15 September 2010
EMA/CVMP/433418/2010
Veterinary Medicines and Product Data Management

Opinion of the Committee for Medicinal Products for Veterinary Use pursuant to Article 30(3) of Regulation (EC) No 716/2004 of the European Parliament and of the Council on retrovirus RD114 in live attenuated vaccines for use in animals

EMEA/V/A/058

Basis for opinion

On 19 April 2010, the European Medicines Agency (the Agency) requested the Committee for Medicinal Products for Veterinary Use (CVMP) to give an opinion under Article 30(3) of Regulation (EC) No 726/2004 on feline endogenous retrovirus RD114 in live attenuated vaccines for use in animals, as a result of a publication of an article in the Journal of Virology presenting new information regarding the detection of feline replication-competent endogenous retrovirus RD114 in some live attenuated vaccines commercially available in the EU.

Specifically, the Committee was requested to provide advice on the following five issues:

1. Whether there is currently a public or animal health concern caused by live attenuated vaccines, or their raw materials, used for dogs and cats in the EU, in light of published information reporting that replication-competent retrovirus RD114 has been detected in such unidentified commercially available vaccines.
2. Whether, in case such concerns exist, there is currently sufficient information to consider that the overall benefit risk balance of the products is affected such as to warrant prompt regulatory action.
3. To identify whether any additional information is required to complete a re-assessment of the benefit-risk balance, and how such might be obtained.
4. To comment on the suitability of the application of novel molecular methods for the detection of extraneous agents, and sub-components thereof, in vaccines and/or their substrates for routine use for regulatory purposes and to indicate if there is a need to update existing guidance related to the testing and elimination of such substances in the context of development and/or testing of live attenuated vaccines.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8447
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

5. To consider the need for appropriate guidance for other vaccines.

On the basis of the request made by the Agency, the CVMP considered that there were sufficient grounds to start the procedure.

The procedure started on 20 May 2010.

Opinion

The CVMP, having considered the matter and the additional information provided in an oral consultation with IFAH-Europe as set out in the appended assessment report (Appendix 1), reviewed the available evidence and came to the following conclusions:

The hazard constituted by replicative retrovirus RD114 cannot currently be defined. Consequently, the risk of its presence in cat and dog vaccines is not quantifiable, however the impact of this risk is probably low on animal health and extremely low on human health.

The benefits of vaccination against cat and dog diseases clearly outweigh the potential risk that is linked to the presence of replicative retrovirus RD114 in vaccines. The threat represented by retrovirus RD114 is currently theoretical. No prompt regulatory action is warranted, although corrective actions need to be undertaken.

Additional information is awaited from ongoing testing of feline cells used in the manufacture of cat and dog vaccines to detect the presence of retrovirus RD114. These data will be necessary to complete the assessment of the benefit-risk balance and to agree on risk management measures, as needed.

On the other hand, it is not considered acceptable to have vaccine batches on the market containing unwanted live virus particles, without trying to investigate and correct this issue. Therefore, considerations for improvement of the vaccines are needed and appropriate actions might include replacement of cell lines, introduction of manufacturing steps to allow clearance of the virus, and inactivation of retrovirus RD114. Implementation of such corrective measures will take a long time, and implies close collaborative studies between authorities and industry. The procedure for cell line replacement in such circumstances needs to be agreed upon, both from an administrative and a scientific point of view.

The Committee recommends for the Agency to liaise with EDQM, to identify to what extent collaborative studies with various OMCLs are feasible to validate the protocol that has been agreed earlier with industry and which is currently used by some companies to test for the presence of retrovirus RD114 in the cell lines of feline origin which are used for manufacturing of vaccines for use in animals. Should the outcome of such a validation study either be satisfactory as such, or lead to amendments of the protocol, this (amended) protocol could then become an Ph. Eur. monograph to be implemented systematically for future feline cell Master Seeds to be used for manufacturing of veterinary vaccines. This would be a significant step forward, although it is not clear at this stage to which extent this protocol could be implemented to test potential contamination of Master Seeds of feline viruses or of feline intracellular bacteria (which that could also convey retrovirus RD114.

In addition to RD114 ad hoc measures (e.g. assay on cell seeds for presence of reverse transcriptase, testing of End of Production cells), it would be advisable to proactively develop general guidance addressing the detection of adventitious genomic fragments or virus particles in immunological medicinal products for veterinary use. Given the CHMP currently considers the drafting of a guideline on a similar topic for human vaccines, the development of a joint CVMP/CHMP guidance could be considered by the parties. This process needs however to be undertaken with caution, as the benefit-risk balance will probably be quite different between human and veterinary vaccines.

The Icelandic and the Norwegian CVMP members agree with the above-mentioned recommendation of the CVMP.

This opinion is forwarded to all Member States, Iceland, Norway and to the European Commission together with its appendix.

The opinion will be published on the Agency website with its appendix.

London, 15 September 2010

Dr. A. Holm,
Chair, on behalf of the CVMP

Appendix 1. CVMP assessment report concerning feline endogenous retrovirus RD114 in some live attenuated vaccines commercially available in the EU for use in animals (EMA/CVMP/300321/2010)