Appendix V

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REPORT OF THE OIE/FAO/WHO MEETING ON THE ASSESSMENT OF FOOD SAFETY RELATED TO THE USE OF RECOMBINANT VACCINES IN FOOD-PRODUCING ANIMALS

Paris, 18–19 January 2010

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An OIE/FAO/WHO meeting on the Assessment of Food Safety Related to the Use of Recombinant Vaccines in Food-Producing Animals was held at the OIE Headquarters in Paris from 18 to 19 January 2010. The meeting was chaired by Dr David Mackay. Dr Donna Hutchings accepted to act as rapporteur. The Agenda and List of Participants are given at Appendices I and II, respectively.

1. Introduction

The Group was welcomed by Dr Elisabeth Erlacher-Vindel (Deputy Head, OIE Scientific and Technical Department), on behalf of Dr Bernard Vallat, Director General of the OIE.

Dr Erlacher-Vindel provided an update on OIE activities related to the *ad hoc* Group on Vaccines in Relation to New and Emerging Technologies, which met in November 2008 and again in November 2009.

2. Adoption of the agenda

The Group accepted the agenda as proposed by OIE. It was noted that observers from industry would be available in the afternoon to provide information upon request.

3. Clarification of the scope of the discussion on the use of recombinant vaccines in food-producing animals

The Group's discussion was focused on non-heritable constructs, as heritable constructs were not considered to fall within the generally understood definition of vaccines, including that used within the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*).

While noting that there was some variation in the use of generic terms such as "genetically modified (GM)", "genetically engineered (GE)" and "recombinant vaccines", the Group chose to use the term GE vaccine as the standard term for this discussion, thus including all common types.

The Group noted that vaccination with GE vaccines, as with conventional vaccines, that result in persistency or latency of the vaccine organism (e.g. Herpesvirus, DNA vaccines) require specific evaluation of safety including food safety, but that animals vaccinated with GE vaccines should not be considered as genetically modified animals.

The Group agreed that the scope of the current discussion was on safety of GE vaccines in food animals, and not on vaccines to reduce shedding of organisms relevant to food safety.

4. Outline of the approach to assessing the safety of recombinant vaccines with examples

The Group discussed international requirements for licensing of GE vaccines for animals, in particular safety requirements, and noted that regional requirements were not well known. This point was confirmed by the observers from industry.

The Group noted that the classification of pathogens with respect to their inherent pathogenicity for humans and animals was important for the safety evaluation of vaccines derived from them, e.g. Class 1 organisms present less of an inherent safety risk than those in Classes 2 or 3, however classification might vary between regions. The Group agreed that the use of an internationally standardised classification of veterinary pathogens was desirable to help in the assessment of safety.

The Group concluded that only general safety guidance could be provided, as the possible situations were so variable that case-by-case evaluation was needed. The way of demonstrating safety was different amongst various products; for example, replication of some vaccine vectors was abortive, and most animal vaccine strains were not zoonotic.

The Group agreed that the general advice and requirements for safety evaluations on all vaccines should also apply to GE vaccines, and that licensing authorities should ensure that food safety is an element included in risk assessments. The type of vaccine, the target species, novelty, dose and route of administration (individual or mass vaccination) might determine the complexity of the safety evaluation, in particular the use of zoonotic agents. If relevant, a withdrawal period for the different food products (e.g. meat, eggs, milk) would be established. MRL (maximum residue limits or tolerance limits) were required to be set for pharmacologically active ingredients, including adjuvants and excipients in vaccines. This could apply to toxins used to enhance immunity to vaccines, e.g. lectins and cholera toxin.

The European Medicines Agency provided two examples of risk assessments for the discussion, including live canarypox vectored vaccines in horses and live Marek's disease vectored vaccines in chickens. It was noted that CFIA (Canadian Food Inspection Agency) had similar conclusions regarding safety of the same products: http://www.inspection.gc.ca/english/anima/vetbio/eaee/eaeee.shtml. In both of these cases, and in many other cases of which the Group was aware, the starting point for producing the GE vaccine strain was a well characterised vaccine strain with a long history of safe use. Indeed some such strains had been investigated for their potential for use in humans and therefore much was known about their safety with respect to human exposure. In such cases it was possible for regulators to adopt an approach similar to that described in the Codex Alimentarius Guidelines for the Conduct of Food Safety Risk Assessments of Foods Produced Using Recombinant-DNA Microorganisms (CAC/GL 46-2003) whereby knowledge of the extensive safe use of the parental organism is fully taken into account when considering the potential impact of introduced genetic changes. The Group recognised that more information would be required in situations where the vector organism had not previously been licensed for use in food-producing species.

