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REGULATORY CONSIDERATIONS FOR EMERGENCY USE OF VACCINES IN THE EUROPEAN UNION

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ABSTRACT

From a regulatory perspective foot-and-mouth disease (FMD) vaccines represent a special case due to the number and antigenic diversity of strains that might be used alone or in combination within the context of an authorisation.

New guidelines have been developed proposing that an FMD vaccine should be defined as a formulation of ingredients including defined amounts of one or more antigens that vary only in the number and types of antigen present. These new guidelines are in line with those previously proposed for equine influenza vaccines. Slaughter policies being less and less popular in the European Union, there is a tendency to use so-called marker vaccines associated with a companion diagnostic test. Such methodology has already been used for vaccination against pseudo-rabies and infectious bovine rhinotracheitis. Sub-unit marker vaccines against classical swine fever have also been developed; such vaccines are also envisaged against foot-and-mouth disease; it would permit, if satisfying defined criteria, to distinguish vaccinated from infected animals.

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Introduction

The recent epidemic of FMD in the United Kingdom, the current Commission reviews of both pharmaceutical and FMD legislation, and a greater perception that future control strategies might involve a policy of "vaccination to live" have all contributed to the Committee for Veterinary Medicinal Products (CVMP) initiating the preparation of guidelines on the requirements for FMD vaccines.

This paper will describe the approach taken in the draft guideline to those features that make FMD vaccines a "special case" in terms of authorisation.

Whether or not the new proposals are ultimately adopted will depend on the outcome of the process of scientific and legal consultation through which the guidelines will now progress. These new guidelines are partly influenced by other guidelines previously developed on the harmonisation of requirements for equine influenza vaccines, namely specific requirements for substitution of a strain or strains.

Slaughter policies being unpopular in the European Union, so-called marker vaccines associated with companion diagnostic tests have been developed which allow the differentiation of infected from vaccinated animals. Such vaccines are already used to protect pigs against pseudo-rabies and cattle against infectious bovine rhinotracheitis.

Sub-unit marker vaccines are already available for vaccinating pigs against classical swine fever and similar approaches could be developed to produce marker vaccines against FMD.

Foot-and-Mouth Disease Vaccines – Regulatory Aspects

In regulatory terms, FMD vaccines are often seen by their manufacturers, and to some extent by their users, as a 'special case' due to the special nature of the disease against which they provide protection. From a legal and regulatory perspective, however, FMD vaccines, like all vaccines, are immunological veterinary medicinal products and are therefore subject to the requirements of the veterinary pharmaceutical Directive 2001/82/EC. This directive requires that all veterinary medicines that are placed on the market within the European Union must be authorised by means of a marketing authorisation and lays down the minimum requirements in terms of quality, safety and efficacy that medicines must meet to obtain an authorisation. The directive provides an exemption from the requirement for an authorisation when a product is to be used in the event of 'serious disease epidemic' provided there is no authorised medicine for use against the disease concerned and provided the European Commission is informed of the detailed conditions of use. The term 'serious disease epidemic' is not further defined but clearly applies to outbreaks of FMD. The European Commission itself utilises this exemption to allow use without an authorisation of vaccines prepared using antigens maintained in the strategic antigen reserves of the EU FMD Antigen Bank.

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New guidelines for FMD vaccines have been prepared by an ad hoc group of the Committee for Veterinary Medicinal Products of the European Medicines Evaluation Agency based in London.

The CVMP ad hoc group comprises members of (i) the Immunological Working Party of the CVMP, (ii) the Research Group of the European Commission for the Control of FMD of the FAO, and (iii) the OIE. Invited as observers are representatives from DG Enterprise and DG SANCO of the European Commission and from the European manufacturers of FMD vaccines. The group has met on several occasions and is currently finalising the first draft of the 'Guideline on requirements for vaccines against foot-and-mouth disease' which will go out for consultation during 2002. Like all CVMP guidelines, the document is intended to provide guidance for manufacturers seeking to place FMD vaccines on the market within the EU. The group has consulted widely with other international organisations to ensure that the draft proposals have wide acceptance. Ultimately the standards set will be those that will apply in the EU and authorities in other regions will have to consider to what extent they may wish to apply them in their own areas.

Within the EU, directive 2001/82/EC requires that any product placed on the market must meet the requirements of the relevant monograph of the European Pharmacopoeia where one exists for the type of product concerned. In the case of FMD vaccines, there is a monograph laying down the minimum requirements for inactivated FMD vaccines for ruminants. Group 15V of the European Pharmacopoeia has published a revision proposal for this monograph and is currently working to develop a monograph for FMD vaccines for pigs. The CVMP ad hoc group has taken account of the revised proposal in preparing the draft guidelines and has put forward a number of proposed amendments to the revised proposal for consideration by Group 15 V. During the consultation process on both documents care will be taken to ensure that they remain compatible and complementary.

The Precedent of equine Influenza Vaccines (EMEA)

Equine influenza has remained among the main acute contagious respiratory diseases of horses world-wide. Equine influenza is represented by two subtypes : Influenza A/equine 2 virus (H_3N_8) which is the most important cause of respiratory diseases in the horse, and Influenza A/equine 1 virus (H_7N_7) which is still circulating subclinically but is almost considered as extinct.

However, a divergence in the evolution of A/equine 2 (H_3N_8) viruses has occurred since 1987 and two families of viruses are now circulating. These were designated European-like and American-like, although representatives of both families had been isolated in both continents [1]. There is increasing evidence from field studies that antigenic drift in the gene coding for the haemagglutinin (HA), which is the major surface protein of these influenza A strains, eventually renders vaccine strains obsolete and is likely to compromise vaccine efficacy [1-3].

