Information on the dissemination of a live canarypox-FeLV recombinant virus (vCP97) in the context of a safety field trial with the RMB696 vaccine

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This information concerns the dissemination of a live canarypox-FeLV recombinant virus (vCP97) as part of a combined feline vaccine (RMB696).

A/ The vCP97

The vCP97 is a potent vaccine against feline leukaemia virus (FeLV) infection, which is one of the major cause of non-accidental death in cats.

FeLV is a common infection of domestic cats throughout the world and a cause of significant morbidity and mortality. For example, in the United Kingdom the prevalence of viraemia is 1-5% in healthy cats and 20% in sick cats (Hosie *et al.*, 1989). FeLV may establish a life-long infection characterised by a persistent viraemia. These viraemic animals are the source of infection for susceptible cats to which they spread virus through contaminated saliva. A significant feature of the diseases caused by the virus is that they are serious and mostly fatal. Among the most frequently diagnosed conditions in FeLV-infected cats are lymphomas, myeloid leukaemias, immunodeficiency and non-regenerative anaemia. Most of these cases of disease occur in cats aged between 2 and 4 years of age. Consequently there is a considerable demand for effective control of the infection. Previously this was achieved by the identification and isolation of persistently viraemic cats which are the source of the infection. More recently vaccination has also contributed to the prevention of spread of the virus. In European countries, several different FeLV vaccines are available all of which comprise inactivated virus or recombinant subunits. Efficacy of 70-100% has been claimed for these vaccines in experimental infections (reviewed in Sparkes, 1997) but little is known of their efficacy in the field. Since apparent vaccine breakdowns have been observed, there is clearly a need for improvement in vaccine efficacy and particularly for more evidence of protection in field conditions. One possible way to improve vaccine efficacy would be to use a live attenuated vaccine. In some occasions, live virus vaccines may have many advantages over inactivated virus vaccines, particularly by inducing a wider range of immune responses. However, it is difficult to imagine that a live attenuated FeLV vaccine would be acceptable for field use since it would be virtually impossible to establish the safety of the product.

The vCP97 is a live recombinant canarypox-FeLV virus expressing the FeLV antigens involved in protection against feline leukaemia. A particular advantage of using canarypox virus as a vector is that it undergoes an abortive infection in mammalian cells so that the virus does not multiply in the cat and therefore the vaccine virus cannot spread from vaccinated animals. The vCP97 does not multiply in cats, but expresses the FeLV protective antigens. *In vivo*, such expression stimulates a very good immune response to the FeLV proteins, and is particularly adapted to the stimulation of the cell mediated immune response. While it is recognised that virus neutralising antibodies are an important indicator of protection from FeLV infection, it is widely believed that cell mediated immunity plays a major role in natural recovery from infection and in vaccinal immunity.

In conclusion, the vCP97 combines efficacy and safety and is therefore an excellent vaccine against FeLV infection.

B/ Risk assessment of the vCP97

Previous experience and know-how at MERIAL concerning live vectored vaccines, and examples of live canarypox-vectored vaccines against HIV in humans (Tartaglia, 1993) led to the concept of a live vectored recombinant canarypox virus for the development a vaccine against feline leukaemia.
The vCP97 has already been used in large scale safety field trials in France (two disseminations) and in Belgium (one dissemination) in the context of a combined vaccine containing the same recombinant. No safety problem has been reported in relation with the dissemination of the vCP97.

The vCP97 is a canarypox-based recombinant expressing the FeLV protective antigens. The canarypox parental strain is derived from an attenuated vaccinal strain contained in KANAPOX® a vaccine against canarypox virus infection in canaries (more than 1.4 million doses have been used in canaries without any safety problem). This canarypox virus strain has been selected for the following reasons:

- canarypox virus does not multiply in cats and more generally in mammals, and therefore does not spread following vaccination,
- canarypox virus has a very narrow host range (the canary is the natural host),
- the vCP97 is very safe for the canary,
- it is genetically stable.

The canarypox virus, as a vector, is very good at stimulating the cellular immune response and is therefore the vector of choice to protect against retroviruses including FeLV. Only the protective immunogens of FeLV (*env* and *gag*) are expressed by the canarypox virus. The vCP97 does not contain any of the genes allowing replication or insertion of the FeLV in the cell genome.

