies is to enhance the efforts of vaccination in animals. After decades of research and development, China has successfully developed safe, effective and purified cellular rabies vaccines, and their quality is comparable to international standards. However, there are certain constraints which includes high manufacture and injection costs, and difficulties in administering vaccines on dogs.

In recent years, both domestic and foreign companies focused their research on the production of the rabies vaccines that are safe, effective, easy to use and economical. In respect of live animal rabies vaccines, the main research trends for both domestic and foreign researchers include immunogenic efficacy with the help of reverse-genetics technology, developing safe vaccine vector and suitable vaccine delivery system. Oral vaccine reduces the level of discomfort and prevents infection associated injection vaccines. The administration procedure and operation process is simple and does not require the presence of healthcare professionals. This particularly useful for vaccination of domestic dogs, wild animals, stray animals and large groups of farm animals. Vaccine injection mainly aims to provoke general immune response of the subject; whereas mucosal vaccine is able to induce

response at a local level, and hence efficiently preventing further invasion from the pathogen. In particular, it is of special significance for the prevention and treatment of diseases caused by mucosal infection. Animals are an enormous natural storage for pathogens. Throughout the history, many human and livestock diseases are closely related to wildlife, for example, AIDS, bird flu, plague, rabies and west Nile fever. Animal plagues not only poses a threat to the lives of wild animals, but is also a major concern for the well-being of humans. To control animal pathogenic diseases and to prevent them from becoming threats to both animals and human is a key concern for researchers around the world, and the research and development of oral vaccines for animals offers promising prospects. Quick and easy immunization methods are the key to disease prevention and control. Developed countries have mostly eliminated rabies among humans and domestic animals, and the focus of their research on animal rabies vaccine is the prevention of rabies in wild animals like raccoons, skunks and foxes. These vaccines are mostly orally-administered, and permits have been obtained for the commercial manufacture and use on wild animals in Europe and the United States. These vaccines are produced with oral cells to culture live attenuated vaccine and live attenuated vaccine vectors (canary pox virus, pox virus and gland virus).

The Company has successfully developed a generation of non-pathogenic oral rabies vaccine and recently obtained the state-authorized patent for Rabies Virus Patent. The patent uses the technology of reverse molecular genetics, which makes the attenuation of rabies virus strain more target-specific. It also provides a stable genetic recombination of rabies virus and allows for the insertion of external genes. The mutation of amino acid Arg333 in the glycoprotein gene of rabies virus results in reduced pathogenicity, so that the rabies virus is no longer virulent to mice. Mutation in other locations, such as glutamic acid, glycine, leucine, cysteine, methionine also reduces the virulence of rabies virus to a non-disease-causing level. In mastomys and mice, a 2-3-copy of glycoprotein gene induces a high level of neutralizing antibodies to enhance the immunogenicity of non-virulent rabies virus. It causes apoptosis of neurons and leads to immunoreaction in the signal transduction pathway of interferon, resulting in a lower death rate for mastomys and mice. The technology of reverse molecular genetics removes the various fixed virus CTN-1 strains, which are naturally passed on in rabies virus, and constructs G protein genes that carry street rabies virus mutated at position 164 (Asn-Ser) and position 333 (Arg-Glu). A brain injection of 2-copy of GAG rabies virus recombinant does not cause disease to a mastomys. It leads to an overload of G protein gene and facilitated cell apoptosis, resulting in a significant enhancement of immunogenicity. Such brain injection does not cause disease to 5-day-old mastomys, mice with congenital immunodeficiency disease, mice and ordinary animal either, which underlines its safety and good immunogenicity. It induces the central nervous system tissue to respond with immunoreaction and eradicates street rabies virus that infects the central nervous system. The advantages of the vaccine before and after exposure to rabies are as follows:

(1) Efficient attenuation and quick design and development of vaccine

## (2) Clear immunity and attenuation mechanisms

It induces decent immunoreaction in mastomys, mice, dogs and other targeted animals. The vaccine causes a more intense reaction than the original ones and stimulates the maturing and transformation of infected mononuclear cells and young dendritic cells, strengthening the expression of interferon- $\alpha$  and interferon- $\beta$  and relevant genes in a stimulated NF $\kappa$ B signaling pathway.

## (3) Higher security

The original attenuated vaccines (fixed virus CTN-1) provides a safe and effective base on which the position of pathogenicity is altered by molecular biology operation. The new vaccines are much more secure due to the possibility of back mutation, and hence the recovery of pathogenicity in live vaccines, is significantly reduced.

## (4) Higher efficiency

In comparison with commercially available rabies vaccines with poxvirus vector recombinant by tests carried out on dogs, with various groups of dogs treated with vaccination dosage of  $10^8$ - $10^9$ TCID<sub>50</sub>/1ml respectively and blood samples taken every week and rabies virus injected into the dogs after five weeks, it was found that neutralizing antibodies for rabies virus were produced in 1-2 weeks after vaccination. Street rabies virus extracted from dog sources were injected into all tested dogs in the experimental and control group. The experimental group all remained alive while the control group all suffered from rabies. One of the dogs in the V-RG group was infected, which highlights the fact that the vaccines possess higher security and immunogenicity than the existing vaccines available in the United States.

An injection of vaccination triggers intense internal and adoptive immunoreaction, which eradicates the rabies viral infection on the central nervous system. It is not only applicable to the prevention of rabies for animal dogs, but also the immunotherapy of later stage of rabies exposure for human. When compared to all the existing vector recombinants in an attenuated vaccine strain, the brain injection of a 2-copy rabies glycoprotein gene in an attenuated vaccine strain does not cause disease to mice, 5-day-gold mice with immunodeficiency and mature animal. It also induces immunoreaction after the infection of pathogenic rabies virus on the central nervous system without the occurrence of symptoms of cephalitis.

## (5) Stable genetic materials that allow easier cultivation, development, mass production and quality control

BHK-21, cell subclone BSR, is used in the cultivation of stroma cells of the virus.  $10^{10}$  virion/ml is yielded through cultivation by biological reactor technology, which is heat-resistant and stable. Gene sequencing demonstrated that the genes remained highly stable

through continuous passage in 10 groups of newborn mice. The virulence-related genetic positions in the virus, Glu333 and Ser164, neither undergo back mutation nor changes.

(6) Availability of both endovaccination and injection vaccination

The domestic vaccination market is in need of the development of efficient and economic injection vaccinations for the non-intestinal immunity of animals such as domestic dogs and cats. The alternative option is to develop oral vaccinations with feeds.

None of the Directors or substantial shareholders of the Company has any interest, directly or indirectly, in the abovementioned transactions.

By Order of the Board  
**China Animal Healthcare Ltd.**  
**Wang Yangang**  
*Chairman, Chief Executive Officer  
and Executive Director*

Hong Kong, 30 April 2014

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*As at the date of this announcement, the executive Directors are Mr. Wang Yangang and Mr. Sun Jinguo, the non-executive Directors are Dr. Ying Du and Mr. Alberto Riva, and the independent non-executive Directors are Mr. Ong Kian Guan, Mdm. Feng Jinglan and Mr. Wong Gang.*

*\* for identification purpose only.*