The Group considered that DNA vaccines (i.e. vaccines consisting of purified recombinant DNA) constituted a special case. However, very few such vaccines had been commercialised for food-producing species and the Group considered that economic and other factors make it unlikely that their use would become widespread. In general, these vaccines were not considered to pose a significant food safety risk, as only low amounts of administered DNA were likely to be present in vaccinated animals at the time of slaughter and any such DNA would rapidly be degraded through digestion.

The Group considered it was important to differentiate clearly between genetically modified foods and the use of GE vaccines. In the case of food, the intention is to introduce a new trait into a food that will still be present when the food is eaten by the consumer. In the case of GE vaccines, the intention is generally to induce a protective immune response by means of an immunogen that is often no longer itself present at the time the animal is slaughtered. The Group recognised that this was a generalisation to which there are exceptions and it was therefore necessary to assess risk on a case-by-case basis. Nevertheless this difference in principle was considered important to emphasise, particularly to those not familiar with the principles of vaccinology.

5. Review of relevant guidance in the OIE *Terrestrial Manual*

The Group reviewed the existing relevant chapters from the OIE *Terrestrial Manual*, including the text of Chapter 1.1.8 Principles of Veterinary Vaccine Production, and recommended addition of a new Appendix to Chapter 1.1.8 on benefit–risk assessment of veterinary vaccines, including GE vaccines, with a specific section on safety including food safety.

It was noted that a paper, available in an OIE publication, could be used as the basis for the safety part of the Appendix on benefit–risk evaluation (Safe use of vaccines and vaccine compliance with food safety requirements, K. Grein *et al., Rev. sci. tech. Off. int. Epiz*. [2007]. **26**, 339–350):

http://www.oie.int/boutique/index.php?page=ficprod&id_prec=119&id_produit=200&lang=en&fichrech=1&PHPSESSID=f16022cedb6ce265c164795d31c9a6cb

6. Conclusions

Considering the following factors:

– Licensed GE vaccines have a history of safe use in animals for about 20 years, as the safety of GE vaccines is currently well defined and predictable due to knowledge of the genetics of these vaccines, and is ensured through a system of thorough review with licensing;

– Types of technology available for GE vaccines are continually evolving, yet those with established safety profiles remain preferred in practice. Current types of technology for GE vaccines are described in the draft *Terrestrial Manual* Chapter 1.1.7 The Application of Biotechnology to the Development of Veterinary Vaccines;

– Food safety aspects of GE vaccines other than the active ingredient (e.g. excipients, adjuvants) are not different from conventional vaccines, and are taken into account during licensing, establishing residue limits and withdrawal periods when necessary;

– An evaluation of food safety is already considered an integral part of the overall benefit–risk assessment that forms the basis of any decision by a regulatory authority to licence (authorise) a vaccine, GE or not;

The Group recommended that:

a) Food safety, as part of overall human safety assessment, should not be separated from overall safety for users and consumers; the review of food safety should therefore be kept in context.

b) The standard of safety should not be different between GE vaccines and conventional vaccines.

c) Animals vaccinated with GE vaccines should not be considered GM animals.

d) At present, no need was identified for new international guidance on risk assessments for GE vaccines other than an update to the OIE *Terrestrial Manual*.

e) A new Appendix should be added to the OIE *Terrestrial Manual* Chapter 1.1.8. on benefit–risk assessment of veterinary vaccines, including GE vaccines, with a specific section on safety including food safety.

The Group further noted that:

f) Although DNA vaccines are not currently used in terrestrial food animals, this type of GE vaccine may require closer scrutiny on a case by case basis as there is currently little experience on which to base an assessment of their safety under normal conditions of use.