The efficacy and safety of the vCP97 have been demonstrated in compliance with the regulation in force. In addition, the safety of the vCP97 was shown to be very good in various species, including canaries (the natural and permissive host), chickens, guinea-pigs, mice and cats. The vCP97 is very satisfactory both in terms of efficacy and safety.

The risk assessment was based on the following analysis:

- assessment of the hazard identification,
- assessment of the likelihood of each hazard,
- assessment of the consequences of the hazard,
- assessment of the overall risk.

This risk assessment was based on the biology of the poxviruses and retroviruses, using when necessary the full nucleotide sequences of the inserts and those of the insertion loci regions.
It was also based on the conditions of use of the vaccine:

- the vCP97 is contained in sealed monodose vials,
- it is administered by the subcutaneous route to the cat by a veterinary surgeon.

Considering the conditions of use and the absence of multiplication and spread of the vCP97 in cats, there is no contact between the recombinant virus and the environment under the normal conditions of vaccination.
In conclusion, the overall risk was estimated as negligible.

C/ Objective and conditions of the present dissemination

1/ Objective of the dissemination

The objective of the present dissemination is to confirm the safety of the RMB696 vaccine in a clinical trial in cats as requested by the regulation in force. This trial aims at confirming in field conditions the good general and local tolerance of the RMB696 vaccine which has previously been demonstrated in regulatory laboratory studies.

The RMB696 vaccine is a combined feline vaccine against rhinotracheitis (inactivated), feline calicivirus (inactivated), infectious panleucopenia (attenuated) and feline leukaemia (vCP97), which are the four main infectious diseases of cats.
The RMB696 vaccine is a freeze-dried pellet (containing the feline leukaemia and infectious panleucopenia components) to be reconstituted by an oily diluent (containing the rhinotracheitis and feline calicivirus components).

2/ Site of the dissemination

The trial will be carried out in Belgium under the control of Merial and veterinary surgeons acting as investigators. The veterinary practises are located in different parts of the country (administrative areas B-1740, B-2100, B-2170, B-2800, B-3001, B-4052, B-4100, B-4432, B-7100 and B-7500).

The trial is carried out by veterinary surgeons according to a written protocol. Cats are vaccinated via the subcutaneous route by the veterinary surgeon. Only healthy cats will be included in the trial. The cat owner is informed about the trial and the recombinant nature of the vaccine; the owner consent is a prerequisite for the inclusion of the cat in the trial. The vaccinated animals are followed-up for 2 weeks by their owner who must contact the veterinary surgeon at the end of the follow-up period and in case of any abnormal event. Used vials, syringes and needles are collected by MERIAL for destruction.

3/ Monitoring of the dissemination

Despite the negligible risk related to the use of the vCP97, an emergency plan was established.
In case of accidental injection to humans, we recommend to seek medical advice immediately and show the package insert or the label to the physician. The risk is not associated with the recombinant FeLV component since the same vector has already been used in humans in phase I and II clinical trials. The risk lies mainly in the oily adjuvant.
In case of accidental breaking of a vial, the contaminated surface should be disinfected with bleach.

In case of an unexpected event, 3 operating phases are implemented:

- Alert phase:
  . any observation which can not be related to the normal post-vaccinal adverse reactions (transient and mild swelling at the injection site and transient lethargy) must be reported to the investigator veterinary surgeon and to the monitor of the trial.
  . the concerned animal will be kept indoors by its owner.

- Investigation phase:
  . appropriate samples are collected and sent to the laboratory for virus isolation and identification,
  . treatment of the animal is immediately prescribed by the veterinary surgeon.

- Action phase:
  . *the diagnosis is known before the end of the trial and the event is not related to the vaccine:* the investigator starts treating the concerned animal.
  . *the diagnosis is known before the end of the trial and the event is related to the vaccine:* the recruitment of cats for the trial is stopped. Owners of cats which have already been vaccinated with the RMB696 are asked to keep their cat indoors for a 1-month follow-up.
  . *the cause of the event is not known by the end of the trial:*
  If the cause of the unexpected event is not established at the end of the trial, an adverse reaction related to the vaccine can not be eliminated. The follow-up of all the animals included in the trial will be extended for 1 month after the end of the trial..