A formal reporting mechanism on antigenic/genetic drift or shift of equine influenza viruses and a vaccine strain selection system has been set up, so that vaccine manufacturers and regulatory authorities are informed of the potential need to update vaccine virus strains.

An Expert Surveillance Panel, including representatives from three WHO Reference Laboratories and from three OIE Reference Laboratories reviews every year the epidemiological and virological information and makes recommendations about suitable vaccine strains. These recommendations are published annually by the OIE in its Bulletin [4], As antigenic drift in equine influenza occurs at a slower rate than in human influenza, it is considered that a regular update of the strains could be necessary every three to five years.

The development of effective vaccines can now be facilitated by the availability of reliable in vitro assays such as :

-Single Radial Diffusion (SRD) to measure vaccine bulk antigen content in terms of HA content

-Single Radial Haemolysis (SRH) to measure serological responses.

For in-process controls, SRD provides a reliable method of measuring HA content of equine influenza bulk antigens, although it cannot be used on final adjuvanted products. Use of SRD tests is therefore limited to the in-process control of adjuvanted vaccines. SRD tests can provide a great improvement on the Chick Cell Agglutination (CCA) test as it is not susceptible to wide test variation and measures immunologically active HA [5],

SRH is a sensitive and reproducible method for measuring antibody to HA.

A new outbreak associated with a possible breakdown of existing vaccines may require a change in the formulation of such vaccines. It is expected that manufacturers will wish to make such changes in response to evidence of antigenic drift and on the need for such a change from the report and recommendation from the Expert Surveillance Panel.

Equine influenza vaccines are well characterised, and it is unlikely that the replacement of one strain by another would lead to such substantial changes as to justify a new full set of safety and efficacy tests to be carried out. In addition, there is a need to consider reduction of the number of animals used in the testing of medicinal products wherever possible. Therefore, provided there have been no or few adverse reactions with the previous formulation, a two-fold approach is proposed for the testing of the new formation :

-cross-references to the original dossier would be accepted for those parts which remain unchanged ;

-where necessary, the analytical, safety and efficacy sections of the original dossier would need to be amended and new additional data generated. The three expert reports will also require updating from those submitted for the previous formulation.

Marker Vaccines Against Classical Swine Fever

Large-scale vaccination against classical swine fever using classical, attenuated vaccines, is no longer allowed in the European Union ; slaughter policy is the rule. Nevertheless, several countries in the Union have to face regular outbreaks mainly due to the existence of a reservoir in wildlife,

the wild boar (*Sus scrofa*) [6]. One solution could be to use marker vaccines. Sub-unit marker vaccines have recently been developed by expressing the major immunogen of classical swine fever pestivirus (CSFV), protein E2, in a baculovirus expression system [7,8], These subunit vaccines would permit vaccinated animals to be distinguished from infected ones by serology. These vaccines have been evaluated and accepted by the European Medicinal Evaluation Agency (EMEA). The companion diagnostic test is based on the detection of antibodies directed against another major immunogen (non-structural protein NS2) not contained in the vaccine.

Unfortunately, independent experiments showed that the system is yet to be improved. In fact, those sub-unit vaccines being inactivated vaccines are not as efficacious as the previous attenuated ones [9]. Moreover, the available companion diagnostic tests are not yet reliable and therefore impede the practical use of these vaccines.

Improved marker vaccines could, nevertheless, help to solve the problem of classical swine fever in Europe since it seems difficult to control the disease without vaccination [10,11].

Towards Foot-and-Mouth Disease Marker Vaccines

An area of particular interest in the new FMD vaccines guidelines is the incorporation of guidance on FMD marker vaccines. These vaccines would be based on the detection of antibodies directed to one or more of the non-structural (NS) proteins of the virus. Manufacturers may therefore wish to provide potential customers with information on whether or not their vaccine induces antibody to NS proteins. Modem FMD vaccines contain purified preparations of virions from which tissue culture components, including NS proteins, have been removed to a greater or lesser degree. There is currently insufficient information on the immunogenicity of the various NS proteins to set levels below which FMD vaccines can be considered to be 'free'. What is important is the ability of any residual, contaminating NS protein to induce an antibody response in the target species that is sufficient to interfere with a diagnostic test. The guideline therefore proposes that manufacturers should look for antibody to defined NS proteins in the sera of cattle (or other species for which the vaccine is indicated) that have been repeatedly immunised with vaccines containing the maximum amount and number of FMD antigens permitted under the authorisation. The guideline does not attempt to prescribe which antigen(s) should be studied nor which test should be used, but requires that the test used is fully validated. The manufacturing process must include a purification step to remove NS protein contamination and manufacturers can support their claim by demonstrating, using suitable immunochemical methods, that their antigen preparations are free from defined NS protein(s) or contain only low levels. There is no EU legislation covering the evaluation or authorisation of diagnostic tests. This, together with the fact that 'vaccinated' and 'infected' states are not mutually exclusive in FMD means that claims to 'differentiate' infection from vaccination or for 'marker' vaccines are inappropriate and should not be included on the summary of product characteristics (SPC) for FMD vaccines authorised in the EU. Claims that vaccines do not interfere with the detection of infected animals by means of NS antibody tests would be acceptable. There is currently no consensus on which NS protein is the most reliable

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marker of infection and the tests available have been validated to different levels. The claims made in relation to NS proteins must clearly reflect the studies presented and should be limited to stating which NS protein has been studied and by which test. In this way, potential customers can make informed decisions on an appropriate choice of a vaccine and a companion diagnostic test to be used when choosing to follow a policy of 'vaccination to live'.

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